

CURRENT APPROACHES IN OBSTETRIC HEMORRHAGES

EDITORS

Dr. Mehmet YILMAZ

Dr. Yasemin ABOALHASAN



İKSAD
Publishing House

CURRENT APPROACHES IN OBSTETRIC HEMORRHAGES

EDITORS

Dr. Mehmet YILMAZ

Dr. Yasemin ABOALHASAN

AUTHORS

Dr. Ahu KORKUT

Dr. Arife Ebru TAŐCI

Dr. Asli ALTINORDU ATCI

Dr. Aysun ALPARSLAN ULHA

Dr. Ayőe GÜLMEZ

Dr. Betül DİK

Dr. Baőak ERGİN

Dr. Bayram CAN

Dr. Cemile ÖZCAN UAR

Dr. Gizem Ceren EKİCİ

Dr. GÜlsüm DOĐAN

Dr. Fatih AKKUŐ

Dr. Melike Pündük YILMAZ

Dr. Mevlüt BUCAK

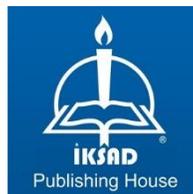
Dr. Sıtkı ÖZBİLGE

Dr. őebnem KARAGÜN

Dr. őükran DOĐRU

Dr. Yasmin ABOALHASAN

Dr. Yusuf DAL



Copyright © 2022 by iksad publishing house
All rights reserved. No part of this publication may be reproduced, distributed or
transmitted in any form or by
any means, including photocopying, recording or other electronic or mechanical
methods, without the prior written permission of the publisher,
except in the case of
brief quotations embodied in critical reviews and certain other
noncommercial uses permitted by copyright law. Institution of Economic
Development and Social
Researches Publications®
(The Licence Number of Publicator: 2014/31220)
TURKEY TR: +90 342 606 06 75
USA: +1 631 685 0 853
E mail: iksadyayinevi@gmail.com
www.iksadyayinevi.com

It is responsibility of the author to abide by the publishing ethics rules.
Iksad Publications – 2022©

ISBN: 978-625-8377-65-1
Cover Design: İbrahim KAYA
June / 2022
Ankara / Turkey
Size = 16 x 24 cm

CONTENTS

EDITED BY

PREFACE

Dr. Mehmet YILMAZ

Dr. Yasemin ABOALHASAN.....1

CHAPTER 1

ETIOLOGY AND EVALUATION OF VAGINAL BLEEDING IN PREGNANCY

Dr. Şükran DOĞRU

Dr. Asli ALTINORDU ATCI.....3

CHAPTER 2

IMAGING METHODS IN OBSTETRIC BLEEDING

Dr. Yusuf DAL.....19

CHAPTER 3

EVALUATION OF ANTEPARTUM BLEEDING

Dr. Mevlüt BUCAK

Dr. Fatih AKKUŞ.....41

CHAPTER 4

CAUSES AND ADMINISTRATION OF ANEMIA IN PREGNANCY

Dr. Ahu KORKUT.....53

CHAPTER 5

FIRST TRIMESTER BLEEDING AND ADMINISTRATION

Dr. Yusuf DAL.....77

CHAPTER 6

2nd AND 3rd TRIMESTER BLEEDING AND ADMINISTRATION

Dr. Ahu KORKUT.....91

CHAPTER 7

BLEEDING DUE TO ECTOPIC PREGNANCY

Dr. Aysun ALPARSLAN ÇULHA

Dr. Fatih AKKUŞ.....129

CHAPTER 8	
GESTATIONAL TROPHOBLASTIC DISEASE AND VAGINAL BLEEDING	
Dr. Şebnem KARAGÜN.....	139
CHAPTER 9	
GENITAL INFECTIONS IN PREGNANCY AND BLEEDING	
Dr. Ayşe GÜLMEZ.....	161
CHAPTER 10	
BLEEDING DUE TO MYOMS DURING PREGNANCY	
Dr. Başak ERGİN.....	183
CHAPTER 11	
BLEEDING DUE TO OBSTETRIC INTERVENTIONAL METHODS: A REVIEW	
Dr. Gizem Ceren EKİCİ.....	195
CHAPTER 12	
VULVOVAGINAL BLEEDING IN PREGNANCY	
Dr. Betül DİK.....	207
CHAPTER 13	
HEMORRHAGE DUE TO OPERATIVE VAGINAL DELIVERY	
Dr. Arife Ebru TAŞCI.....	223
CHAPTER 14	
PERIOPERATIVE MANAGEMENT OF BLEEDING PREGNANT: AN OVERVIEW	
Dr. Gizem Ceren EKİCİ.....	241
CHAPTER 15	
MEDICAL TREATMENT OF OBSTETRIC BLEEDINGS	
Dr. Cemile ÖZCAN UÇAR.....	255
CHAPTER 16	
SURGICAL TREATMENT METHODS IN OBSTETRIC HEMORRHAGES	
Dr. Bayram CAN.....	275

CHAPTER 17

**DISSEMINATED INTRAVASCULAR COAGULATION IN
PREGNANCY: AN OVERVIEW**

Dr. Asli ALTINORDU ATCI

Dr. Şükran DOĞRU.....289

CHAPTER 18

FEMALE GENITALIA ANATOMY

Dr. Cemile ÖZCAN UÇAR.....

301

CHAPTER 19

BLOOD TRANSFUSION IN OBSTETRICS: AN OVERVIEW

Dr. Gülsüm DOĞAN.....

319

CHAPTER 20

ALLOIMMUNIZATION IN PREGNANCY: A REVIEW

Dr. Gülsüm DOĞAN.....

333

CHAPTER 21

PLACENTA ACCRETA SPECTRUM

Dr. Sıtkı ÖZBİLGEÇ.....

349

CHAPTER 22

THROMBOPHILIAS IN PREGNANCY: AN OVERVIEW

Dr. Yasmin ABOALHASAN.....

383

CHAPTER 23

POSTOPERATIVE AND POSTPARTUM HEMORRHAGE

Dr Melike Pündük YILMAZ.....

397

CHAPTER 24

UTERINE ATONY AND ASSOCIATED HEMORRHAGES

Dr. Melike Pündük YILMAZ.....

417

PREFACE

Obstetric hemorrhage, with related complications, remains a significant and often preventable cause of maternal morbidity and mortality. Changes in definitions, an expansion of the spectrum of causes, variation in interventions and guidelines and lack of innovation are some of the issues that pose ongoing challenges for meaningful risk reduction. What is the most common cause of obstetrical hemorrhage and first line management? What are priority nursing interventions for postpartum hemorrhage?

Protocols should provide a standardized approach to evaluate and monitor the patients. A standard protocol must be recognized by the institution and must be accepted and known by all team members. Is it time for a more personalised approach? Here in this chapter reader may find current approaches in obstetric hemorrhages including etiology, pathophysiology, symptoms, signs, diagnosis & prognosis with the help of international quality articles published mostly in the last few years.

CHAPTER 1

ETIOLOGY AND EVALUATION OF VAGINAL BLEEDING IN PREGNANCY

Dr. Şükran DOĞRU¹

Dr. Asli ALTINORDU ATCI²

¹ Necmettin Erbakan University Meram Faculty of Medicine Department of Obstetrics and Gynecology Perinatology Clinic
Corresponding author: sukrandogru-2465@hotmail.com ORCID: 0000-0002-3383-2837

² Necmettin Erbakan University Meram Faculty of Medicine Department of Obstetrics and Gynecology Perinatology Clinic ORCID: 0000-0002-2637-3150

INTRODUCTION

Bleeding from the vagina is a common event at all stages of pregnancy. The source is virtually never fetal. Bleeding usually results from disruption of blood vessels in the decidua or from discrete cervical or vaginal lesions. The clinician typically makes a provisional clinical diagnosis based upon the gestational age and the character of bleeding. Laboratory and imaging tests are then used to confirm or revise the initial diagnosis.

First-trimester bleeding

Vaginal bleeding is common in the first trimester, occurring in 20 to 40 percent of pregnancies (Everett, 1997). Bleeding can be any combination of light or heavy, intermittent or constant, painless or painful.

Causes — The five major sources of nontraumatic bleeding in early pregnancy are:

- Ectopic pregnancy
- Early pregnancy loss
- Threatened abortion
- Implantation of the pregnancy
- Cervical, vaginal, or uterine pathology (eg, polyps, inflammation/infection, gestational trophoblastic disease)

Bleeding related to early pregnancy loss or threatened abortion is the most common nontraumatic cause of first-trimester bleeding (prevalence: 15 to 20 percent of pregnancies). Although bleeding may be heavy, almost all patients remain hemodynamically stable; only an approximate 1 percent of expectantly managed patients require blood transfusion (Nanda, Lopez, Grimes, Pelligia, & Nanda, 2012). Ectopic pregnancy is much less common but is the most serious etiology of first-trimester bleeding. Rupture of an ectopic pregnancy is a potentially life-threatening complication; therefore, this diagnosis must be excluded in every pregnant patient with bleeding.

Evaluation

The extent of bleeding should be determined: Do they have significant pelvic pain or cramping? Have they passed any tissue? If the patient answers yes to any of these questions, then ectopic pregnancy and early pregnancy

loss are much more likely diagnoses than implantation bleeding, threatened abortion, or cervicovaginal disorders. A past history of ectopic pregnancy or risk factors for ectopic pregnancy increase the probability of this disorder. A history of two or more consecutive early pregnancy losses or a condition associated with early pregnancy loss (eg, chromosomal translocation in either parent, maternal antiphospholipid syndrome, uterine anomaly) increases the likelihood that bleeding is related to impending pregnancy loss.

Physical examination

Any tissue the patient has passed should be examined. An abdominal examination should be performed before the internal examination. Midline pain is more consistent with early pregnancy loss, while lateral pain is more consistent with ectopic pregnancy. Nongynecologic causes of pain should also be considered. Doppler confirmation of fetal cardiac activity is reassuring, as it indicates bleeding is not related to fetal demise and unlikely to be related to an ectopic pregnancy. The clinician should determine whether uterine size is appropriate for the estimated gestational age. A speculum is then inserted into the vagina to assess the volume and source of bleeding. Speculum examination may reveal a source of bleeding unrelated to pregnancy; in such cases, further evaluation depends upon the nature of the abnormality: Vaginal laceration ,Vaginal neoplasm ,Vaginal warts ,Vaginal discharge ,Cervical polyps, fibroids, ectropion ,Mucopurulent cervical discharge or friability at the cervical os ,Cervical neoplasm. Visualization of the internal cervical os is possible in some cases and helps to distinguish between a threatened and a true early pregnancy loss. A closed internal cervical os is most consistent with a threatened abortion, but not diagnostic. In contrast to the internal os, an open external cervical os is usually not helpful diagnostically because it is a normal finding, especially in parous patients.

One review of data from observational studies concluded that ultrasound examination and human chorionic gonadotropin (hCG) concentration could replace pelvic examination in the initial evaluation of patients with early pregnancy bleeding(Isoardi, 2009).

Transvaginal ultrasonography — Transvaginal ultrasonography is the cornerstone of the evaluation of bleeding in early pregnancy. It is most useful in bleeding patients with a positive pregnancy test in whom an

intrauterine pregnancy has not been previously confirmed by imaging studies. In these patients, ultrasound examination is performed to determine whether the pregnancy is intrauterine or extrauterine (ectopic) and, if intrauterine, whether the pregnancy is viable (fetal cardiac activity present) or nonviable. Rarely, ultrasound examination reveals unusual causes of vaginal bleeding, such as gestational trophoblastic disease or loss of one fetus from a multiple gestation.

Other imaging tests — If transvaginal ultrasound is not readily available to assess the uterus, transabdominal ultrasound is useful. Transvaginal ultrasound allows for earlier and more reliable detection of an intrauterine or ectopic pregnancy and is more sensitive for detecting embryonic cardiac activity at very early gestational ages compared with transabdominal ultrasound, but the latter is useful for assessing free fluid in the abdomen (eg, bleeding from an ectopic pregnancy) and abnormalities beyond the field of view of a high-frequency vaginal probe.

Magnetic resonance imaging (MRI) is rarely indicated but may be used as a second-line imaging modality for further evaluation of limited and nondiagnostic ultrasound, an unusual ectopic pregnancy, gestational trophoblastic disease, and differentiating causes of severe pelvic pain and adnexal masses.

Computed tomography (CT) may be useful in pregnant patients with trauma or acute nongynecologic pain, for staging of malignancy, or if magnetic resonance imaging is not possible

Laboratory tests — There is no role for monitoring hCG concentration once the presence of an intrauterine pregnancy has been established sonographically. Serial measurements of hCG are helpful. In hemodynamically stable patients, a baseline hemoglobin/hematocrit measurement can be useful in those with heavy vaginal bleeding, particularly if persistent, and in those with ruptured ectopic pregnancy. During the first six weeks of pregnancy if ultrasonography is nondiagnostic.

Differential diagnosis and management — The information gleaned from the evaluation described above is used to determine a diagnosis and plan of management. Patients with significant first-trimester vaginal bleeding (ie, more than spotting) should have a red blood cell antibody screen checked. Those who are RhD-negative are generally given anti-D

immune globulin to protect against RhD alloimmunization, unless the vaginal bleeding is clearly due to a nonplacental, nonfetal source, such as a vaginal laceration. Some guidelines do not administer anti-D immune globulin to patients with threatened abortion or complete or incomplete pregnancy loss <12 weeks of gestation (Sperling, Dahlke, Sutton, Gonzalez, & Chauhan, 2018).

Ectopic pregnancy — All patients with early pregnancy bleeding and pain are assumed to have ectopic pregnancy until this diagnosis has been excluded by laboratory and imaging studies. Ectopic pregnancy (EP) is a term used to describe any pregnancy which does not implant into the uterine cavity. There are several types of EPs: tubal, interstitial, ovarian, abdominal, heterotopic, cervical, and cesarean scar (Houser, Kandalaft, & Khati, 2022). Ectopic pregnancies can acutely rupture and are the number one cause of maternal death in the first trimester of pregnancy. Patients with a history of ectopic pregnancy or other risk factors for the disorder are at highest risk, but many patients with ectopic pregnancy have no risk factors.

The discriminatory zone is the serum hCG level above which a gestational sac should be visualized by transvaginal ultrasound if an intrauterine pregnancy is present. The discriminatory zone varies somewhat by laboratory and institution; some institutions set the discriminatory zone at 2000 and others use 3510 milli-international units/mL. Other findings that should be considered when making a diagnosis are whether an adnexal mass is present and the likely etiology of the mass (ectopic pregnancy versus corpus luteum cyst) and whether the patient is hemodynamically unstable or has a tender abdomen, which suggests a ruptured ectopic pregnancy or corpus luteum cyst. Management of ectopic pregnancy is generally medical (methotrexate therapy) or surgical. Expectant management can be dangerous for the patient, but may be possible in rare cases. Even if an intrauterine pregnancy is diagnosed, the possibility of heterotopic pregnancy should be kept in mind, even though rare (1 in 30,000 pregnancies). Cervical pregnancy is a rare form of ectopic pregnancy in which the pregnancy implants in the lining of the endocervical canal. Management of cervical ectopic pregnancies should be guided by patient stability, β -hCG level, size of pregnancy, and fetal cardiac activity but may benefit from a planned multimodal approach (Fowler et al., 2021). Cesarean scar pregnancy occurs from implantation of the pregnancy into either a wedge defect in the lower

uterine segment at the site of the hysterotomy for a previous cesarean birth or a microscopic fistula within the hysterotomy scar. when counseling patients undergoing treatment for CSP regarding their risk of recurrence. We found no obvious causal relationship or association between the type of treatment of the previous CSP and recurrence of CSP. Patients who become pregnant after treatment of a CSP should be encouraged to have an early (5-7-week) first-trimester transvaginal scan to determine the location of the gestation(Timor-Tritsch et al., 2021).

Early pregnancy loss

Threatened abortion — Vaginal bleeding in the presence of a closed cervix and sonographic visualization of an intrauterine pregnancy with detectable fetal cardiac activity is diagnostic of threatened early pregnancy loss. When an intrauterine pregnancy is detected on ultrasonography but viability is uncertain, repeat ultrasonography should be performed in seven to 10 days to confirm viability("The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss," 2015; Doubilet et al., 2013; Rodgers, Chang, DeBardleben, & Horrow, 2015). The term "threatened" is used to describe these cases because early pregnancy loss does not always follow vaginal bleeding, even after repeated episodes or large amounts of bleeding. In fact, 90 to 96 percent of pregnancies with both fetal cardiac activity and vaginal bleeding at 7 to 11 weeks of gestation are not lost; the 96 percent ongoing pregnancy rate is associated with bleeding at the later end of this gestational age range (Tannirandom et al., 2003; Tongsong et al., 1995). Bleeding in these cases is likely due to disruption of decidual vessels at the maternal-fetal interface. Ultrasonography is helpful in the diagnosis of spontaneous abortion, but other testing may be needed if an ectopic pregnancy cannot be ruled out. Chromosomal abnormalities are causative in approximately 50 percent of spontaneous abortions; multiple other factors also may play a role. Management is expectant; available evidence does not support a benefit of progesterone supplementation in patients with threatened abortion and zero or one previous pregnancy loss(Coomarasamy et al., 2020).

Complete pregnancy loss — When a pregnancy loss occurs before 12 weeks of gestation, it is common for the entire contents of the uterus to be expelled, thereby resulting in complete pregnancy loss. For women with

incomplete spontaneous abortion, expectant management for up to two weeks usually is successful, and medical therapy provides little additional benefit. When patients are allowed to choose between treatment options, a large percentage will choose expectant management. Expectant management of missed spontaneous abortion has variable success rates, but medical therapy with intravaginal misoprostol has an 80 percent success rate (Griebel, Halvorsen, Golemon, & Day, 2005). Watchful waiting is recommended as first-line treatment for patients with incomplete abortion; more than 90% of these patients will complete the process spontaneously within four weeks (Luise et al., 2002).

Incomplete early pregnancy loss — When early pregnancy loss is inevitable, the internal os of the cervix is dilated, vaginal bleeding is increasing, and painful uterine cramps/contractions are present.

Missed abortion — A missed abortion refers to in-utero death of the embryo or fetus prior to the 20th week of gestation, with retention of the pregnancy for a prolonged period of time. Patients may notice that symptoms associated with early pregnancy have abated and they do not "feel pregnant" anymore. Vaginal bleeding may occur. The internal cervical os usually remains closed. Ultrasound reveals an intrauterine gestational sac with or without an embryonic/fetal pole, but no embryonic/fetal cardiac activity.

Vanishing twin — The term "vanishing twin" has been used to describe a singleton pregnancy which results from very early loss of one member of a multiple gestation. Vanishing twins are often the product of assisted reproduction techniques and can be associated with vaginal bleeding (De Sutter et al., 2006). The prognosis for continuing a pregnancy associated with the vanishing twin phenomenon is good, regardless of the chorionic status. Although some reports have linked twin death later in gestation with complications such as disseminated intravascular coagulation or brain damage in the surviving co-twin, especially with monochorionic twins, such events have not been described in association with disappearance at this early stage in pregnancy (Landy & Keith, 1998).

Vaginitis, trauma, tumor, warts, polyps, fibroids — These conditions are diagnosed by visual inspection, with ancillary tests as indicated.

Ectropion — Cervical ectropion is a common and normal finding in pregnancy. The exposed columnar epithelium is prone to light bleeding when touched, such as during vaginal intercourse, insertion of a speculum, bimanual examination, or when a cervical specimen is obtained for cytology or culture. Therapy is unnecessary.

Physiologic or implantation bleeding — This is a diagnosis of exclusion. It is characterized by a small amount of spotting or bleeding approximately 10 to 14 days after fertilization.

Prognosis — Studies consistently show an association between first-trimester bleeding and adverse outcome later in pregnancy. The prognosis is best when bleeding is light and limited to early pregnancy and worsens when bleeding is heavy or extends into the second trimester (Harville, Wilcox, Baird, & Weinberg, 2003; Hasan et al., 2009). A retrospective registry-based study including over one million pregnant patients found that, compared with patients without bleeding, first-trimester bleeding increased the risk of preterm birth at 28 to 31 weeks (0.9 versus 0.3 percent, OR 2.98, 95% CI 2.50-3.54) and at 32 to 36 weeks (6.1 versus 3.6 percent, OR 1.65, 95% CI 1.57-1.77), and increased the risk of placental abruption (1.4 versus 1.0 percent, OR 1.48, 95% CI 1.30-1.68) (Lykke, Dideriksen, Lidegaard, & Langhoff-Roos, 2010). In addition, patients with first-trimester bleeding in their first pregnancy were more likely to bleed in their second pregnancy than those with no bleeding in their first pregnancy (8.2 versus 2.2 percent, OR 4.05, 95% CI 3.78-4.34).

SECOND- AND THIRD-TRIMESTER BLEEDING

Vaginal bleeding is less common in the second trimester (14+0 to 27+6 weeks) and third trimester (28+0 weeks to birth). The major causes of bleeding at these times are:

- Bloody show associated with labor (by definition, labor occurs after 20 weeks of gestation) or, less commonly, cervical insufficiency
- Pregnancy loss (defined here as a loss between 14 and 20 weeks of gestation)

- Placenta previa
- Placental abruption
- Uterine rupture
- Vasa previa

Cervical, vaginal, or uterine pathology and nontubal ectopic pregnancy are other etiologies.

Prior to 20 weeks of gestation

Evaluation — The evaluation of pregnant patients with vaginal bleeding prior to 20 weeks is similar to that in the first trimester. The first step in the evaluation is to determine the extent of bleeding and whether bleeding is accompanied by pain. The presence of only light, intermittent, painless bleeding suggests bloody show from cervical insufficiency, a small marginal placental separation, or a cervical or vaginal lesion. Heavier bleeding, particularly when associated with pain, is more consistent with impending pregnancy loss or a larger placental separation. After the abdominal examination, the patient is placed in the lithotomy position. The external genitalia are examined and then a speculum is inserted into the vagina. Physical examination may reveal a nonpregnancy-related source of bleeding,

Transvaginal ultrasonography is the cornerstone in the evaluation of bleeding in the second trimester. The primary goals are to determine whether the placenta is covering the cervical os (placenta previa), whether there is evidence of decidual hemorrhage causing placental separation (ie, placental abruption), and whether the cervix shows signs suggestive of cervical insufficiency (short length, dilated internal os, prolapsed fetal membranes).

Placental abruption

It is the premature separation of the placenta from the uterine wall before or during childbirth. It is seen at a rate of 1%. Placental abruption is also one of the most important causes of maternal morbidity and perinatal mortality. Maternal risks include obstetric hemorrhage, need for blood transfusions, emergency hysterectomy, disseminated intravascular coagulopathy and renal failure. Maternal death is rare but seven times higher than the overall maternal mortality rate. Perinatal consequences include low birthweight, preterm delivery, asphyxia, stillbirth and perinatal death. In

developed countries, approximately 10% of all preterm births and 10-20% of all perinatal deaths are caused by placental abruption (Tikkanen, 2011). Previous cesarean section, > 35 years of age, history of abruption, sickle cell anemia, high blood pressure, trauma to the abdomen, smoking and cocaine use are risk factors. It is the cause of vaginal bleeding in the last trimester of pregnancy. The most common complaints and findings are vaginal bleeding, abdominal or back pain. Frequently, the anterior abdominal wall becomes stiff due to continuous contraction. If it is not diagnosed early, it can lead to the death of the baby and mother. Because the baby does not get enough oxygen, the mother may also lose a large amount of blood.

Placenta previa

A condition in which the placenta partially or completely covers the cervix. It occurs at a rate of 1 in 200. Having given birth before, a history of previa, a history of previous uterine surgery and multiple pregnancies are risk factors. It can cause vaginal bleeding. This type of bleeding is often painless. Caesarean section is required in more advanced cases. PP occasionally combines with placenta adhesion and abnormal placentation, referred to as placenta accreta, which includes accreta, increta, and percreta. These conditions can cause massive peripartum hemorrhage, which increases the probability of requiring blood transfusions (Lal & Hibbard, 2015). Thus, PP is associated with maternal morbidity and mortality (Fan et al., 2017; Say et al., 2014). The risk of life-saving hysterectomy after cesarean section (CS) for PP is 30 times higher than that for patients without PP, in addition to longer hospital stay after delivery (Park & Cho, 2020).

Placenta accreta

If part or all of the placenta adheres to the uterine wall beyond a certain degree, it is no longer separable after delivery. In the last trimester, placenta accreta may bleed. However, the actual bleeding at birth is due to the inability of the placenta to separate after the baby is born. In most cases, the location of the placenta is detected and suspected by ultrasound. Since it is a situation that threatens the mother's life, it is necessary to enter the birth in a planned manner with blood supplied. It can go as far as getting the uterus.

Uterin rüptür

1)Primary uterine rupture

(intact scarless uterus)

2)Secondary uterine rupture

(in the uterus with myometrial incision, injury, anomaly)

Incidence of uterine rupture 1/480

1) Complete Rupture

(all floors opened)

a- Traumatic

b- Spontaneous

2)Incomplete Rupture

(visceral peritoneum intact)

Uterine Rupture Risk Factors

A. Disrupting the integrity of the uterus in the pre-pregnancy period situations

I. Myomectomy

II. C/S or hysterotomy

III. Interstitial Oviduct metroplasty Deep coronalresection

IV. instrumentation, curettage

V. Congenital anomaly (such as myometrium, because a congenital defect may be naturally weak Ehlers-Danlos type IV)(Pepin, Schwarze, Superti-Furga, & Byers, 2000)

B. Uterine occurring in current pregnancy Injury

Prenatal

I. Persistent intense spontaneous contraction

II. Labor Induction (Oxytocin or prostaglandin)

III. external trauma

IV. external version

B. At Birth

a: Internal version

b: Difficult delivery with intervention (forceps use)

c:Breech delivery, macrosomia, fetal anomaly

III. acquired

a. Placenta increta or percreta

b. GTD

c. adenomyosis

IV. Other

Uterine closure techniques

Vasa previa

Vasa previa is defined when unprotected umbilical vessels run through the amniotic membranes, and pass over the cervix.

Diagnosis:

- Routine ultrasound evaluation of lower uterine segment and placenta
- Detection rate 93% and specificity 99%
- Often made 18-26 weeks of gestation
- If diagnosed in the second trimester, 20% will be resolved
- Placental location and the relationship between the placenta and internal cervical os should be evaluated
- Placental cord insertion site be documented when technically possible

Epidemiology/Incidence: 1/2500 deliveries; perinatal mortality rate for pregnancies complicated by vasa previa <10%.

Goal to prolong the pregnancy safely but in the same time to avoid complications that occur if in labor or with rupture of membranes.

References

- The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss. (2015). *Obstet Gynecol*, 125(5), 1258-1267. doi:10.1097/01.Aog.0000465191.27155.25
- Coomarasamy, A., Devall, A. J., Brosens, J. J., Quenby, S., Stephenson, M. D., Sierra, S., . . . Gallos, I. D. (2020). Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. *Am J Obstet Gynecol*, 223(2), 167-176. doi:10.1016/j.ajog.2019.12.006
- De Sutter, P., Bontinck, J., Schutysers, V., Van der Elst, J., Gerris, J., & Dhont, M. (2006). First-trimester bleeding and pregnancy outcome in singletons after assisted reproduction. *Hum Reprod*, 21(7), 1907-1911. doi:10.1093/humrep/del054
- Doubilet, P. M., Benson, C. B., Bourne, T., Blaivas, M., Barnhart, K. T., Benacerraf, B. R., . . . Timor-Tritsch, I. E. (2013). Diagnostic criteria for nonviable pregnancy early in the first trimester. *N Engl J Med*, 369(15), 1443-1451. doi:10.1056/NEJMra1302417
- Everett, C. (1997). Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. *Bmj*, 315(7099), 32-34. doi:10.1136/bmj.315.7099.32
- Fan, D., Xia, Q., Liu, L., Wu, S., Tian, G., Wang, W., . . . Liu, Z. (2017). The Incidence of Postpartum Hemorrhage in Pregnant Women with Placenta Previa: A Systematic Review and Meta-Analysis. *PLoS One*, 12(1), e0170194. doi:10.1371/journal.pone.0170194
- Fowler, M. L., Wang, D., Chia, V., Handal-Orefice, R., Latortue-Albino, P., Mulekar, S., . . . Perkins, R. (2021). Management of Cervical Ectopic Pregnancies: A Scoping Review. *Obstet Gynecol*, 138(1), 33-41. doi:10.1097/aog.0000000000004423
- Griebel, C. P., Halvorsen, J., Golemon, T. B., & Day, A. A. (2005). Management of spontaneous abortion. *Am Fam Physician*, 72(7), 1243-1250.
- Harville, E. W., Wilcox, A. J., Baird, D. D., & Weinberg, C. R. (2003). Vaginal bleeding in very early pregnancy. *Hum Reprod*, 18(9), 1944-1947. doi:10.1093/humrep/deg379
- Hasan, R., Baird, D. D., Herring, A. H., Olshan, A. F., Jonsson Funk, M. L., & Hartmann, K. E. (2009). Association between first-trimester vaginal bleeding and miscarriage. *Obstet Gynecol*, 114(4), 860-867. doi:10.1097/AOG.0b013e3181b79796
- Houser, M., Kandalaft, N., & Khati, N. J. (2022). Ectopic pregnancy: a resident's guide to imaging findings and diagnostic pitfalls. *Emerg Radiol*, 29(1), 161-172. doi:10.1007/s10140-021-01974-7
- Isoardi, K. (2009). Review article: the use of pelvic examination within the emergency department in the assessment of early pregnancy bleeding. *Emerg Med Australas*, 21(6), 440-448. doi:10.1111/j.1742-6723.2009.01227.x

- Lal, A. K., & Hibbard, J. U. (2015). Placenta previa: an outcome-based cohort study in a contemporary obstetric population. *Arch Gynecol Obstet*, 292(2), 299-305. doi:10.1007/s00404-015-3628-y
- Landy, H. J., & Keith, L. G. (1998). The vanishing twin: a review. *Hum Reprod Update*, 4(2), 177-183. doi:10.1093/humupd/4.2.177
- Luise, C., Jermy, K., May, C., Costello, G., Collins, W. P., & Bourne, T. H. (2002). Outcome of expectant management of spontaneous first trimester miscarriage: observational study. *Bmj*, 324(7342), 873-875. doi:10.1136/bmj.324.7342.873
- Lykke, J. A., Dideriksen, K. L., Lidegaard, Ø., & Langhoff-Roos, J. (2010). First-trimester vaginal bleeding and complications later in pregnancy. *Obstet Gynecol*, 115(5), 935-944. doi:10.1097/AOG.0b013e3181da8d38
- Nanda, K., Lopez, L. M., Grimes, D. A., Peloggia, A., & Nanda, G. (2012). Expectant care versus surgical treatment for miscarriage. *Cochrane Database Syst Rev*, 2012(3), Cd003518. doi:10.1002/14651858.CD003518.pub3
- Park, H. S., & Cho, H. S. (2020). Management of massive hemorrhage in pregnant women with placenta previa. *Anesth Pain Med (Seoul)*, 15(4), 409-416. doi:10.17085/apm.20076
- Pepin, M., Schwarze, U., Superti-Furga, A., & Byers, P. H. (2000). Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med*, 342(10), 673-680. doi:10.1056/nejm200003093421001
- Rodgers, S. K., Chang, C., DeBardleben, J. T., & Horrow, M. M. (2015). Normal and Abnormal US Findings in Early First-Trimester Pregnancy: Review of the Society of Radiologists in Ultrasound 2012 Consensus Panel Recommendations. *Radiographics*, 35(7), 2135-2148. doi:10.1148/rg.2015150092
- Say, L., Chou, D., Gemmill, A., Tunçalp, Ö., Moller, A. B., Daniels, J., . . . Alkema, L. (2014). Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*, 2(6), e323-333. doi:10.1016/s2214-109x(14)70227-x
- Sperling, J. D., Dahlke, J. D., Sutton, D., Gonzalez, J. M., & Chauhan, S. P. (2018). Prevention of RhD Alloimmunization: A Comparison of Four National Guidelines. *Am J Perinatol*, 35(2), 110-119. doi:10.1055/s-0037-1606609
- Tannirandorn, Y., Sangsawang, S., Manotaya, S., Uerpairojkit, B., Samritpradit, P., & Charoenvithya, D. (2003). Fetal loss in threatened abortion after embryonic/fetal heart activity. *Int J Gynaecol Obstet*, 81(3), 263-266. doi:10.1016/s0020-7292(03)00076-6
- Tikkanen, M. (2011). Placental abruption: epidemiology, risk factors and consequences. *Acta Obstet Gynecol Scand*, 90(2), 140-149. doi:10.1111/j.1600-0412.2010.01030.x
- Timor-Tritsch, I. E., Horwitz, G., D'Antonio, F., Monteagudo, A., Bornstein, E., Chervenak, J., . . . Cali, G. (2021). Recurrent Cesarean scar pregnancy: case series and literature review. *Ultrasound Obstet Gynecol*, 58(1), 121-126. doi:10.1002/uog.23577
- Tongsong, T., Srisomboon, J., Wanapirak, C., Sirichotiyakul, S., Pongsatha, S., & Polsrisuthikul, T. (1995). Pregnancy outcome of threatened abortion with

demonstrable fetal cardiac activity: a cohort study. *J Obstet Gynaecol (Tokyo 1995)*, 21(4), 331-335. doi:10.1111/j.1447-0756.1995.tb01019.x

CHAPTER 2

IMAGING METHODS IN OBSTETRIC BLEEDING

Dr. Yusuf DAL¹

¹ Mersin University Medical School, Department Of Obstetric And Gynecology
dryusufdal@gmail.com ORCID ID: 0000-0001-7162-4644

INTRODUCTION

Obstetric hemorrhages maintain importance as one of the prominent causes of maternal morbidity and mortality (Van de Velde et al., 2015). Advances in imaging methods provide advantages in terms of rapid evaluation and diagnosis. However, the main pathology cannot always be detected with the first evaluation and more than one imaging method can be applied. Ultrasonography (USG) is the most commonly used imaging method for fetal and placental imaging in obstetrics practice. Diagnostic sensitivity of USG in detecting existing bleeding varies depending on the cause of bleeding and its sensitivity may be low. Magnetic resonance imaging (MRI) can be used in cases where no results can be obtained from USG during pregnancy (such as fetal anomaly, antepartum or postpartum hemorrhage, adnexal mass evaluation). With the rapid imaging technique, it is possible to obtain an artifact-free fetal MRI examination without being affected by fetal movement and maternal respiration. MRI has the advantage of multiplanar imaging, wide field of view, good soft tissue contrast, and high sensitivity in detecting blood and blood products (Masselli et al., 2011). The main advantage of MRI is its ability to image deep soft tissues without the operator and without using ionizing radiation. In the study of Masselli et al., 42 patients with painless vaginal bleeding were evaluated with USG and MRI. The diagnostic accuracy of MRI was found to be significantly higher than that of USG. MRI can provide new and additional data when accurate assessment of pregnancy bleeding or USG is inconclusive. Contrast-enhanced computed tomography (CT) is also used in the evaluation and management of obstetric hemorrhages. Using extravasation of intravenous contrast agent, it can accurately show the anatomical localization of bleeding.

IMAGING METHODS IN THE FIRST TRIMESTER BLEEDING

Vaginal bleeding is the most common reason for admission to the hospital in the first trimester. Abnormal vaginal bleeding on part of sexually active women and in particular of women who are not on birth control, need to be considered as pregnancy-related until proven otherwise (Snell, 2009). The incidence of bleeding in the first trimester is approximately 20% (Hendriks et al., 2019). Bleeding may be a normal sign of implantation, a precursor to the onset of spontaneous abortion, or a sign of a pathological

condition such as an ectopic pregnancy or gestational trophoblastic disease. The main causes of first trimester bleeding are; implantation bleeding, early pregnancy loss, threat of miscarriage, and ectopic pregnancies. USG is the most commonly used imaging method in early pregnancy bleeding (Knez et al., 2014). Clinical evaluation is not always easy and sonography is required to determine the usual location and viability of a normal fetus and to exclude other causes of bleeding (Dighe et al., 2008).

Miscarriages

Abortion imminens is seen in 20-25% of all pregnancies (Zhou et al., 2019). Bleeding observed in the presence of an intrauterine pregnancy with sonographically detectable fetal cardiac activity while the cervix is closed is called abortus imminens. He or she may use sonography to determine the location of the pregnancy and the viability of the fetus. Detailed evaluation can be made with transvaginal ultrasonography. There is an intrauterine gestational sac with sonographically detectable fetal cardiac activity.

Abortion is defined as spontaneous or induced termination of pregnancy before fetal viability occurs (Cunnigham et al., 2013). Correlation of USG and serum Beta HCG levels usually provides adequate diagnosis in the diagnosis of low and additional imaging methods are not needed. Miscarriage may manifest itself as missed abortion, incomplete abortion or complete abortion. In missed abortion, the embryo or fetus may be small for the gestational age sonographically and fetal cardiac activity cannot be detected. In incomplete abortion, there are incompletely excreted pregnancy products in the endometrial cavity. Endometrial blood, irregular endometrial cavity and placental tissue can be detected sonographically. In complete abortion, the fetus and placental attachments are completely thrown out of the uterine cavity. On sonography, the endometrial cavity appears empty and normal.

Gestational Sac

The size of the gestational sac (GS) is also related to the health of the developing fetus. If the GS is small for gestational age, it carries a poor prognosis and serial sonographic examination should be performed to assess growth rate. A GS with a growth rate of <1 mm/day usually has a poor prognosis (Dighe et al., 2008). GS can be shown sonographically at the 4th and 5th gestational weeks. If the GS is larger than 17 mm and no embryo is

observed in transvaginal USG, this is not a healthy pregnancy. A decidual reaction smaller than 2 mm, low placement, no double decidual sac appearance, decreased echogenicity of the choriodecidual reaction, and a small sac size are findings related to an abnormal sac (Dighe et al., 2008). Yolk sac is seen at 5 weeks of gestation, when the mean GS is 10 mm. Yolk sac increases in size in the first 6-10 weeks of pregnancy and then gradually gets smaller (Harris et al., 1988). When the GS is 13 mm and above, if the yolk sac is not observed in the transvaginal USG, this is not a healthy pregnancy. To be able to monitor fetal cardiac activity in a patient experiencing vaginal bleeding does not ensure prospective fetal viability, however its presence significantly reduces the risk of future pregnancy loss. Embryonic loss can be diagnosed in the absence of cardiac activity of an embryo with a CRL measured as 5 mm (Dighe et al., 2008).

Subchorionic Bleeding

Subchorionic bleeding is defined as bleeding that results in separation of the chorion from the endometrial layer. The defined separation may extend up to the edge of the placenta. Subchorionic hemorrhages generally occur in the later stage of the first trimester and the prognosis is generally accurate provided that fetal heartbeat is heard and the bleeding is not excessive (Dighe et al., 2008). Subchorionic hemorrhage or hematoma is associated with an increased risk of pregnancy loss, especially when it accounts for 25 percent or more of the GS volume (Pearstone et al., 1993). According to monitoring with sonography, subchorionic hemorrhage is either hypoechoic or hyperechoic, depending on the time of formation of blood products during scanning (Dighe et al., 2008). After the hemorrhage, the sonography image is hyperechoic or isoechoic in the first week, hypoechoic in the second week, and anechoic fluid collection after the second week. It has been reported that bleeding in the uterine fundus has a poor prognosis compared to that in the lower uterine segment (Kurjak et al., 1996).

Ectopic Pregnancy

It is defined as the implantation of the fertilized ovum outside the uterine cavity and the incidence is monitored to be approximately 2% (Moonen-Delarue et al., 1996). It is commonly seen in the 35-44 age range. Ectopic pregnancies constitute 9% of pregnancy-related maternal deaths.

Although ectopic pregnancy is less common, it is the most serious condition of first trimester bleeding.

Transvaginal USG is performed on a woman with suspected ectopic pregnancy. In the case of intrauterine pregnancy, GS is usually detected at the 5th gestational week, the yolk sac at the 5th and 6th gestational weeks, and the fetal tissue with fetal cardiac activity at the 5th-6th gestational week. In transabdominal USG, these findings are detected a little later. GS (double decidual ring appearance), located eccentrically in the endometrial cavity and seen as a fluid cavity surrounded by a thick echogenic ring, is the earliest ultrasonographic finding of intrauterine pregnancies. In ectopic pregnancies, there is usually a single-layered decidual ring and the GS is centrally located (pseudosac) (Hill et al., 1990). The presence of yolk sac in the intrauterine GS is superior to the double decidual ring in excluding ectopic pregnancy. Fetal cardiac activity in intrauterine GS is the most valuable USG finding in excluding ectopic pregnancy.

Intrauterine centrally located pseudosac appearance, fluid collection in the douglas, and mass in the adnexal region are important USG findings in terms of ectopic pregnancy. In the differential diagnosis, corpus luteum, endometrioma, hydrotube, ovarian cyst and masses or pedunculated subserous myoma should be considered.

Intrauterine pregnancies can be detected by abdominal USG when serum Beta HCG is 6500 mIU/ml and by transvaginal USG when serum Beta HCG is 1500-2000 mIU/ml. If an intrauterine pregnancy cannot be detected at these levels, ectopic pregnancies should be suspected and additional diagnostic methods should be applied.

Ectopic pregnancy bleeding is the most serious condition that increases morbidity and mortality in the first trimester. In cases of hemodynamic instability, the patient should be evaluated for hemoperitoneum. Sonographically, there is anechoic or hypoechoic fluid in hemoperitoneum. The blood first accumulates in the douglas cavity and, as its amount increases, surrounds the uterus. When the amount of blood in the abdomen increases, it fills the Morison cavity next to the liver. In this case, the amount of accumulated blood is approximately 400-700 ml (Rose, 2004). The presence of fluid in the abdomen together with the adnexal mass is important for the diagnosis of ectopic pregnancy.

USG is the first-line imaging method of choice in the diagnosis of ectopic pregnancy. In some cases, USG cannot distinguish bleeding from other fluids. In these cases, MRI can be used in the diagnosis of bleeding due to ectopic pregnancy. MRI is increasingly used as an additional imaging modality in cases of unusually located ectopic pregnancy. Other advantages of MRI include the absence of ionizing radiation, multi-plane imaging, and excellent soft tissue contrast (Masselli et al., 2011). The extraordinary features of MRI are its potential to identify fresh bleeding, to accurately localize the abnormal implantation site with excellent spatial resolution, and to identify associated congenital uterine anomalies or Müllerian abnormalities (Srisajjakul et al., 2017). However, the role of MRI may be restricted for hemodynamically unstable patients who are diagnosed as cases of ruptured ectopic pregnancy in particular. The MRI scan time is extremely long and these cases often require immediate surgical treatment.

CT is not the imaging modality of choice for diagnosing ectopic pregnancy, but it can sometimes be used when other pathologies are suspected or in case of trauma. CT shows the hemoperitoneum surrounding the uterus with or without contrast extravasation, but it has low soft tissue resolution to identify the gestational sac in ectopic pregnancy (Srisajjakul et al., 2017).

Gestational Trophoblastic Diseases

Gestational trophoblastic diseases are comprised of hydatiform mole, invasive mole, and choriocarcinoma. Bleeding during the first trimester is one of the most common clinical conditions in terms of this group of diseases. Rapid uterine enlargement, excessive uterine size for gestational age, hyperemesis gravidarum, or preeclampsia are within the scope of other clinical signs and symptoms (Elsayes et al., 2009). The common feature of this group of diseases is excessive production of Beta HCG and abnormal proliferation of trophoblastic tissue.

Mol hydatidiform is a potentially malignant complication that occurs in one of every 1,000-2,000 pregnancies. There are 2 types: complete and partial molar pregnancy.

Gestational trophoblastic disease is encountered as the most common complete hydatidiform mole. The genetic structure is diploid and of paternal origin. It occurs as a result of duplication or dispersion. Abnormal vaginal bleeding is the most common symptom. Vesicular appearance (snowfall

scene) on sonography is typical in complete mole (AboEllail et al., 2016). There is a heterogeneous echogenic endometrial mass with no visible embryos. Merely more than half of first trimester molar pregnancies demonstrate a conventional appearance (Benson et al., 2020). Doppler examination in complete hydatidiform mole reveals increased uterine vascularity. High velocity measurements with low resistance index in the main and arcuate uterine arteries are intrinsic to molar pregnancy compared to low velocity measurements of normal pregnancy (Kurjak et al., 1994). Theca lutein cysts resulting from overstimulation of the ovaries due to excessive production of Beta HCG by abnormal trophoblastic tissue are found in 50% of complete hydatidiform mole cases. Theca lutein cysts typically appear as multiple, large, bilateral, multipartite ovarian cysts, some of which may be hemorrhagic (Dighe et al., 2008).

In partial hydatidiform mole, the genetic structure is triploid and is of both maternal and paternal origin. Most of the cases present with a clinic similar to missed abortion or incomplete abortion. There are placental focal cystic areas on sonography. An increase in the transverse diameter of the GS is diagnostic. A GS containing embryo or fetal tissue is followed. The placenta is expanded and there are hydropic villi with multicystic appearance available in certain parts of the placenta, although the amount is less than encountered in complete mole hydatidiform (Dighe et al., 2008). On sonographic view, there is an enlarged placenta with multiple cystic foci. Multiple congenital anomalies and growth retardation in the fetus is observed in the fetus (Dighe et al., 2008).

MRI is not used in the routine evaluation of mole hydatiformes. With MRI, the myometrium is clearly shown as a separate structure, determining whether the molar tissue extends into the myometrium or outside the uterus. This ensures an accurate assessment of invasion (Powell et al., 1986).

Invasive mole is a picture in which partial or complete mole invades the myometrium (Lurain et al., 1990). It is a disease in which chorionic villi are found in the myometrium or myometrial vessels or in distant places. Persistent gestational diseases following non-molar pregnancies show the histological features of choriocarcinoma (Shapter et al., 2001). Invasive moles and choriocarcinoma are often indistinguishable during the process of imaging (Elsayes et al., 2009). On sonography, there is insufficient uterine involution or asymmetric growth in the uterus. Sonography may show the presence of a uterine mass resembling a complete mole hydatidiform and

sometimes myometrial or adnexal invasion. CT is useful for detecting distant involvements (metastases to the lung (75%) and pelvis (50%). MRI can better show myometrial and vaginal invasions.

IMAGING METHODS IN ANTEPARTUM BLEEDING

Antepartum hemorrhages are defined as bleeding in the genital tract after 28 weeks of gestation and prior to delivery (Van den Elzen et al., 1995). 95% of antepartum hemorrhages are due to obstetric reasons, the most common conditions are placental abruption, placenta previa, vasa previa, uterine rupture. Non-obstetric causes may include cervicitis, cervical polyps, vaginal lacerations, vaginitis, cervical cancer or dysplasia, and coagulation disorders. It is asserted as one of the leading causes of maternal and fetal morbidity and mortality.

Placental Hematoma

Placental hematomas may arise at the maternal or fetal interface of the placenta or in the central part of the placenta (Redline, 2008). They are classified as preplacental, subchorionic, retroplacental, or placental bleeding (Ozcan et al., 2008). In USG, placental hematomas have different appearances according to the time of bleeding. They appear as hyperechoic or isoechoic in the first stages of bleeding, then as heterogeneous and anechoic in the chronic period (Fadl et al., 2017). Absence of vascularity on Doppler examination enables hematomas to be distinguished from other placental masses.

USG is the first preferred imaging method in the detection of placental hemorrhages. However, other imaging methods can be preferred in case of clinical suspicion. The sensitivity of MRI in detecting blood products is quite high. T1 gradient echo and diffusion-weighted imaging are the most useful sequences (Çakır, 2020).

Placental Abruption

It is the premature separation of the placenta from the implantation site before the delivery of the fetus. It is the most common cause of third trimester bleeding. The overall incidence of ablatio placenta is approximately 1 in 100 births (Prata et al., 2010). After the 20th week of pregnancy, it can be diagnosed. Defective maternal vessels in the decidua basalis rupture, causing separation. Damaged vessels cause decidual

hematoma formation, causing bleeding. Decidual hematoma: causes placental separation, damage to placental tissue, loss of maternal fetal surface area required for nutrient and gas exchange.

Early diagnosis of abruption placenta can be made rarely by USG. Only 2% of placental abruptions can be visualized by USG. More than 300 ml of retroplacental hemorrhage is required for it to be visualized sonographically. Bleeding in the acute phase is hyperechoic or isoechoic, after resolution of the hematoma, it becomes hypoechoic within 1 week and anechoic within 2 weeks. Three localizations of ablation can be identified by USG: subchorionic, retroplacental, and placental.

The amount and localization of abruption placenta detected on sonography are of clinical importance. Retroplacental hematomas have a worse prognosis in terms of fetal complications than subchorionic hematomas. Large retroplacental hemorrhage is associated with higher fetal mortality than the same amount of subchorionic hemorrhage (Spong et al., 2011).

MRI is sometimes used for diagnosis when placental abruption cannot be fully detected by ultrasonography. In a study including 39 pregnant women who gave birth 10 days after MRI, abruption placenta was detected during delivery in 19 pregnant women. Ablation was detected in 10 (52%) of 19 patients with USG and in all 19 patients (100%) with MRI. It was concluded that MR imaging can accurately show placental abruption, and if the diagnosis of abruption will change treatment, it should be considered after negative USG findings in the presence of late pregnancy bleeding (Masselli et al., 2011).

Placenta Previa

Partial or complete implantation of the placenta in the lower uterine segment. It occurs in 0.5% of pregnancies. It accompanies placenta accreta at a rate of 10%. Placenta previa can be named as total placenta previa, partial placenta previa, marginal placenta previa (at the edge of the internal cervical os) and inferior placenta (located in the lower uterine segment). It is characterized by painless vaginal bleeding and the bleeding is of maternal origin.

Transabdominal or transvaginal sonography is used to diagnose placenta previa. Transabdominal USG may be sufficient in the diagnosis of placenta previa, but in uncertain cases, transvaginal USG should be used.

Transvaginal USG can also be used as the first imaging method. Transvaginal USG is reliable and close to 100% diagnosis can be made with this method.

In some cases, MRI is used to diagnose placenta previa. If a clear result cannot be obtained with MRI ultrasound, it can be used in posterior placenta previa or to identify invasion (Moodley et al., 2004).

Vasa Previa

Vasa previa is observed as vementous insertion of fetal vessels over the cervical os (Erfani et al., 2019). Under these circumstances, abnormal fetal vessels are available within the amniotic membranes that cross the cervical internal os (Elsayes et al., 2009). Fetal vessels are not protected by Wharton gel and are prone to rupture. Bleeding is of fetal origin. Its incidence is 1 in 2500 births.

The diagnosis of vasa previa can be made with Doppler USG in the antenatal period. Diagnosis can be made by visualization of umbilical vessels on the cervical os with color Doppler USG (Facilitators, 2019). Transabdominal or transvaginal USG can be used.

Placenta Implantation Disorders

These are the conditions in which trophoblastic tissues invade the myometrium at different depths. There is an increase in the frequency of these invasion anomalies due to the increased cesarean section numbers. Its incidence is 1:210. There is a risk of peripartum bleeding; It is asserted as one of the leading causes of peripartum hysterectomies. They are named as placenta accreta, placenta increta and placenta percreta according to the degree of invasion;

- Placenta accreta (80%): Invasion up to the superficial myometrium.
- Placenta increta (15%): Invasion is in the myometrium.
- Placenta percreta (5%): Invasion reaches to the serosa.

USG is used for primary screening in the diagnosis of placental invasion anomaly. Decreased myometrial thickness, loss of retroplacental space, and intraplacental lacunae are sonographic findings (Kumar et al., 2017).

In placenta accreta, the border between the myometrium and the bladder can be demonstrated by USG. In placenta percreta, herniation of the placenta within the bladder is observed (Jauniaux et al., 2012).

Presence of intraplacental lacunae may be a sign of placenta accreta. These lacunae contain slow-moving maternal blood on sonography and are defined as intraplacental lakes (Hornemann et al., 2011). These lacunae may be a completely normal variant and may not be of any clinical significance.

Loss of the myometrial interface with enlargement of the uterine vascularity is the most common sonographic finding (Jauniaux et al., 1996). The increase in the use of Doppler USG has increased the diagnosis rates of invasion anomalies.

MRI is an imaging method that can be used to evaluate the invasion anomaly. MRI can be used if clear information cannot be obtained with USG or in posterior previa. Swelling of uterus, heterogeneous signal intensity in the placenta, and a dark intraplacental band are observed on T2 images (Petrov et al., 2018). Abnormal placentation areas can be identified with MRI and myometrial invasion can be evaluated. In a meta-analysis including 1010 pregnant women, the sensitivity of MRI in the antenatal diagnosis of invasion anomaly was 94.4% and the specificity was 84% (D'antonio et al., 2014). On T2 imaging, focal disruption of the myometrium and presence of dark intraplacental bands showed the best sensitivity, while bladder tenting and uterine ridge showed the best specificity (D'antonio et al., 2014).

Studies comparing MRI and USG did not find a significant difference in sensitivity and specificity between the two imaging methods for the diagnosis of placental invasion anomalies.

IMAGING METHODS IN POSTPARTUM BLEEDING

Postpartum hemorrhage is defined as blood loss of more than 500 ml after vaginal or cesarean delivery (Jin et al., 2019). Postpartum bleeding is an obstetric emergency. It is asserted as one of the leading causes of maternal and fetal morbidity and mortality. Average blood loss is 500 ml in vaginal deliveries, 1000 ml in cesarean deliveries, and 1500 ml in cesarean hysterectomies (Stafford et al., 2008).

Postpartum hemorrhages are classified as early or late. Bleeding before the first 24 hours is early postpartum bleeding, bleeding after 24 hours before 12 weeks is late postpartum bleeding (Table 1).

Postpartum bleeding is an emergency and the primary imaging method in the evaluation of these patients is USG. USG is safe, practical, inexpensive and allows bedside patient evaluation. CT or MRI is not the primary diagnostic method, but they can show the localization and amount of hematomas or puerperal genital hematomas that cannot be detected by USG.

Primary (Early)	Secondary (Late)
Uterine atony Lower genital tract lacerations Upper genital tract lacerations Lower urinary tract injuries Retention products of conception Placental invasion anomalies Uterine rupture Uterine inversion Coagulopathy	Infections Retention products of conception Subinvolution of the placenta Coagulopathy

Uterine Atony

It is the most common cause of early postpartum bleeding. It is responsible for 80% of postpartum hemorrhages and is seen in 1 in 20 births (Dildy et al., 2002).

The diagnosis of uterine atony is diagnosed clinically. After excluding other primary postpartum bleeding causes, bleeding due to myometrial contraction failure is considered as uterine atony. USG and other imaging methods can be helpful in excluding other causes of postpartum hemorrhage, USG has no direct involvement in the diagnosis.

CT is not deemed as a first-line diagnostic procedure for the evaluation of postpartum hemorrhage caused by uterine atony (Lee et al., 2010). In case the clinical diagnosis of uterine atony is not fully established, CT can help to detect the presence of arterial or venous leakage due to ineffective myometrial contraction in the uterine cavity, thus CT imaging may directly demonstrate the presence of uterine atony (Lee et al., 2010). Actively characterised bleeding specified and identified on contrast-enhanced CT images may be interpreted as intravenous contrast agent extravasation. Significant arterial bleeding can be detected on contrast-

enhanced CT images during the arterial phase, whereas minor arterial or venous leakage can often be detected in the delayed phases (Lee et al., 2010). The presence of focal or diffused intravenous contrast extravasation and/or a hematoma in the enlarged postpartum uterine cavity on CT images may assist for the diagnosis of uterine atony in case the clinical diagnosis of uterine atony is unclear (Novelline et al., 1999).

Puerperal Hematoma

Puerperal genital hematomas are rare, but they can be a cause of serious maternal morbidity and mortality (Lee et al., 2010). It is rather challenging to diagnose because symptoms can be nonspecific and bleeding is often concealed (Lee et al., 2010). They may result from episiotomy trauma or birth canal trauma (Ridgway, 1995). It is accompanied by severe pain and greater blood loss than anticipated. Puerperal hematomas are classified as vulvar, vulvovaginal, paravaginal and retroperitoneal (Bhansakarya et al., 2019).

USG is administered to detect pelvic extraperitoneal hematomas in patients who are diagnosed with suspicion of puerperal hematoma. CT and MRI can show the localization and exact size of the puerperal genital hematoma. Contrast-enhanced CT can detect the presence of a hematoma in the perivaginal region and/or the broad ligament. Puerperal hematoma can often extend into the paravesical, pararectal, or presacral space (Lee et al., 2010).

Uterine Rupture

It is one of the most rare postpartum complications. It is the non-surgical full-thickness separation of all uterine layers. It can occur spontaneously or due to traumatic causes. The most common cause is separation of the previous cesarean section scar (Siddiqui et al., 2002). Its incidence is 1 in 2000 births.

There are both maternal and fetal clinical signs. Uterine tenderness and vaginal bleeding can be seen in ruptures that develop before labor. In cases of rupture during labor, suprapubic pain, sudden disappearance of labor pains, fetal bradycardia or decelerations, regression of the anterior part of the birth canal and vaginal bleeding are observed.

Although ultrasound can show a hematoma adjacent to the uterus, it is not as sensitive to detachment of the uterine wall layers and may fail to diagnose uterine rupture (Hasbargen et al., 2002).

Early detection of uterine rupture can be difficult because in general there are no distinguishable clinical features prior to hypovolemic shock (Lee et al., 2010). In case nonspecific symptoms or signs such as unexplained postpartum pelvic pain or fullness and shock are present, CT can be a useful imaging modality for the detection and diagnosis of postpartum uterine rupture. CT can be administered to detect focal disruption of the uterine wall, a hematoma in the broad ligament, and hemoperitoneum. Focal disruption of the uterine wall appears as a hypoattenuating lesion within the myometrium with intense contrast. Hypoattenuating fluid with or without air bubbles in the disrupted area often extends into the endometrial cavity and the extrauterine region (Lee et al., 2010).

Sagittal MRI is the best imaging modality for demonstrating uterine wall defects. In addition, T2-weighted MRI can distinguish between uterine rupture and separation by showing detached uterine wall layers (Maldjian et al., 1998).

Retained products of conception

Retention products of conception (RPOC) are the most common cause of late postpartum hemorrhage after vaginal or cesarean delivery (Iraha et al., 2018). With respect to the patients diagnosed with placenta accreta, the incidence of RPOC increases (Lee et al., 2010). The most common symptoms are pelvic pain and vaginal bleeding. Postpartum prolonged bleeding may be associated with RPOCs.

Transabdominal and transvaginal pelvic USG is the first choice imaging method. It should be ensured that the images are obtained using gray scale and colored Doppler modes, attention is to paid to the presence of any focal mass, to the degree of vascularity of solid or echogenic areas in the endometrial cavity, and endometrial thickness measurement (Kamaya et al., 2009). Color Doppler USG has high velocity, low resistance flow (Durfee et al., 2005). Enlargement of the endometrial cavity with an echogenic vascularized mass is helpful in diagnosing RPOC (Kamaya et al., 2009).

Clinical and USG findings are usually sufficient to diagnose RPOC (Lee et al., 2010). MRI can be used in cases where USG is insufficient and further imaging is required for diagnosis. On MRI, RPOC is generally seen

as an intracavitary soft tissue mass with varying degrees of contrasting tissue and varying degrees of myometrial thinning and obliteration of the junctional region (Lee et al., 2010). Although MRI findings of RPOC demonstrate certain variations in signal intensity and contrast enhancement, RPOC usually demonstrates areas with substantially high density on T2-weighted images (Gui et al., 2016). It suggests that the normally vascularized placenta may show very high density on T2-weighted images, as seen in the prenatal placenta (Tanaka et al., 2004).

Subinvolution of the Placenta

Subinvolution of the placental region is encountered as a rare cause of late postpartum hemorrhage (Khong et al., 1993). The clinical manifestation of subinvolution ranges from mildly delayed vaginal bleeding to massive and sudden uterine bleeding, and is most common during the second postpartum week, but may occur 6 weeks after delivery (Costa et al., 2005).

Sonographic evaluation may show an enlarged uterus with enlarged and tortuous vessels (Kamaya et al., 2009). Intrauterine blood clots that may resemble RPOC may be present. In RPOC, echogenic material has vascularity, but vascularity is not observed in these blood clots.

Puerperal Infections

Endometritis is a common cause of postpartum fever and occurs in approximately 2-5% of vaginal deliveries and 5-30% of cesarean deliveries (Tharpe, 2008). Endometritis is an infection of the endometrium of the uterus. Endometritis is usually a diagnosis of exclusion.

USG findings of endometritis are usually nonspecific and may be similar to USG findings in RPOC (Kamaya et al., 2009), including increased endometrial wall thickness and increased myometrial vascularity and echogenicity (Mulic-Lutvica et al., 2007).

REFERENCES

- AboEllail, M. A. M., Ishimura, M., Sajapala, S., Yamamoto, K., Tanaka, T., Nitta, E., ... & Hata, T. (2016). Three-Dimensional Color/Power Doppler Sonography and HD live Silhouette Mode for Diagnosis of Molar Pregnancy. *Journal of Ultrasound in Medicine*, 35(9), 2049-2052.
- Abortion. Cunningham F, & Leveno K.J., & Bloom S.L., & Spong C.Y., & Dashe J.S., & Hoffman B.L., & Casey B.M., & Sheffield J.S.(Eds.), (2013). *Williams Obstetrics*, Twenty-Fourth Edition. McGraw Hill.
- Benson, C. B., Genest, D. R., Bernstein, M. R., Soto-Wright, V., Goldstein, D. P., & Berkowitz, R. S. (2000). Sonographic appearance of first trimester complete hydatidiform moles. *Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, 16(2), 188-191.
- Bhansakarya, R., & Subedi, S. (2019). Broad Ligament Hematoma Following Vaginal Delivery—A Rare Entity. *Journal of Nobel Medical College*, 8(1), 63-65.
- Costa, M. A., Calejo, L. I., Martinez-de-oliveira, J., & Laurini, R. (2005). Late-onset postpartum hemorrhage from placental bed subinvolution: a case report. *The Journal of reproductive medicine*, 50(7), 557–560.
- Çakır IM. (2020). *Obstetrik Kanamalarda Görüntüleme Yöntemleri:Obstetrik Kanamalar*. Akademisyen Kitabevi. Ankara, 37.
- D'antonio, F., Iacovella, C., Palacios-Jaraquemada, J., Bruno, C. H., Manzoli, L., & Bhide, A. (2014). Prenatal identification of invasive placentation using magnetic resonance imaging: systematic review and meta-analysis. *Ultrasound in Obstetrics & Gynecology*, 44(1), 8-16.
- Dighe, M., Cuevas, C., Moshiri, M., Dubinsky, T., & Dogra, V. S. (2008). Sonography in first trimester bleeding. *Journal of Clinical ultrasound*, 36(6), 352-366.

- Dildy Iii, G. A. (2002). Postpartum hemorrhage: new management options. *Clinical obstetrics and gynecology*, 45(2), 330-344.
- Durfee, S. M., Frates, M. C., Luong, A., & Benson, C. B. (2005). The sonographic and color Doppler features of retained products of conception. *Journal of ultrasound in medicine*, 24(9), 1181-1186.
- Elsayes, K. M., Trout, A. T., Friedkin, A. M., Liu, P. S., Bude, R. O., Platt, J. F., & Menias, C. O. (2009). Imaging of the placenta: a multimodality pictorial review. *Radiographics*, 29(5), 1371-1391.
- Erfani, H., Haeri, S., Shaanker, S. A., Saad, A. F., Ruano, R., Dunn, T. N., ... & Shamshirsaz, A. A. (2019). Vasa previa: a multicenter retrospective cohort study. *American journal of obstetrics and gynecology*, 221(6), 644-e1.
- Facilitators, D. (2019). Vasa Praevia. *Obstetric Decision-Making Simulation*, 202.
- Fadl, S., Moshiri, M., Fligner, C. L., Katz, D. S., & Dighe, M. (2017). Placental imaging: normal appearance with review of pathologic findings. *Radiographics*, 37(3), 979-998.
- Gui, B., Danza, F. M., Valentini, A. L., Laino, M. E., Caruso, A., Carducci, B., Rodolfo, E., Devicienti, E., & Bonomo, L. (2016). Multidetector CT appearance of the pelvis after cesarean delivery: normal and abnormal acute findings. *Diagnostic and interventional radiology (Ankara, Turkey)*, 22(6), 534-541.
- Harris, R. D., Vincent, L. M., & Askin, F. B. (1988). Yolk sac calcification: a sonographic finding associated with intrauterine embryonic demise in the first trimester. *Radiology*, 166(1), 109-110.
- Hasbargen, U., Summerer-Moustaki, M., Hillemanns, P., Scheidler, J., Kimmig, R., & Hepp, H. (2002). Uterine dehiscence in a nullipara, diagnosed by MRI, following use of unipolar electrocautery during laparoscopic myomectomy: case report. *Human Reproduction*, 17(8), 2180-2182.
- Hendriks, E., MacNaughton, H., & MacKenzie, M. C. (2019). First trimester bleeding: evaluation and management. *American family physician*, 99(3), 166-174.

- Hill, L. M., Kislak, S. A. N. D. R. A., & Martin, J. G. (1990). Transvaginal sonographic detection of the pseudogestational sac associated with ectopic pregnancy. *Obstetrics and gynecology*, 75(6), 986-988.
- Hornemann, A., Bohlmann, M. K., Diedrich, K., Kavallaris, A., Kehl, S., Kelling, K., & Hoellen, F. (2011). Spontaneous uterine rupture at the 21st week of gestation caused by placenta percreta. *Archives of gynecology and obstetrics*, 284(4), 875-878.
- Iraha, Y., Okada, M., Toguchi, M., Azama, K., Mekaru, K., Kinjo, T., ... & Murayama, S. (2018). Multimodality imaging in secondary postpartum or postabortion hemorrhage: retained products of conception and related conditions. *Japanese Journal of Radiology*, 36(1), 12-22.
- Jauniaux, E., Toplis, P. J., & Nicolaides, K. H. (1996). Sonographic diagnosis of a non-previa placenta accreta. *Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, 7(1), 58-60.
- Jauniaux, E., & Jurkovic, D. (2012). Placenta accreta: pathogenesis of a 20th century iatrogenic uterine disease. *Placenta*, 33(4), 244-251.
- Jin, X. H., Li, D., & Li, X. (2019). Carbetocin vs oxytocin for prevention of postpartum hemorrhage after vaginal delivery: A meta-analysis. *Medicine*, 98(47).
- Kamaya, A., Ro, K., Benedetti, N. J., Chang, P. L., & Dessler, T. S. (2009). Imaging and diagnosis of postpartum complications: sonography and other imaging modalities. *Ultrasound quarterly*, 25(3), 151-162.
- Khong, T. Y., & Khong, T. K. (1993). Delayed postpartum hemorrhage: a morphologic study of causes and their relation to other pregnancy disorders. *Obstetrics and gynecology*, 82(1), 17-22.
- Knez, J., Day, A., & Jurkovic, D. (2014). Ultrasound imaging in the management of bleeding and pain in early pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 28(5), 621-636.

- Kumar, I., Verma, A., Ojha, R., Shukla, R. C., Jain, M., & Srivastava, A. (2017). Invasive placental disorders: a prospective US and MRI comparative analysis. *Acta Radiologica*, 58(1), 121-128.
- Kurjak, A., Zalud, I., Predanic, M., & Kupesic, S. (1994). Transvaginal color and pulsed Doppler study of uterine blood flow in the first and early second trimesters of pregnancy: normal versus abnormal. *Journal of ultrasound in medicine*, 13(1), 43-47.
- Kurjak, A., Schulman, H., Zudenigo, D., Kupesic, S., Kos, M., & Goldenberg, M. (1996). Subchorionic hematomas in early pregnancy: clinical outcome and blood flow patterns. *Journal of Maternal-Fetal Medicine*, 5(1), 41-44.
- Lee, N. K., Kim, S., Lee, J. W., Sol, Y. L., Kim, C. W., Sung, K. H., ... & Suh, D. S. (2010). Postpartum hemorrhage: clinical and radiologic aspects. *European journal of radiology*, 74(1), 50-59.
- Lurain, J. R. (1990). Gestational trophoblastic tumors. In *Seminars in surgical oncology* (Vol. 6, No. 6, pp. 347-353). New York: John Wiley & Sons, Inc..
- Maldjian, C., Milestone, B., Schnell, M., & Smith, R. (1998). MR appearance of uterine dehiscence in the post-cesarean section patient. *Journal of computer assisted tomography*, 22(5), 738-741.
- Masselli, G., Brunelli, R., Casciani, E., Poletini, E., Bertini, L., Laghi, F., ... & Gualdi, G. (2011). Acute abdominal and pelvic pain in pregnancy: MR imaging as a valuable adjunct to ultrasound?. *Abdominal imaging*, 36(5), 596-603.
- Masselli, G., Brunelli, R., Di Tola, M., Anceschi, M., & Gualdi, G. (2011). MR imaging in the evaluation of placental abruption: correlation with sonographic findings. *Radiology*, 259(1), 222-230.
- Masselli, G., Brunelli, R., Parasassi, T., Perrone, G., & Gualdi, G. (2011). Magnetic resonance imaging of clinically stable late pregnancy bleeding: beyond ultrasound. *European radiology*, 21(9), 1841-1849.
- Moodley, J., Ngambu, N. F., & Corr, P. (2004). Imaging techniques to identify morbidly adherent placenta praevia: a prospective study. *Journal of Obstetrics and Gynaecology*, 24(7), 742-744.

- Moonen-Delarue, M. W. G., & Haest, J. W. G. (1996). Ectopic pregnancy three times in line of which two advanced abdominal pregnancies. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 66(1), 87-88.
- Mulic-Lutvica, A., & Axelsson, O. (2007). Postpartum ultrasound in women with postpartum endometritis, after cesarean section and after manual evacuation of the placenta. *Acta obstetricia et gynecologica Scandinavica*, 86(2), 210–217.
- Novelline, R. A., Rhea, J. T., Rao, P. M., & Stuk, J. L. (1999). Helical CT in emergency radiology. *Radiology*, 213(2), 321-339.
- Ozcan, T., & Pressman, E. K. (2008). Imaging of the placenta. *Ultrasound Clinics*, 3(1), 13-22.
- Pearlstone, M. E. L. I. S. S. A., & Baxi, L. A. X. M. I. (1993). Subchorionic hematoma: a review. *Obstetrical and Gynecological survey*, 48, 65-65.
- Petrov, D. A., Karlberg, B., Singh, K., Hartman, M., & Mittal, P. K. (2018). Perioperative internal iliac artery balloon occlusion, in the setting of placenta accreta and its variants: the role of the interventional radiologist. *Current Problems in Diagnostic Radiology*, 47(6), 445-451.
- Powell, M. C., Buckley, J., Worthington, B. S., & Symonds, E. M. (1986). Magnetic resonance imaging and hydatidiform mole. *The British Journal of Radiology*, 59(702), 561-564.
- Prata, N., & Gerdts, C. (2010). Measurement of postpartum blood loss. *Bmj*, 340.
- Redline, R. W. (2008). Placental pathology: a systematic approach with clinical correlations. *Placenta*, 29, 86-91.
- Ridgway, L. E. (1995). Puerperal emergency: vaginal and vulvar hematomas. *Obstetrics and gynecology clinics of North America*, 22(2), 275-282.
- Rose, J. S. (2004). Ultrasound in abdominal trauma. *Emergency Medicine Clinics*, 22(3), 581-599.
- Shapter, A. P., & McLellan, R. (2001). Gestational trophoblastic disease. *Obstetrics and Gynecology Clinics*, 28(4), 805-817.

- Siddiqui, M. N., & Ranasinghe, J. S. (2002). Spontaneous rupture of uterus. *Journal of clinical anesthesia*, 14(5), 368-370.
- Snell, B. J. (2009). Assessment and management of bleeding in the first trimester of pregnancy. *Journal of midwifery & women's health*, 54(6), 483-491.
- Spong, C. Y., Mercer, B. M., D'Alton, M., Kilpatrick, S., Blackwell, S., & Saade, G. (2011). Timing of indicated late-preterm and early-term birth. *Obstetrics and gynecology*, 118(2 Pt 1), 323.
- Srisajjakul, S., Prapaisilp, P., & Bangchokdee, S. (2017). Magnetic resonance imaging in tubal and non-tubal ectopic pregnancy. *European journal of radiology*, 93, 76–89.
- Stafford, I., Dildy, G. A., Clark, S. L., & Belfort, M. A. (2008). Visually estimated and calculated blood loss in vaginal and cesarean delivery. *American journal of obstetrics and gynecology*, 199(5), 519-e1.
- Tanaka, Y. O., Shigemitsu, S., Ichikawa, Y., Sohda, S., Yoshikawa, H., & Itai, Y. (2004). Postpartum MR diagnosis of retained placenta accreta. *European radiology*, 14(6), 945-952.
- Tharpe N. (2008). Postpregnancy genital tract and wound infections. *Journal of midwifery & women's health*, 53(3), 236–246.
- Van de Velde, M., Diez, C., & Varon, A. J. (2015). Obstetric hemorrhage. *Current Opinion in Anesthesiology*, 28(2), 186-190.
- Van den Elzen, H. J., Cohen-Overbeek, T. E., Grobbee, D. E., Quartero, R. W. P., & Wladimiroff, J. W. (1995). Early uterine artery Doppler velocimetry and the outcome of pregnancy in women aged 35 years and older. *Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, 5(5), 328-333.
- Zhou, J., Huang, Z., Pan, X., Leung, W. T., Li, C., Chen, L., ... & Wang, L. (2019). New thoughts in exploring the pathogenesis, diagnosis, and treatment of threatened abortion. *BioScience Trends*, 13(3), 284-285.

CHAPTER 3

EVALUATION OF ANTEPARTUM BLEEDING

Dr. Mevlüt BUCAK¹

Dr. Fatih AKKUŞ²

¹ Etlik Zübeyde Hanım Gynecology Training and Research Hospital / Perinatology Department ORCID ID: 0000-0002-5035-8727 / mevlutbucak@gmail.com

² Necmettin Erbakan University, Meram Faculty of Medicine, Department of Obstetrics and Gynecology / Perinatology Department ORCID ID: 0000-0001-7037-9165 / fakkus1987@gmail.com

EVALUATION OF ANTEPARTUM BLEEDING

INTRODUCTION

Antepartum hemorrhage (APH) is bleeding that occurs after the 24th week of pregnancy and before delivery. APH occurs in 3-5% of pregnancies and is one of the leading causes of maternal death(Calleja-Agius et al., 2006). The main causes of bleeding are: Placenta previa and ablation placenta. Less common are uterine rupture and vasa previa. cervical, vaginal and uterine pathologies (polyp, infection, etc.) should be kept in mind.

EVALUATION

The first step in the evaluation is to check whether the patient's vital signs are stable. If vital signs are stable, intrauterine live pregnancy is confirmed by ultrasound. The placenta is evaluated. The external genitalia are examined, then the vagina and cervix are evaluated with a speculum. Antepartum evaluation distinguishes patients at high risk of bleeding. Such patients can be referred for delivery in appropriate centers. Determination of bleeding etiology is very important for maternal and fetal prognosis. Because bleeding can result from placenta previa or accreta, which results in serious morbidity and mortality, or it can be caused by a small polyp. With antepartum evaluation, patients with high risk can be referred for delivery in appropriate centers(Kuribayashi et al., 2021).

DIFFERENTIAL DIAGNOSIS

Placenta previa

Placenta previa is the extension of the placenta to the cervical os. The need for cesarean delivery, severe antepartum hemorrhage, preterm delivery and postpartum hemorrhage are at high risk. Since the vaginal examination of the patient with antepartum bleeding may cause severe bleeding, the placental location should be determined sonographically before the vaginal examination is performed. Placenta previa occurs 4 per 1000 births(Cresswell et al., 2013). A history of placenta previa, previous cesarean delivery and multiple gestations are major risk factors for placenta previa(Downes et al., 2015; Gurol-Urganci et al., 2011). Previous uterine surgical procedure, parity, maternal age, infertility treatment, pregnancy termination, maternal smoking, male fetus are other risk factors(King et al., 2020). The most common symptom of placenta previa is painless vaginal bleeding(Fan et al., 2017).

Bleeding is mainly maternal blood in the intervillous space, but fetal hemorrhage may occur if the fetal vascular structure in the terminal villi is impaired. The number of antepartum bleeding episodes and the need for blood transfusion are independent predictors of emergency cesarean delivery (Ruiter et al., 2016).

Transabdominal ultrasonography (TAUS) is the standard first sonographic approach in antepartum hemorrhage. While obtaining sagittal, parasagittal and transverse sonographic images with TAUS, an over distended bladder of the patient should be avoided. Transvaginal Ultrasonography (TVUS) examination is possible for the best visualization of the relationship between the placenta and the cervix. Randomized controlled studies have shown that TVUS is superior to TAUS for the diagnosis of placenta previa (Sherman et al., 1992; Sunna & Ziadeh, 1999). Magnetic resonance imaging (MRI) is not used in the diagnosis of placenta previa due to its high cost and limited availability. MRI is most useful in the differential diagnosis of previa-accreta spectrum (Thurmond et al., 2000; Warshak et al., 2006).

Maternal morbidity from placenta previa is associated with postpartum hemorrhage as well as antepartum hemorrhage (Crane et al., 2000). Maternal neonatal effects of placenta previa are explained in the table below (Table 1.) (Fan et al., 2017; Gibbins et al., 2018; Vahanian et al., 2015).

Table 1. Adverse maternal and neonatal outcomes of placenta previa

Maternal outcomes	Neonatal outcomes
<ul style="list-style-type: none"> • Antepartum hemorrhage (52%) • Postpartum bleeding (22%) • Maternal death (<1%) • Need for blood transfusion (x3.8) • Uterine atony (x3.1) • Postpartum hysterectomy (x5.1) 	<ul style="list-style-type: none"> • Preterm Birth (X5.32) • Admission To Neonatal Intensive Care Unit (X4.09) • Neonatal Death (X5.44) • Perinatal Death (X3.01) • Neonatal Anemia

Placenta accreta spectrum

Spectrum placenta accreta (PAS) is formed by abnormal invasion of the myometrium of placental villi. The severity of PAS varies according to the degree of villus invasion. It is a term that includes three subtypes (Accreta, increta, percreta) (Jauniaux, Ayres-de-Campos, et al., 2019). In a systematic

review made in 2019, the overall prevalence was 0.17% (0.01-1.1)(Jauniaux, Bunce, et al., 2019). The increase in PAS prevalence in the last 30 years is explained by the increasing cesarean section rates. Placenta accreta constitutes approximately 2/3 of PAS(Jauniaux, Bunce, et al., 2019).

The pathogenesis of PAS is not known exactly. Various hypotheses have been put forward. Damage to the endometrial-myometrial interface and direct attachment of anchor villi from the damaged decidua to the myometrium are a few of them. Presence of previous cesarean section and previous uterine surgery (myomectomy, D&C etc.) in most of the patients with PAS supports the above hypotheses(Khong, 2008; Tantbiroj et al., 2008). The most important risk factor for PAS development is placenta previa after previous cesarean delivery(Silver et al., 2006).

Table 2. The effect of placenta previa and cesarean section history on PAS development

	Previa Previous C/S	+	Only Previous C/S
First cesarean section	3		0.03
Second cesarean section	11		0.2
Third cesarean section	40		0.1
Fourth cesarean section	61		0.8
Five or more cesarean sections	67		4.7

After a previous cesarean delivery, patients with placenta previa and low placenta should be screened for invasion anomaly at 18-24 weeks of pregnancy. Prenatal diagnosis of PAS can be made antenatally with 90% accuracy(Fitzpatrick et al., 2014; Thurn et al., 2016).

The use of color Doppler together with ultrasound findings is frequently used to confirm the diagnosis of PAS(Comstock, 2005). MRI can be used in the diagnosis of PAS. However, its usefulness in diagnosis has not been clearly demonstrated

Ultrasound findings; Multiple plasental lacunae, disruption of the bladder line, loss of the clear zone, myometrial thinning, abnormal vascularity, abnormal uterine contour, exophytic mass. Presence of multiple

placental lacunae and disruption of the bladder line are the most reliable diagnostic ultrasonographic findings.

Color Doppler findings: Turbulent lacunar blood flow (>15 cm/sec), bridging vessels, diffuse or focal intraparenchymal flow, hypervascularity of serosa-bladder interface, prominent subplacental venous complex(Shih et al., 2009).

MRI findings: Uterine bulging into the bladder ("placental/uterine bulge"), Interruption of the bladder Wall, Loss of retroplacental hypointense line on T2W images, Abnormal vascularization of the placental bed, Dark intraplacental bands on T2W imaging ("T2-dark bands"), Myometrial thinning, Focal exophytic mass(Jha et al., 2020). MRI is an auxiliary diagnostic method when the diagnosis is uncertain, the placenta is posterior and the size of the placental invasion area needs to be measured.

Placental abruption

Ablatio placenta refers to the partial or complete separation of the placenta after 20 weeks of pregnancy before the fetus is born. The main clinical findings are painful vaginal bleeding, uterine tachysystole and abnormal fetal heart rate. Ablatio placenta is a true obstetric emergency. Most placental abruptions are related to a chronic pathological vascular process, but some are due to acute events such as trauma or vasoconstriction. While a history of detachment is the most important risk factor, abdominal trauma, substance abuse (cocaine, etc.), preclampsia, eclampsia, premature rupture of membranes (PROM) are among other risk factors(Ananth et al., 2001). Vaginal bleeding is not seen in 10-20% of patients. Occult ablative placenta may be asymptomatic(Oyelese & Ananth, 2006). Detachment of more than half of the placental area increases the risk of DIC (Dissemine Intravascular Coagulation) and fetal mortality(Ananth et al., 1999). In mild separation and bleeding, no abnormality may be found in hemostasis tests. DIC development and the need for blood transfusion are common in severe bleeding, and fibrinogen <200 mg/dL is a strong predictor of DIC development(Wang et al., 2016). The sensitivity of ultrasound for the diagnosis of ablatio placenta is between 25-60%. While there are no ultrasound findings in non-severe bleeding, the positive predictive value of ultrasound findings is high in patients with severe bleeding(Glantz & Purnell, 2002; Shinde et al., 2016). These findings consist of subchorionic fluid deposits, echogenic eruptions in the amniotic fluid, or a thickened placenta, especially if it shines with maternal

movement ("Jello" sign)(Ananth & Kinzler, 2018). Maternal and fetal conditions related to ablatio placenta are given in the table below(Table 3)(Downes et al., 2017; Tikkanen, 2011).

Table 3. Maternal and Fetal outcomes of ablation placenta

Maternal outcome	Fetal outcome
<ul style="list-style-type: none"> • Blood transfusion • Hypovolemic shock • Kidney failure • Multiple organ failure • DIC • Maternal death 	<ul style="list-style-type: none"> • Hypoxemia • Asphyxia • Preterm delivery • Perinatal Mortality • Neonatal Neurodevelopmental Problems

Uterine rupture

Uterine rupture is a complete division of all 3 layers of the uterus. It is a fatal complication for mother and fetus(Herrera et al., 2011). It has started to be seen more frequently with the start of normal birth trials after cesarean section("ACOG Practice Bulletin No. 205: Vaginal Birth After Cesarean Delivery," 2019). Conditions such as trauma, a genetic disease associated with uterine muscle weakness, prolonged labor induction, and excessive stretching of the uterine wall can rupture the uterus without a history of surgery. Uterine rupture occurs in every 5,000 to 7,000 births(Porreco et al., 2009). Uterine rupture is more common in women who have had a previous cesarean delivery(Guiliano et al., 2014). As the number of cesarean sections increases, the risk of rupture also increases. Patients with uterine rupture may describe an acute onset of tearing sensation in their abdomen. Chest pain may occur if blood enters the peritoneum. Blood in the peritoneum can irritate the diaphragm and cause shoulder pain(Rottenstreich et al., 2021). Classic symptoms described for uterine rupture include acute onset abdominal pain, vaginal bleeding, unreliable fetal heart, and change in contraction pattern(Guiliano et al., 2014). Neonatal mortality after uterine rupture is between 6% and 25%(Kwee et al., 2006).

Vasa previa

Vasa previa is the presence of fetal blood vessels in the membranes that cover the internal cervical os. The membranous vessels may be in a velamentous placental structure or in a bilobed placenta. Multiple pregnancy and in vitro fertilization (IVF) are risk factors for vasa previa. Vasa previa bleeding is a very urgent situation and can cause fetal death from blood loss. Because bleeding is entirely of fetal origin.

Regardless of the cause, antepartum hemorrhage in the second half of pregnancy is known to increase the risk of preterm delivery 2-3 times(Bhandari et al., 2014; Magann et al., 2005).

REFERENCES

- ACOG Practice Bulletin No. 205: Vaginal Birth After Cesarean Delivery. (2019). *Obstet Gynecol*, 133(2), e110-e127. <https://doi.org/10.1097/aog.0000000000003078>
- Ananth, C. V., Berkowitz, G. S., Savitz, D. A., & Lapinski, R. H. (1999). Placental abruption and adverse perinatal outcomes. *Jama*, 282(17), 1646-1651. <https://doi.org/10.1001/jama.282.17.1646>
- Ananth, C. V., & Kinzler, W. L. (2018). Placental abruption: pathophysiology, clinical features, diagnosis, and consequences. *Recuperado de https://www.uptodate.com/contents/placental-abruption-pathophysiology-clinicalfeatures-diagnosis-andconsequences*.
- Ananth, C. V., Smulian, J. C., Demissie, K., Vintzileos, A. M., & Knuppel, R. A. (2001). Placental abruption among singleton and twin births in the United States: risk factor profiles. *Am J Epidemiol*, 153(8), 771-778. <https://doi.org/10.1093/aje/153.8.771>
- Bhandari, S., Raja, E. A., Shetty, A., & Bhattacharya, S. (2014). Maternal and perinatal consequences of antepartum haemorrhage of unknown origin. *Bjog*, 121(1), 44-50; discussion 50-42. <https://doi.org/10.1111/1471-0528.12464>
- Calleja-Agius, J., Custo, R., Brincat, M. P., & Calleja, N. (2006). Placental abruption and placenta praevia. *European Clinics in Obstetrics and Gynaecology*, 2(3), 121-127.
- Comstock, C. H. (2005). Antenatal diagnosis of placenta accreta: a review. *Ultrasound Obstet Gynecol*, 26(1), 89-96. <https://doi.org/10.1002/uog.1926>
- Crane, J. M., Van den Hof, M. C., Dodds, L., Armson, B. A., & Liston, R. (2000). Maternal complications with placenta previa. *Am J Perinatol*, 17(2), 101-105. <https://doi.org/10.1055/s-2000-9269>
- Cresswell, J. A., Ronsmans, C., Calvert, C., & Filippi, V. (2013). Prevalence of placenta praevia by world region: a systematic review and meta-analysis. *Trop Med Int Health*, 18(6), 712-724. <https://doi.org/10.1111/tmi.12100>
- Downes, K. L., Hinkle, S. N., Sjaarda, L. A., Albert, P. S., & Grantz, K. L. (2015). Previous prelabor or intrapartum cesarean delivery and risk of placenta previa. *Am J Obstet Gynecol*, 212(5), 669.e661-666. <https://doi.org/10.1016/j.ajog.2015.01.004>
- Downes, K. L., Shenassa, E. D., & Grantz, K. L. (2017). Neonatal Outcomes Associated With Placental Abruption. *Am J Epidemiol*, 186(12), 1319-1328. <https://doi.org/10.1093/aje/kwx202>
- Fan, D., Wu, S., Liu, L., Xia, Q., Wang, W., Guo, X., & Liu, Z. (2017). Prevalence of antepartum hemorrhage in women with placenta previa: a systematic review and meta-analysis. *Sci Rep*, 7, 40320. <https://doi.org/10.1038/srep40320>
- Fitzpatrick, K. E., Sellers, S., Spark, P., Kurinczuk, J. J., Brocklehurst, P., & Knight, M. (2014). The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based descriptive study. *Bjog*, 121(1), 62-70; discussion 70-61. <https://doi.org/10.1111/1471-0528.12405>

- Gibbins, K. J., Einerson, B. D., Varner, M. W., & Silver, R. M. (2018). Placenta previa and maternal hemorrhagic morbidity. *J Matern Fetal Neonatal Med*, *31*(4), 494-499. <https://doi.org/10.1080/14767058.2017.1289163>
- Glantz, C., & Purnell, L. (2002). Clinical utility of sonography in the diagnosis and treatment of placental abruption. *J Ultrasound Med*, *21*(8), 837-840. <https://doi.org/10.7863/jum.2002.21.8.837>
- Guiliano, M., Closset, E., Therby, D., LeGoueff, F., Deruelle, P., & Subtil, D. (2014). Signs, symptoms and complications of complete and partial uterine ruptures during pregnancy and delivery. *Eur J Obstet Gynecol Reprod Biol*, *179*, 130-134. <https://doi.org/10.1016/j.ejogrb.2014.05.004>
- Guro-Urganci, I., Cromwell, D. A., Edozien, L. C., Smith, G. C., Onwere, C., Mahmood, T. A., Templeton, A., & van der Meulen, J. H. (2011). Risk of placenta previa in second birth after first birth cesarean section: a population-based study and meta-analysis. *BMC Pregnancy Childbirth*, *11*, 95. <https://doi.org/10.1186/1471-2393-11-95>
- Herrera, F. A., Hassanein, A. H., & Bansal, V. (2011). Atraumatic spontaneous rupture of the non-gravid uterus. *J Emerg Trauma Shock*, *4*(3), 439. <https://doi.org/10.4103/0974-2700.83896>
- Jauniaux, E., Ayres-de-Campos, D., Langhoff-Roos, J., Fox, K. A., & Collins, S. (2019). FIGO classification for the clinical diagnosis of placenta accreta spectrum disorders. *Int J Gynaecol Obstet*, *146*(1), 20-24. <https://doi.org/10.1002/ijgo.12761>
- Jauniaux, E., Bunce, C., Grønbeck, L., & Langhoff-Roos, J. (2019). Prevalence and main outcomes of placenta accreta spectrum: a systematic review and meta-analysis. *Am J Obstet Gynecol*, *221*(3), 208-218. <https://doi.org/10.1016/j.ajog.2019.01.233>
- Jha, P., Pöder, L., Bourgioti, C., Bharwani, N., Lewis, S., Kamath, A., Nougaret, S., Soyer, P., Weston, M., Castillo, R. P., Kido, A., Forstner, R., & Masselli, G. (2020). Society of Abdominal Radiology (SAR) and European Society of Urogenital Radiology (ESUR) joint consensus statement for MR imaging of placenta accreta spectrum disorders. *Eur Radiol*, *30*(5), 2604-2615. <https://doi.org/10.1007/s00330-019-06617-7>
- Khong, T. Y. (2008). The pathology of placenta accreta, a worldwide epidemic. *J Clin Pathol*, *61*(12), 1243-1246. <https://doi.org/10.1136/jcp.2008.055202>
- King, L. J., Dhanya Mackeen, A., Nordberg, C., & Paglia, M. J. (2020). Maternal risk factors associated with persistent placenta previa. *Placenta*, *99*, 189-192. <https://doi.org/10.1016/j.placenta.2020.08.004>
- Kuribayashi, M., Tsuda, H., Ito, Y., Tezuka, A., Ando, T., Tamakoshi, K., & Mizuno, K. (2021). Evaluation of the risk factors for antepartum hemorrhage in cases of placenta previa: a retrospective cohort study. *J Int Med Res*, *49*(11), 3000605211054706. <https://doi.org/10.1177/03000605211054706>
- Kwee, A., Bots, M. L., Visser, G. H., & Bruinse, H. W. (2006). Uterine rupture and its complications in the Netherlands: a prospective study. *Eur J Obstet Gynecol Reprod Biol*, *128*(1-2), 257-261. <https://doi.org/10.1016/j.ejogrb.2006.02.005>
- Magann, E. F., Cummings, J. E., Niederhauser, A., Rodriguez-Thompson, D., McCormack, R., & Chauhan, S. P. (2005). Antepartum bleeding of unknown

- origin in the second half of pregnancy: a review. *Obstet Gynecol Surv*, 60(11), 741-745. <https://doi.org/10.1097/01.ogx.0000182881.53139.f7>
- Oyelese, Y., & Ananth, C. V. (2006). Placental abruption. *Obstet Gynecol*, 108(4), 1005-1016. <https://doi.org/10.1097/01.AOG.0000239439.04364.9a>
- Porreco, R. P., Clark, S. L., Belfort, M. A., Dildy, G. A., & Meyers, J. A. (2009). The changing specter of uterine rupture. *Am J Obstet Gynecol*, 200(3), 269.e261-264. <https://doi.org/10.1016/j.ajog.2008.09.874>
- Rottenstreich, M., Rotem, R., Hirsch, A., Farkash, R., Rottenstreich, A., Samueloff, A., & Sela, H. Y. (2021). Delayed diagnosis of intrapartum uterine rupture - maternal and neonatal consequences. *J Matern Fetal Neonatal Med*, 34(5), 708-713. <https://doi.org/10.1080/14767058.2019.1613366>
- Ruiter, L., Eschbach, S. J., Burgers, M., Rengerink, K. O., van Pampus, M. G., Goes, B. Y., Mol, B. W., Graaf, I. M., & Pajkrt, E. (2016). Predictors for Emergency Cesarean Delivery in Women with Placenta Previa. *Am J Perinatol*, 33(14), 1407-1414. <https://doi.org/10.1055/s-0036-1584148>
- Sherman, S. J., Carlson, D. E., Platt, L. D., & Medearis, A. L. (1992). Transvaginal ultrasound: does it help in the diagnosis of placenta previa? *Ultrasound Obstet Gynecol*, 2(4), 256-260. <https://doi.org/10.1046/j.1469-0705.1992.02040256.x>
- Shih, J. C., Palacios Jaraquemada, J. M., Su, Y. N., Shyu, M. K., Lin, C. H., Lin, S. Y., & Lee, C. N. (2009). Role of three-dimensional power Doppler in the antenatal diagnosis of placenta accreta: comparison with gray-scale and color Doppler techniques. *Ultrasound Obstet Gynecol*, 33(2), 193-203. <https://doi.org/10.1002/uog.6284>
- Shinde, G. R., Vaswani, B. P., Patange, R. P., Laddad, M. M., & Bhosale, R. B. (2016). Diagnostic Performance of Ultrasonography for Detection of Abruption and Its Clinical Correlation and Maternal and Foetal Outcome. *J Clin Diagn Res*, 10(8), Qc04-07. <https://doi.org/10.7860/jcdr/2016/19247.8288>
- Silver, R. M., Landon, M. B., Rouse, D. J., Leveno, K. J., Spong, C. Y., Thom, E. A., Moawad, A. H., Caritis, S. N., Harper, M., Wapner, R. J., Sorokin, Y., Miodovnik, M., Carpenter, M., Peaceman, A. M., O'Sullivan, M. J., Sibai, B., Langer, O., Thorp, J. M., Ramin, S. M., & Mercer, B. M. (2006). Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol*, 107(6), 1226-1232. <https://doi.org/10.1097/01.Aog.0000219750.79480.84>
- Sunna, E., & Ziadeh, S. (1999). Transvaginal and transabdominal ultrasound for the diagnosis of placenta praevia. *J Obstet Gynaecol*, 19(2), 152-154. <https://doi.org/10.1080/01443619965471>
- Tantbirojn, P., Crum, C. P., & Parast, M. M. (2008). Pathophysiology of placenta creta: the role of decidua and extravillous trophoblast. *Placenta*, 29(7), 639-645. <https://doi.org/10.1016/j.placenta.2008.04.008>
- Thurmond, A., Mendelson, E., Böhm-Vélez, M., Bree, R., Finberg, H., Fishman, E. K., Hricak, H., Laing, F., Sartoris, D., & Goldstein, S. (2000). Role of imaging in second and third trimester bleeding. American College of Radiology. ACR Appropriateness Criteria. *Radiology*, 215 Suppl, 895-897.

- Thurn, L., Lindqvist, P. G., Jakobsson, M., Colmorn, L. B., Klungsoyr, K., Bjarnadóttir, R. I., Tapper, A. M., Børdahl, P. E., Gottvall, K., Petersen, K. B., Krebs, L., Gissler, M., Langhoff-Roos, J., & Källen, K. (2016). Abnormally invasive placenta-prevalence, risk factors and antenatal suspicion: results from a large population-based pregnancy cohort study in the Nordic countries. *Bjog*, *123*(8), 1348-1355. <https://doi.org/10.1111/1471-0528.13547>
- Tikkanen, M. (2011). Placental abruption: epidemiology, risk factors and consequences. *Acta Obstet Gynecol Scand*, *90*(2), 140-149. <https://doi.org/10.1111/j.1600-0412.2010.01030.x>
- Vahanian, S. A., Lavery, J. A., Ananth, C. V., & Vintzileos, A. (2015). Placental implantation abnormalities and risk of preterm delivery: a systematic review and metaanalysis. *Am J Obstet Gynecol*, *213*(4 Suppl), S78-90. <https://doi.org/10.1016/j.ajog.2015.05.058>
- Wang, L., Matsunaga, S., Mikami, Y., Takai, Y., Terui, K., & Seki, H. (2016). Pre-delivery fibrinogen predicts adverse maternal or neonatal outcomes in patients with placental abruption. *J Obstet Gynaecol Res*, *42*(7), 796-802. <https://doi.org/10.1111/jog.12988>
- Warshak, C. R., Eskander, R., Hull, A. D., Scioscia, A. L., Mattrey, R. F., Benirschke, K., & Resnik, R. (2006). Accuracy of ultrasonography and magnetic resonance imaging in the diagnosis of placenta accreta. *Obstet Gynecol*, *108*(3 Pt 1), 573-581. <https://doi.org/10.1097/01.AOG.0000233155.62906.6d>

CHAPTER 4
**CAUSES AND ADMINISTRATION OF ANEMIA IN
PREGNANCY**

Dr. Ahu KORKUT¹

¹ Eskişehir Osmangazi University, Medical School of Department of Obstetric and Gynecology, Orcid ID: 0000-0002-1693-6212, E-mail: ahuorta@hotmail.com

1. INTRODUCTION

Metabolic requirements of the maternal and fetoplacental unit increase during pregnancy. In order to meet these needs, changes occur in all systems in the body. The most important physiological change is the increase in blood volume. The increase is mainly due to an increase in plasma volume. Plasma volume begins to increase after the 6th week of pregnancy. It increased 40-50% above pre-pregnancy level at 34 weeks (ACOG Practise Bulletins No.233, 2021). At term, the plasma volume increases by an average of 1100-1600 ml, and the plasma volume returns to pre-pregnancy levels at 6 weeks postpartum (Kaur et al., 2014). The increase in the amount of erythrocytes starts to increase between the 8-10th weeks of pregnancy and increases to approximately 20-30% above the pre-pregnancy values at term (Antony et al., 2021). Since the increase in the amount of erythrocytes is less than the increase in the plasma ratio, there is a decrease in hemoglobin levels during pregnancy. This condition has been defined as the physiological anemia of pregnancy. Since anemia can lead to important maternal and neonatal health problems, it is important to distinguish physiological anemia of pregnancy from other causes of anemia.

Anemia is one of the most important health problems in the world and is detected in 30% of women of reproductive age (de Benoist et al., 2008; Reveiz et al., 2011). Although this rate is much higher during pregnancy, it is estimated to be more than 40% by the World Health Organization (WHO). The prevalence of anemia in pregnancy shows regional differences in the world due to socioeconomic level and nutritional deficiencies (WHO, 2013). The prevalence of anemia is 27% among African American women and 7% among non-Hispanic white women (Mohamed et al., 2012). While the prevalence of anemia is 52% in developing countries, it is around 10-20% in developed countries (WHO, 2011). As the weeks of pregnancy proceeds, the incidence of anemia increases (Mei et al., 2011).

The reason for the high prevalence of anemia among women of reproductive age is iron deficiency anemia, which is caused by a deficiency or insufficient amount of iron stores, and this is the most common cause of anemia in the world.

2. DEFINITION AND CLASSIFICATION

The definition of anemia differs between pregnant and non-pregnant women. It is important to have a certain cut-off value of hemoglobin and

hematocrit for the evaluation of the presence and severity of anemia. Although different populations have different hemoglobin concentrations, we do not use individual cut-off values.

Anemia in pregnancy: According to the Centers for Disease Control and Prevention (CDC), anemia is defined once the threshold values of hemoglobin levels are below 11 g/dl of hemoglobin, 33% of hematocrit in the 1st trimester, below 10.5 g/dl of hemoglobin, 32% of hematocrit in the 2nd trimester, below 11 g/dl of hemoglobin, 33% of hematocrit in the 3rd trimester (CDC, 1989). The World Health Organization (WHO) defines anemia once hemoglobin value is below 11 g/dl and hematocrit value are below 33% and postpartum hemoglobin value is below 10 g/dl for all three trimesters (WHO, 2001; Ruiz et al., 2021). Anemia according to hemoglobin (Hb) value is classified as severe if < 7 g/dl, as moderate if between 7 -9.9 g/dl and as mild if between 10-10.9 g/dl mild.

Although physiological anemia and iron deficiency anemia are the two most common causes in pregnancy, other causes of anemia should not be disregarded (ACOG Practise Bulletins No.233, 2021). Despite the fact that there is no standard hemoglobin value for physiological anemia, it usually results in mild anemia (Hb 10-10.9 g/dl).

Anemia cases can be hereditary and acquired. Classification according to its pathophysiological mechanism;

- Hemodilution
 - ✓ Pregnancy
 - ✓ Hyperglobulinemia
 - ✓ Massive splenomegaly
- Decreased erythrocyte production
 - ✓ Iron deficiency
 - ✓ B 12 vitamin deficiency
 - ✓ Folic acid deficiency
 - ✓ Bone marrow deficiency
 - ✓ Low levels of erythropoietin
 - ✓ Hypothyroidism
- Increased erythrocyte loss
 - ✓ Acute hemorrhage (gastrointestinal bleeding)
 - ✓ Hemolysis

- Hereditary: Hemoglobinopathies, erythrocyte enzyme defects, membrane defects and porphyrias can be listed.
- Acquired: Autoimmune hemolytic anemia, thrombotic thrombocytopenia purpura, hemolytic uremic syndrome, malaria, paroxysmal nocturnal hemoglobinuria, lead poisoning can be listed.

We can classify anemia according to erythrocyte mean cell volume (MCV). A distinction is made between microcytic anemia if the MCV is <80 fL, normocytic anemia if MCV is between 80-100 fL, and macrocytic anemia if MCV is >100 fL.

- We can list microcytic anemia as iron deficiency anemia, thalassemias, anemia of chronic disease, sideroblastic anemia, anemia associated with copper deficiency and anemia associated with lead excess.
- Normocytic anemias include early stages of iron deficiency anemia, anemia associated with bleeding, anemia of chronic disease, anemia associated with chronic renal failure, autoimmune hemolytic anemia, hypothyroidism associated anemia, hereditary spherocytosis, anemia associated with bone marrow suppression, and paroxysmal nocturnal hemoglobinuria.
- Microcytic anemia, folic acid deficiency anemia, vitamin B 12 deficiency anemia, ethanol-associated anemia, reticulocytosis related anemia, drug-induced hemolytic anemia (zidovudine), anemia associated with acute myelodysplastic syndrome, and anemia associated with liver disease.

2.a. Iron Deficiency Anemia

It is the second most common cause of anemia in pregnancy. While women have a total of 2.3 g iron in the body, 1 g iron supplementation is needed for increased erythrocyte mass during pregnancy, fetal erythrocyte production, placental growth and blood loss support accompanying delivery. While the typical diet provides 15 mg of elemental dietary support, the recommended iron intake is 27 mg during pregnancy and 10 mg during lactation with iron preparations (Institute of Medicine Panel on

Micronutrients, 2001). When adequate iron support is provided, 70% of it is functional iron and the remainder is available as storage iron. More than 80% of functional iron is available in erythrocyte as hemoglobin and the remainder is available in myoglobin and respiratory enzymes (ACOG Practise Bulletins No.95, 2008).

We can define iron deficiency with abnormal values in laboratory test results, empty bone marrow iron stores determined by bone marrow iron smear, and a 1 g/dl increase in Hb concentration with iron preparation supplementation (ACOG Practise Bulletins No. 233, 2021). A serum ferritin level <15 µg/L was considered an indicator of iron deficiency, but recent studies have shown that the use of ferritin values <30 µg/L has higher specificity and sensitivity in diagnosing iron deficiency (Van den Broek et al., 1998; WHO, 2017; Daru et al., 2017).

A wide spectrum is observed in patients, from asymptomatic iron deficiency to symptomatic anemia (fatigue, weakness, headache, hair loss, concentration disorder, exertional dyspnea, restless legs syndrome, pica, tachycardia, and palpitations).

Risk factors for iron deficiency and iron deficiency anemia in pregnancy and women of reproductive age;

- Iron-poor diet (not consuming iron-rich foods such as red meat, oysters, shrimp, breakfast cereals, beans, lentils)
- Diet poor in foods that increase iron absorption (not consuming foods rich in vitamin C such as orange juice, broccoli, peppers, or consuming foods that reduce absorption such as coffee, tea and spinach)
- Pica (consuming substances such as clay)
- Gastrointestinal system diseases that impair absorption
- Heavy menstrual bleeding
- Excessive postpartum bleeding
- Short pregnancy interval
- High parity
- Multiple pregnancies
- Low socioeconomic level

It is important to treat iron deficiency anemia with iron supplementation because of the increased risk of preterm delivery, low birth weight (SGA) and perinatal mortality in the fetus (Zhou et al., 1998; Alwan et al., 2015). There are studies demonstrating a connection between postpartum depression and maternal iron deficiency (Corvin et al., 2003). In addition, patients with maternal iron deficiency need postpartum blood transfusion (Drukker et al., 2015; Aurbach et al., 2017).

Although serum hemoglobin and hematocrit concentrations are first-line tests used to determine anemia, they are not specific for iron deficiency anemia. Typical laboratory results of iron deficiency anemia are hypochromic microcytic anemia with low serum iron, low serum ferritin levels, increased plasma total iron binding capacity, and increased free erythrocyte protoporphyrin level. Normal iron parameters are summarized in table 1 (ACOG Practise Bulletins No.233, 2021).

Table 1: Normal iron parameters during pregnancy

Test	Normal Value
Plasma iron level	40-175 µg/dl
Plasma total iron binding capacity	216-400 µg/dl
Transferrin saturation	16-60%
Serum ferritin level	>30 µg/dl
Free erythrocyte protoporphyrin level	<3 µg/dl

2.b. Megaloblastic Anemia

Megaloblastic anemia occurs in folic acid and vitamin B12 deficiency and in pernicious anemia. Vitamin B12 and folate are important in nucleic acid and DNA synthesis, and many cells are affected in their deficiency. Because erythroid cells cycle fast, symptoms occur more quickly.

Folate deficiency is the most common cause of megaloblastic anemia in pregnancy. It is associated with a diet low in green leafy vegetables, animal foods, and legumes (Campbell, 1995). Folate is stored in the liver. If

enough folate is not taken in the diet, serum folate levels decrease after 3 weeks, hypersegmentation occurs in neutrophils after 2 weeks, and after 17 weeks, the folate level decreases in erythrocytes and megaloblasts appear in the bone marrow (Samuels, 2021). The diagnosis of folate deficiency is made when the serum folic acid level is <2 ng/mL. Folic acid levels 2-4 ng/ml are the limit values and at these values, erythrocyte folate levels (<160 ng/mL) are evaluated for diagnosis (Achebe et al., 2017). It is recommended to use 400 mcg folic acid preconceptionally and during pregnancy to prevent neural tube defects due to folate deficiency during pregnancy (Bibbins-Domingo et al., 2017). Preconceptional dose of 1 mg/day in patients with a diagnosis of folic acid deficiency is sufficient for the treatment of insufficiency and prevention of neural tube defects. The preconception recommended daily folic acid is 4 mg/day in patients using anticonvulsant drugs and in patients with a history of children with neural tube defects (ACOG, 2003).

Vitamin B12 is necessary for neurological functions, erythrocyte production and growth. It is found in food of animal origin (meat, milk, eggs). It is absorbed from the ileum by binding to the intrinsic factor secreted from the parietal cells of the stomach. Vitamin B 12 deficiency occurs as a result of intrinsic factor deficiency (pernicious anemia) and inadequate diet (vegetarians). At the same time, those who have undergone bariatric surgery, patients with malabsorption syndrome and inflammatory bowel disease are risky groups for vitamin B12 deficiency (Samuels, 2021). Since vitamin B 12 is stored in high amounts in the body, it takes a long time for deficiency to occur (Roy et al., 2018). Pregnant women with vitamin B12 deficiency may have symptoms such as anemia, paresthesia in the hands and feet, weakness, unsteady gait, ataxia, depression, hallucinations, and confusion due to peripheral and spinal nerve involvement. It has been reported that children born from these pregnancies have retarded developmental, hypotonia and neuromotor developmental problems (Achebe et al., 2017). The diagnosis can be made by looking at the complete blood count, B12 levels and bone marrow smear. In the treatment of B12 deficiency, 1 mg/day intramuscular hydroxycobalamin is administered three times a week for 2 weeks and repeated every 3 months (Roy et al., 2018).

2.c. Other Causes of Anemia

It is observed less frequently in pregnancy.

Hereditary spherocytosis occurs due to a defect in the genes encoding erythrocyte membrane proteins. It is an autosomal dominant genetic disease. Diagnosis is made by family history, hemolytic anemia findings, reticulocytosis, peripheral smear findings, osmotic fragility test and flow cytometric tests (Kilpatrick et al, 2019). Hemolytic crises can occur during pregnancy. Blood transfusion or splenectomy can be performed in the treatment of hemolytic crisis.

Autoimmune hemolytic anemia, autoantibodies against erythrocytes cause destruction in erythrocytes and hemolytic anemia occurs (Maroto et al., 2020). Peripheral smear shows spherocytes and normoblasts, reticulocytosis and macrocytic anemia. Direct Coombs test is positive (Kilpatrick et al, 2019). Hot antibodies (Ig G) pass through the placenta, so middle cerebral artery peak systolic flow velocity (MCA PSV) should be followed in terms of fetal anemia. Cold antibodies (Ig M) do not cross the placenta, causing hemolysis. In the treatment, corticosteroid therapy and blood transfusion are performed first, immunosuppressive therapy and splenectomy can be applied in resistant cases.

Sickle cell anemia is caused by the formation of an abnormal hemoglobin, Hb S. Hemoglobin S is formed by substitution of valine for glutamic acid at the 6th position of the β -globin chain in hemoglobin A. It shows autosomal recessive inheritance (Patila et al., 2017). Hb S causes erythrocytes to take the shape of a sickle at low oxygen pressure (Howard et al., 2012). As a result of sickle erythrocytes, hemolytic anemia, vascular occlusion and related microinfarcts develop. Hypoxia, cold weather, dehydration, acidosis, infection, stress and excessive exercise are factors that increase the risk of sickening and crisis. Diagnosis is made by demonstrating HbSS with hemoglobin electrophoresis (Howard et al., 2012). Patients with sickle cell anemia are adversely affected by pregnancy. Anemia deepens during pregnancy, the risk of painful crisis increases, the risk of infection and thromboembolism increases. In addition, fetal growth restriction, low birth weight, preterm delivery, perinatal mortality, preeclampsia and eclampsia risk are increased in these pregnant women (Boafor et al., 2016). Pre-pregnancy counseling should be given and parents should be informed about prenatal diagnosis or preimplantation diagnosis methods in cases where both parents are carriers or one is a patient and the other is a carrier

due to genetic transmission. In these patients, preconceptional high-dose folic acid supplementation is started. Pneumonia and influenza vaccines are recommended because of the increased risk of infection. Low-dose aspirin prophylaxis is recommended after 12 weeks of gestation to reduce the risk of preeclampsia in patients with sickle cell anemia. Low molecular weight heparin prophylaxis (LMWH) is not routinely applied, it is applied in inpatients. There is no indication for cesarean section.

Thalassemia is a disease that causes hypochromic, microcytic anemia, which occurs as a result of a defect in the synthesis of one or more of the hemoglobin chains (α , β , γ , δ). The most common is alpha and beta thalassemia. It shows autosomal recessive inheritance. 3% of the population in the world is a carrier of beta thalassemia. Thalassemia trait is common in Turkey, especially in the Mediterranean, Aegean and Marmara regions. In the case of alpha thalassemia major form (Hb Bart), there is a deletion in 4 alpha genes, hydrops fetalis, high-output heart failure and fetal death occur, incompatible with life. The form of HbH disease occurs with the deletion of the 3-alpha gene, causes moderate or severe hemolytic anemia, and it has been reported that fetal growth restriction, low birth weight and preterm birth rates are high (Tongsong et al., 2009). Alpha thalassemia minor form has 2 gene deletions and causes mild microcytic anemia. Alpha thalassemia carrier form, on the other hand, has a single gene deletion and does not provide clinical findings. Pregnancy outcomes of alpha thalassemia minor and carrier forms are similar to other individuals in the community. There are many mutations in beta thalassemia. In prenatal diagnosis, first of all, mutations of the mother and father should be determined, and which mutation should be sought in the fetus should be determined. Beta thalassemias are clinically evaluated in four groups:

- Silent carrier form: HbA2 levels are normal, MCV is slightly low
- Thalassemia minor: HbA2 levels are high, MVC is low, and mild hypochromic microcytic anemia. Heterozygous trait.
- Thalassemia intermedia: Hb 6-10 g/dL, MCV, MCH, MCHC are low, HbF is high, transfusion needs are not much. Homozygous sickness.
- Thalassemia Major: It starts in childhood and is transfusion dependent (Republic of Turkey Ministry of Health, 2016).

Pregnancy outcomes for beta thalassemia minor and traits are similar to the general population. Folic acid supplementation should be given to these patients. If there is no iron deficiency, iron supplements are not given. Prenatal genetic counseling should be given to patients whose parents are both carriers because of the risk of fetal disease.

Some nutritional deficiencies (such as vitamin A), chronic infections (such as parasitic infections), hypothyroidism, chronic diseases and other causes of anemia should definitely be kept in mind during pregnancy.

3. SCANNING

All pregnant women should be screened for anemia with a complete blood count according to the American College of Obstetricians and Gynecologists (ACOG), the Centers for Disease Control and Prevention (CDC), and a 2019 United Kingdom (UK) guideline at the first prenatal visit (Pavord et al., 2020; ACOG Practise Bulletins No.233, 2021). While The American Society of Hematology recommends screening with ferritin in all pregnant women, ACOG and British Society for Haematology recommends it only in pregnant women with risk factors (ACOG Practise Bulletins No.95, 2008; Breyman et al., 2017; Munoz et al., 2018; Pavord et al. al., 2020). The United States Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to evaluate the benefits of screening in pregnant women without symptoms of anemia and recommended the evaluation of ferritin only in women with anemia (McDonagh et al., 2015; Siu 2015). At 24-28 weeks of gestation, we screen the patients again with a complete blood count.

Individuals with anemia should be screened for the cause, the most common cause is iron deficiency. It is also recommended that some high-risk patients be screened. These include a history of iron deficiency, diabetes, smoking, multiparity, Human Immunodeficiency Virus (HIV) infection, inflammatory bowel disease, short interval between births, history of abnormal uterine bleeding, high body mass index, and vegetarians should be screened for anemia.

According to the UK 2019 guideline, after taking the history to determine the iron deficiency, either direct prophylactic iron supplementation is started or the ferritin level is checked in the high-risk groups we mentioned above, and iron supplementation is administered for the low-risk groups (Pavord et al., 2020).

Since iron-related neurogenesis is at its maximum in the third trimester and early neonatal period, iron deficiency needs to be corrected before the third trimester (Radlowski et al., 2013). Babies of pregnant women with iron deficiency are also at risk for iron deficiency once born (MacQueen et al., 2017). The ferritin level on screening is sufficient for iron deficiency. However, since ferritin is an acute phase reactant, it can be found to be high in some cases (such as infection, inflammation, malignancy, etc.) even if there is iron deficiency. In this case, the combined use of ferritin and transferrin saturation is recommended (Auerbach et al., 2021).

Screening and treating anemia, if detected, is important in terms of maternal and fetal outcomes. In a study including more than 160,000 pregnant women in the United States, antepartum maternal anemia was found to be 6.1% (Harrison et al., 2021). Compared to those without anemia, the risk of maternal death, eclampsia, need for transfusion, admission to intensive care and hysterectomy was 2 times higher in patients with anemia. Postpartum hemorrhage, infection, cesarean delivery and preeclampsia complications were also common in patients with anemia. Fetal growth retardation, low birth weight, preterm delivery and neonatal intensive care admission were high in babies born to mothers with anemia.

In the study conducted by the World Health Organization (WHO), it was demonstrated that there is a relationship between antenatal and postnatal maternal anemia and increased maternal mortality risk (Daru et al., 2018). In addition, other studies have shown that maternal anemia increases the rate of transfusion need, sepsis, cardiovascular disease and cesarean section (Azulay et al., 2015).

4. EVALUATION

In the evaluation of anemia in pregnancy, first of all, a detailed clinical history should be taken, erythrocyte indices should be checked, and parameters in the complete blood count should be evaluated.

- **Evaluation of microcytic anemia (Hgb <10.5–11 g/dL and MCV <80 μ m³):**

In order to investigate iron deficiency anemia, which is the most common cause of anemia in these patients, we first check the ferritin levels. In case the ferritin level is <15-30 ng/ml, we can diagnose iron deficiency. If the ferritin level is between 30-40 ng/ml, it is controlled by transferrin

saturation, and those with a transfusion saturation <20% support the diagnosis of iron deficiency. Hemoglobin electrophoresis is recommended in patients with normal ferritin levels (>40 ng/ml). Genetic consultation should be requested from patients with hemoglobinopathy (sickle cell anemia, thalassemia). Peripheral smear is requested from patients with ferritin level >40 ng/ml and whose hemoglobin electrophoresis is normal, and if ring sideroblasts are detected, sideroblastic anemia is diagnosed. Patients who do not have any finding in peripheral smear may have anemia of chronic disease and investigation can be done for the cause.

- **Evaluation of normocytic anemia (Hgb 10.5–11 g/dL and MCV ≥80–100 μm):**

We perform a reticulocyte count to assess whether anemia is due to underproduction and hemolysis. We take a detailed history to evaluate chronic diseases, genetic diseases and drug exposure. In case normocytic anemia and reticulocyte count is >3%, we request direct Coombs test. For patients with positive direct Coombs test, autoimmune hemolytic anemia is considered, and rheumatology consultation may be requested. Hematology consultation may be requested for patients with negative direct Coombs test, considering glucose 6-phosphate dehydrogenase deficiency, hemoglobinopathies, and microangiopathic anemias.

Red blood cell distribution width (RDW) is evaluated in patients with normocytic anemia and reticulocyte count <3%. Infection, drugs, chronic disease and aplastic anemia can be considered as the cause of anemia in patients with RDW between 12-15% and the patient is referred for further examination. Ferritin, B12 and folate levels are measured in patients with an RDW >15%. In normal cases, anemia of chronic disease is considered, and erythropoietin treatment may be considered.

- **Evaluation of macrocytic anemia (Hgb 10.5–11 g/dL and MCV >100 μm³):**

In these patients, the missing vitamin should be supplemented by looking at B12 and erythrocyte folate levels. Chronic diseases (liver diseases, renal failure, hypothyroidism, chronic infections and malignancies) are often associated with normocytic anemia. For these diseases, a detailed history should be taken, risk factors should be determined, liver function

tests, urea, creatinine, thyroid-stimulating hormone (TSH) laboratory tests should be performed. Pregnancy-specific normal values are given in Table 2. (Ashley et al., 2022)

Table 2: Trimester Specific Pregnancy Reference Ranges

	First Trimester	Second Trimester	Third Trimester
Serum ferritin level (ng/mL)	6-130	2-230	0-116
Total iron-binding capacity µg/d	278-403	Not reported	359-609
Transferrin saturation (%)	Not reported	10-44	5-37
Plasma iron level (µg/dL)	72-113	44-178	30-193
Folate (RBC) (ng/mL)	137-589	94-828	109-663
Folate (serum) (ng/mL)	2.5-15	0.8-24	1.4-20.7
B12 (cobalamin) pg/mL	118-438	130-656	99-526
MCV µm ³	81-96	82-97	81-99

5. PROFILAXIS

Anemia should be diagnosed and treated preconceptionally. Chronic infections (parasites cause blood loss and iron deficiency anemia) should be treated, and chronic diseases should be controlled.

The Centers for Disease Control and Prevention (CDC) recommends oral iron prophylaxis of 30mg/day for pregnant women (CDC, 1989) according to the guide. WHO recommended 60 mg oral elemental iron supplementation during pregnancy and six weeks postpartum in risky regions where iron deficiency anemia is endemic, and 30 mg oral iron supplementation in regions with a prevalence of less than 40% (WHO, 2012).

Daily or intermittent use of iron supplementation during pregnancy prevented low hemoglobin values in the antepartum and sixth week of postpartum. However, there is not enough data showing that it prevents poor perinatal outcomes such as low birth weight, infection, and preterm delivery

(Cantor et al., 2015; Pena-Rosas et al., 2015). In studies, maternal and fetal outcomes of daily and intermittent iron use were found to be similar, and it was shown that there were fewer side effects in intermittent use.

Gastrointestinal system side effects (nausea, vomiting, constipation) of oral iron intake are dose dependent. The dose can be reduced. Foods that increase iron absorption should be consumed and foods that decrease absorption should be avoided. Pregnant women are informed about diet and nutrition (Pavord et al., 2012).

According to the guidelines of the Ministry of Health, 40-60 mg/day oral iron supplementation is recommended for all pregnant women from the second trimester to the sixth postpartum week (T.R. Ministry of Health, 2007). It recommends follow-up of pregnant women three times during antepartum and once during postpartum in terms of anemia.

It is recommended to start a daily 400 µg folic acid supplementation in order to reduce the rate of neural tube defects for women planning pregnancy, this also prevents maternal folic acid deficiency.

B12 supplementation should be made for patients who have undergone bariatric surgery, have a vegetarian diet, malabsorption syndrome, inflammatory bowel disease, and patients with vitamin B12 deficiency due to pernicious anemia.

6. ADMINISTRATION

Oral and intravenous iron are effective for the treatment of iron deficiency. Recombinant erythropoietin use and blood transfusion can be used when necessary. Treatment for iron deficiency should be individualized. Oral therapy is recommended in the first trimester of pregnancy and in all women with iron deficiency who can tolerate oral therapy. Higher doses of iron should be given to these pregnant women than the iron in prenatal vitamins. However, intravenous preparations can be used in pregnant women with severe anemia, who cannot tolerate oral iron use, and who are in the third trimester (Pavord et al., 2020).

The benefits and risks of intravenous and oral iron therapy in pregnant women and postpartum women diagnosed with iron deficiency were compared in three meta-analyses evaluated in 2018-2019 (Govindappagari et al., 2019; Sultan et al., 2019). Ferritin and hemoglobin values increased in both groups, but hemoglobin values were found to be higher in patients who received intravenous (IV) treatment. In another meta-analysis, it was found

that side effects and early discontinuation of IV iron treatment were less frequent (Lewkowitz et al., 2019). Oral iron treatment was applied to pregnant women with Hb 9.5-11 g/dl in the second and third trimesters in the screening and management of iron deficiency, and IV iron treatment protocol was applied to pregnant women with Hb <9 g/dl (Hamm et al., 2022). Although there were higher Hb values at birth with this protocol, no significant decrease was observed in blood transfusion.

Oral iron therapy is the first, reliable, inexpensive and easily accessible option. The treatment is sufficient. Ferrous sulfate is most preferred. Other preparations are ferrous gluconate and ferrous fumarate. The recommended daily dose is 40-200 mg of elemental iron. Higher and more frequent doses do not increase iron absorption, and there is a tendency to use the intermittent day method due to the side effects (Pavord et al., 2020). Intermittent oral iron therapy method increases iron absorption and reduces gastrointestinal symptoms (Stoffel et al., 2017). It has been observed that absorption is increased when tea, coffee and milk are avoided during oral iron therapy. Gastrointestinal side effects such as constipation, heartburn, nausea, darkening of the stool are observed. In a meta-analysis of 43 randomized studies, it was reported that 70% of patients using oral iron preparations experienced gastrointestinal disturbances and decreased adherence to treatment (Tolkien et al., 2015). In patients who cannot tolerate it, the dose can be reduced, or IV iron preparations are used (Pavord et al., 2020). As all oral iron preparations have similar efficacy and side effects, preparation changes are not recommended. We do not prefer to use enteric-coated and timed formulations as they reduce absorption and have the potential to impair treatment (Pavord et al., 2012).

Since iron absorption is impaired in patients with inflammatory bowel disease (ulcerative colitis, Crohn's disease) and undergoing bariatric surgery, IV iron therapy is recommended.

The use of intravenous iron therapy in the first trimester is also not recommended because there is no safe data. It can be initiated after 13-14 weeks (Achebe et al., 2017). IV iron preparations used are Iron dextran, Ferric gluconate, Iron sucrose, Ferric carboxymaltose, ferumoxytol and ferric derisomaltose. Studies on the use of IV iron in the second and third trimesters have shown that it provides less side effects and faster effectiveness. In the study in which IV iron treatment was applied due to iron deficiency anemia in the later weeks of pregnancy; Iron deficiency

anemia was not found in any of the newborns (Auerbach et al., 2017). We have a low threshold for switching from an oral preparation to an IV preparation for iron deficiency anemia in the second and third trimesters of pregnancy (Auerbach et al., 2020). Studies show that all IV iron products have equivalent efficacy and safety (Froessler et al., 2018; Govindappagari et al., 2019; Weström et al., 2020). We avoid using formulations containing only benzyl alcohol (due to potential risks to the fetus) (Hiller et al., 1986; Hardin et al., 1987). In addition, we do not prefer to use iron sucrose as it requires 4-5 infusions instead of a single infusion. The choice of product depends on the cost and load. There is no need for premedication. A single dose of glucocorticoid and histamine receptor blocker (ranitidine, famotidine) can be administered to prevent minor infusion reactions in patients with a history of inflammatory arthritis and inflammatory bowel disease or in patients with drug allergies.

Response to iron therapy; Approximately one week later, an increase in erythrocyte production is observed, which starts with reticulocytosis. It is a 1 g/dl increase in Hb levels within 2-3 weeks and serum ferritin returns to the normal range after three weeks (Prewusnyk et al., 2002; Cristoph et al., 2012). The response to oral and IV iron therapy is similar. If the response to treatment is inadequate, non-adherence to treatment, continued bleeding, impaired absorption, or other causes of anemia may be considered (Pavord et al., 2020). For patients receiving oral iron therapy, hemoglobin and reticulocyte counts are evaluated approximately 2-3 weeks later, and whether the patient tolerates oral preparations is questioned. If the desired response is obtained in laboratory values and can tolerate oral treatment, it is continued until the end of pregnancy and postpartum. However, if we did not get the expected response and patients who cannot tolerate oral iron, IV iron treatment (second and third trimester pregnant women) is initiated. In patients treated with intravenous iron, iron parameters are evaluated after approximately 4-8 weeks (Kitasi et al., 2015). In the UK 2019 guideline, it has been suggested that it can be followed by Hb levels without looking at iron parameters (Pavord et al., 2020). When hemoglobin reaches the normal range, oral iron therapy should be continued for three months and for six weeks postpartum.

Erythrocyte transfusion is preferred in cases where vital signs such as postpartum hemorrhage with intervention, atonia, ablatio placenta, placenta previa and coagulopathy are unstable (ACOG Practice Bulletin No: 95,

2008). Severe anemia (Hb <6 g/dl) in pregnancy is associated with abnormal fetal heart rate beat, oligohydramnios and fetal death. Transfusion should be considered in these patients as well. Transfusion is also considered in pregnant women with acute blood loss and Hb <7.

Evaluation of postpartum anemia is based on clinical experience. Postpartum routine complete blood count and ferritin control are not recommended. We recommend appropriate vitamin and iron replacement for 6-8 weeks for patients to replenish their iron stores due to postpartum blood loss. After discharge, symptoms such as fatigue, depressed mood, or exercise intolerance may also be suspected, and a complete blood count can be performed. Patients with anemia are treated. It is reasonable to check ferritin levels and transferrin saturation 2-3 weeks later in patients who start postpartum anemia treatment before discharge. Some studies evaluating the prevalence of postpartum anemia have revealed the incidence to be common (Swaim et al., 1999; Medina et al., 2018).

REFERENCES

- Achebe M.M., Gafter-Gvili A. (2017). How I treat anemia in pregnancy: iron, cobalamin, and folate. *Blood*; 129:940-949
- ACOG Practice Bulletin No. 95. (2008). Anemia in pregnancy. *Obstetrics and Gynaecology*; 112:201.
- ACOG Practice Bulletin Number.233.(2021). *Obstetrics. Anemia in Pregnancy*:. *Obstetrics and Gynecology*; 138:e55.
- Alwan N.A., Cade J.E., McArdle H.J., Greenwood D.C., Hayes H.E., Simpson N.A. (2015). Maternal iron status in early pregnancy and birth outcomes: insights from the Baby's Vascular health and Iron in Pregnancy study. *British Journal of Nutrition*; 113(12):1985–1992.
- American College of Obstetricians and Gynecologists (ACOG). (2003). Folic Acid for the Prevention of Recurrent Neural Tube Defects. ACOG Committee Opinion No. 252. Washington, DC,
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins *Obstetrics. Anemia in Pregnancy: ACOG Practice Bulletin, Number 233. (2021). Obstetrics and Gynecology*; 138:e55.
- American College of Obstetricians and Gynecologists. (2008). ACOG Practice Bulletin No. 95: anemia in pregnancy. *Obstetrics and Gynecology*;112(1):201. [Review]
- Antony K.M., Racusin D.A., Aagaard K., Dildy G.A. (2021). Maternal Physiology. In London M.B, Galan H.L., Jauniaux E.R.M., Driscoll D.A. (eds). *Gabbe's Obstetrics: Normal and Problem Pregnancies, Eighth Edition Philadelphia, Elsevier pp 43- 67*
- Ashley E. Benson, Marcela C. Smid. (2022). Maternal Anemia. In Berghella V (ed). *Maternal- Fetal Evidence Based Guidelines, Fourth Edition. Philadelphia, Taylor & Francis Group pp: 142-152.*
- Auerbach M., Abernathy J., Juul S., et al. (2021). Prevalence of iron deficiency in first trimester, nonanemic pregnant women. *Journal of Maternal-Fetal and Neonatal Medicine*; 34:1002.
- Auerbach M., Georgieff M.K. (2020). Guidelines for iron deficiency in pregnancy: hope abounds: Commentary to accompany: UK guidelines on the management of iron deficiency in pregnancy. *British Journal of Haematology*; 188:814.
- Auerbach M., James S.E., Nicoletti M., et al. (2017). Results of the First American Prospective Study of Intravenous Iron in Oral Iron-Intolerant Iron-Deficient Gravidas. *The American Journal of Medicine*; 130:1402
- Auerbach M., James S.E., Nicoletti M., Lenowitz S., London N., Bahrain H.F., Derman R., Smith S. (2017). Results of the First American Prospective Study of Intravenous Iron in Oral Iron-Intolerant Iron-

- Deficient Gravidas. *The American Journal of Medicine*; 130:1402–1407.
- Azulay C.E., Pariente G., Shoham-Vardi I., et al. (2015). Maternal anemia during pregnancy and subsequent risk for cardiovascular disease. *Journal of Maternal-Fetal and Neonatal Medicine*; 28:1762.
- Bibbins-Domingo K., Grossman D.C., et al. (2017). Folic Acid Supplementation for the Prevention of Neural Tube Defects: US Preventive Services Task Force Recommendation Statement. *JAMA*; 317:183.
- Boafor T.K., Olayemi E., Galadanci N. et al. (2016) Pregnancy outcomes in women with sickle-cell disease: a systematic review and meta-analysis. *BJOG*, 123:691–698.
- Breymann C., Auerbach M. (2017). Iron deficiency in gynecology and obstetrics: clinical implications and management. *Hematology: the American Society of Hematology Education Program*; 2017(1):152–159. [Review]
- Campbell B.A. (1995). Megaloblastic anemia in pregnancy. *Clinical Obstetrics and Gynecology*; 38:455.
- Cantor A.G., Bougatsos C., Dana T., Blazina I., McDonagh M. (2015). Routine iron supplementation and screening for iron deficiency anemia in pregnancy: a systematic review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*; 162(8):566–576.
- Centers for Disease Control (CDC). (1989). Criteria for anemia in children and childbearing-aged women. *MMWR, Morbidity and Mortality Weekly Report*; 38:400–404.
- Christoph P., Schuller C., Studer H., et al. (2012). Intravenous iron treatment in pregnancy: comparison of high-dose ferric carboxymaltose vs. iron sucrose. *Journal of Perinatal Medicine*; 40:469.
- Corwin E.J., Murray-Kolb L.E., Beard J.L. (2003). Low hemoglobin level is a risk factor for postpartum depression. *Journal of Nutrition*; 133(12):4139–4142.
- Daru J., Allotey J., Peña-Rosas J.P., Khan K.S. (2017). Serum ferritin thresholds for the diagnosis of iron deficiency in pregnancy: a systematic review. *Transfusion Medicine*; 27(3):167–174. [Systematic Review, 76 trials]
- Daru J., Zamora J., Fernández-Félix B.M., et al. (2015) Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. *Lancet Global Health*; 6:e548.
- de Benoist B., McLean E., Egli I., Cogswell M. (2008). Worldwide prevalence of anaemia 1993-2005. World Health Organization; WHO Global Database on Anaemia, Geneva.

- Drukker L., Hants Y., Farkash R., Ruchlemer R., Samueloff A., Grisaru-Granovsky S. (2015). Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. *Transfusion*; 55:2799–2806.
- Froessler B., Gajic T., Dekker G., Hodyl N.A. (2018). Treatment of iron deficiency and iron deficiency anemia with intravenous ferric carboxymaltose in pregnancy. *Archives of Gynecology and Obstetrics*; 298:75.
- Govindappagari S., Burwick R.M. (2019). Treatment of Iron Deficiency Anemia in Pregnancy with Intravenous versus Oral Iron: Systematic Review and Meta-Analysis. *American Journal of Perinatology*; 36:366.
- Hamm R.F., Wang E.Y., Levine L.D., et al. (2022). Implementation of a protocol for management of antepartum iron deficiency anemia: a prospective cohort study. *American Journal of Obstetrics and Gynecology*; 4:100533.
- Hardin B.D., Schuler R.L., Burg J.R., et al. (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratog Carcinog Mutagen*; 7:29.
- Harrison R.K., Lauhon S.R., Colvin Z.A., McIntosh J.J. (2021). Maternal anemia and severe maternal morbidity in a US cohort. *American Journal of Obstetrics and Gynecology*; 3:100395
- Hiller J.L., Benda G.I., Rahatzad M., et al. (1986). Benzyl alcohol toxicity: impact on mortality and intraventricular hemorrhage among very low birth weight infants. *Pediatrics*; 77:500.
- Howard J., Oteng-Ntim E. (2012). The obstetric management of sickle cell disease. *Best Prac Res Clin Obstetrics and Gynecology*; 26 25–36
- Institute of Medicine Panel on Micronutrients. (2001). *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. A report of the panel on micronutrients and of interpretation and uses of dietary reference intakes, and the standing committee on the scientific evaluation of dietary reference intakes.* National Academy Press. [Review]
- Kaur S., Khanz S., Nigam A. (2014). Hematological profile and pregnancy: a review. *International Journal Of Advances In Medicine*; 1:68-70
- Kılpatrick S.J., Kitahara S. (2019). Anemia and Pregnancy. In Resnik R., Lockwood C.J., Greene M.F., Copel JA, Silver RM (eds) *Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice, Eighth Edition.* Philadelphia, Elsevier pp 991- 1006

- Kitsati N., Liakos D., Ermeidi E., et al. (2015). Rapid elevation of transferrin saturation and serum hepcidin concentration in hemodialysis patients after intravenous iron infusion. *Haematologica*; 100:e80
- Lewkowitz A.K., Gupta A., Simon L., et al. (2019). Intravenous compared with oral iron for the treatment of iron-deficiency anemia in pregnancy: a systematic review and meta-analysis. *Journal of Perinatology*; 39:519.
- MacQueen B.C., Christensen R.D., Ward D.M., et al. (2017). The iron status at birth of neonates with risk factors for developing iron deficiency: a pilot study. *Journal Perinatology*; 37:436.
- Maroto A., Martinez-Diago C., Tio G. et al. (2020). Autoimmune hemolytic anemia in pregnancy: a challenge for maternal and fetal follow-up, *Journal of Maternal-Fetal and Neonatal Medicine*; DOI: 10.1080/14767058.2020.1732344
- McDonagh M., Cantor A., Bougatsos C., et al. (2015). Routine iron supplementation and screening for iron deficiency anemia in pregnant women: A systematic review to update the US Preventive Services Task Force recommendation. Agency for Healthcare Research and Quality (US); US Preventive Services Task Force Evidence Syntheses, Rockville.
- Medina Garrido C., León J., Román Vidal A. (2018). Maternal anaemia after delivery: prevalence and risk factors. *Journal of Obstetrics and Gynaecology*; 38:55.
- Mei Z., Cogswell M.E., Looker A.C. et al. (2011). Assessment of iron status in US pregnant women from the National Health and Nutrition Examination Survey (NHANES), 1999-2006. *The American Journal of Clinical Nutrition*; 93:1312–20
- Mohamed M.A., Ahmad T., Macri C., Aly H. (2012). Racial disparities in maternal hemoglobin concentrations and pregnancy outcomes. *Journal of Perinatal Medicine*; 40:141.
- Muñoz M., Peña-Rosas J.P., Robinson S., Milman N., Holzgreve W., Breyman C., et al. (2018). Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. *Transfusion Medicine*; 28(1):22–39. [Review]
- Patila V., Ratnayake G., Fastovets G. (2017). Clinical ‘pearls’ of maternal critical care Part 2: sickle-cell disease in pregnancy. *Current Opinion in Anesthesiology*; 30:326–334
- Pavord S., Daru J., Prasannan N., Robinson S., Stanworth S., Girling J., BSH Committee. (2020). UK guidelines on the management of iron deficiency in pregnancy. *British Journal of Haematology*; 188(6):819–830. [Review]

- Pavord S., Myers B., Robinson S. et al. (2012). UK guidelines on the management of iron deficiency in pregnancy. *British Journal of Haematology*; 156:588–600
- Peña-Rosas J.P., De-Regil L.M., Gomez Malave H., Flores-Urrutia M.C., Dowswell T. (2015). Intermittent oral iron supplementation during pregnancy. *Cochrane Database System Review*; (10):CD009997.
- Perewusnyk G., Huch R., Huch A., Breymann C. (2002). Parenteral iron therapy in obstetrics: 8 years experience with iron-sucrose complex. *British Journal of Nutrition*; 88:3
- Radlowski E.C., Johnson R.W. (2013). Perinatal iron deficiency and neurocognitive development. *Frontiers in Human Neuroscience*; 7:585.
- Revez L., Gyte G.M., Cuervo L.G., Casasbuenas A. (2011). Treatments for iron-deficiency anaemia in pregnancy. *Cochrane Database Systems Review*; CD003094.
- Roy N.B.A., Pavord S. (2018). The management of anaemia and haematinic deficiencies in pregnancy and post-partum. *Transfusion Medicine*; 28: 107–116
- Ruiz de Viñaspre-Hernández R., Gea-Caballero V., Juárez-Vela R., Iruzubieta-Barragán F.J. (2021). The definition, screening, and treatment of postpartum anemia: A systematic review of guidelines. *Birth*; 48:14.
- Samuels P. (2021). Hematologic Complications of Pregnancy. In London MB, Galan HL, Jauniaux ERM, Driscoll DA (eds) *Gabbe's Obstetrics: Normal and Problem Pregnancies, Eighth Edition Philadelphia, Elsevier* pp 954- 971
- Siu A.L. (2015). Screening for iron deficiency anemia and iron supplementation in pregnant women to improve maternal health and birth outcomes: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*; 163(7):529–536. [Review]
- Stoffel N.U., Cercamondi C.I., Brittenham G., et al. (2017). Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *The Lancet Haematology*; 4:e524.
- Sultan P., Bampoe S., Shah R., et al. (2019). Oral vs intravenous iron therapy for postpartum anemia: a systematic review and meta-analysis. *American Journal of Obstetrics and Gynecology*; 221:19.
- Swaim L.S., Perriatt S., Andres R.L., et al. (1999). Clinical utility of routine postpartum hemoglobin determinations. 1 *American Journal of Perinatology*; 16:333.

- T.C. SAĞLIK BAKANLIĞI. (2007). Gebelerde demir destek programı uygulaması yönergesi 2007/6. Sayı: B100AÇS0120000/010.06.01.122
- Tolkien Z., Stecher L., Mander A.P., et al. (2015). Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS One*; 10:e0117383.
- Tongsong T., Srisupundit K., Luewan S. (2009). Outcomes of pregnancies affected by hemoglobin H disease. *International Journal of Gynecology & Obstetrics*; 104:206-8
- Van den Broek N.R., Letsky E.A., White S.A., Shenkin A. (1998). Iron status in pregnant women: which measurements are valid? *British Journal of Haematology*; 103(3): 817–824.
- Wesström J. (2020). Safety of intravenous iron isomaltoside for iron deficiency and iron deficiency anemia in pregnancy. *Archives of Gynecology and Obstetrics*; 301:1127
- WHO. (2001). Iron deficiency anaemia. Assessment prevention, and control. A guide for programme managers. Geneva (Switzerland): World Health Organization
- WHO. (2012). World Health Organization. Daily iron and folic acid supplementation in pregnant women. Geneva
- WHO. (2017). Nutritional anaemias: tools for effective prevention and control. World Health Organization; <https://apps.who.int/iris/bitstream/handle/10665/259425/9789241513067-eng.pdf> [Review]
- World Health Organization (WHO). (2011). Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations. Vitamin and Mineral Nutrition Information System April 29
- World Health Organization. (2013). Preconception care to reduce maternal and childhood mortality and morbidity. WHO HQ; Geneva.
- Zhou L.M., Yang W.W., Hua J.Z., Deng C.Q., Tao X., Stoltzfus R.J. (1998). Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China.

CHAPTER 5

FIRST TRIMESTER BLEEDING AND ADMINISTRATION

Dr. Yusuf DAL¹

¹ Mersin University Medical School Department Of Obstetric And Gynecology
dryusufdal@gmail.com ORCID ID: 0000-0001-7162-4644

INTRODUCTION

Vaginal bleeding is a frequently seen common condition during all stages of pregnancy. Approximately 20% of pregnant women happen to experience vaginal bleeding during the first trimester (Krause et al., 1999). Determining and evaluating the common causes of vaginal bleeding during pregnancy varies according to the gestational week. Spontaneous abortion and ectopic pregnancy are among the most common identifiable causes of vaginal bleeding in the early stages of pregnancy (McKennett et al., 1995). Between 50% and 70% of spontaneous abortions are due to genetic abnormalities. Bleeding may result from disruption of the vascularity in the decidua or from various cervical or vaginal lesions. In case of vaginal bleeding, further evaluation to determine the normal or abnormal development of pregnancy or a pathological condition that necessitates intervention is required. The widespread use of transvaginal ultrasound in first trimester pregnancies has provided us with an increasing amount of data on the first trimester embryo. Pelvic ultrasound and quantitative beta-human chorionic gonadotropin (Beta HCG) measurements are administered for the evaluation of bleeding in early stages during pregnancy (McKennett et al., 1995). In case of a patient with first trimester bleeding, sonographic findings should correlate with serum Beta HCG levels to arrive at an appropriate clinical diagnosis.

The topic we address here is to provide an overview of the etiology and evaluation of the first trimester bleeding during pregnancy. The specific causes and administration of bleeding are discussed in detail separately.

FIRST TRIMESTER BLEEDING

First trimester vaginal bleeding is bleeding up to 13 weeks and 6 days of gestational age. Abnormal vaginal bleeding on part of sexually active women and in particular of women who are not on birth control, need to be considered as pregnancy-related until proven otherwise (Snell, 2009). Vaginal bleeding in the first trimester is a common condition (Wittels et al., 2008). The incidence of bleeding in the first trimester is approximately 20% (Hendriks et al., 2019), and approximately half of these pregnancies result in miscarriage. Bleeding may be a normal sign of implantation, a precursor to the onset of spontaneous abortion, or a sign of a pathological condition such as an ectopic pregnancy or gestational trophoblastic disease. Bleeding can be

any combination of mild or heavy, intermittent or continuous, painless or painful.

The five main causes of first trimester bleeding are implantation bleeding, early pregnancy loss, threatened miscarriage, ectopic pregnancies, and cervical, vaginal or uterine pathologies.

The most common causes of first trimester bleeding are early pregnancy loss and bleeding due to the threatened miscarriage. Although ectopic pregnancy is less common, it is the most serious condition of first trimester bleeding. Ectopic pregnancy rupture is a complication that potentially increases mortality.

IMPLANTATION BLEEDING

In the first weeks of the gestational period, the term implantation bleeding is used to describe spotting or bleeding that does not exceed one sanitary pad per day. Due to the fact that timing is rather early, bleeding during early pregnancy can be mistaken for menstrual bleeding (Harville et al., 2003).

According to a study published by Harville et al. in 2003, 221 healthy women trying to conceive were included in the study and clinical pregnancy occurred in 151 women during the study. A total of 9% of women with clinical pregnancies reported bleeding for at least 1 day during early pregnancy. The bleeding was typically observed as mild and only one or two sanitary pads or tampons were required throughout 24 hours. The data in this study suggest that bleeding for several days in early pregnancy is not an uncommon event, and that such bleeding also has little to do with the eventual success of the pregnancy. An increased risk of miscarriage has not been demonstrated in pregnant women experiencing this condition.

ABORTUS IMMINENS

It is seen in 20-25% of all pregnancies and is a threatened miscarriage (Zhou et al., 2019). Bleeding observed in the presence of an intrauterine pregnancy with sonographically detectable fetal cardiac activity while the cervix is closed is called abortus imminens. Bleeding is mild, there may be mild pain, and cervical movements are allowed. It should be differentiated from implantation bleeding observed at the expected menstrual date.

Bleeding in these cases is likely due to disruption of the decidual vessels at the maternal-fetal interface. These separations are usually not

visualized by ultrasound, but sometimes emerge as a subchorionic hematoma. The risk of early pregnancy loss increases in the presence of subchorionic hematoma and bleeding.

About half of early pregnancy bleedings result in miscarriage, but this risk decreases drastically once fetal cardiac activity occurs. In a study by Tongsong et al., the risk of miscarriage was found to be significantly higher in low-threat pregnancies when compared to those with sonographically visible heartbeat and those with abortion threat and normal pregnancies (relative miscarriage risk is 2.91).

While 50% of the threats of abortion with sonographically intrauterine pregnancy and before detectable fetal cardiac activity result in miscarriage, it is predicted to reach the 24th week of gestation and beyond at a rate of 85-90% after detectable fetal cardiac activity occurs (Chung et al., 1999). In a study published by Tannirandom et al. in 2003, the incidence of fetal loss was found to be 3.4% in the threatened miscarriage after the detection of fetal cardiac activity.

Most cases of abortion imminens do not cause pregnancy loss but are associated with increased complications in late pregnancy:

- The risk of pregnancy loss increases: Approximately 12%, this risk is 5-6% in those who do not have bleeding.
- Preterm birth
- Intrauterine growth retardation
- Preterm premature rupture of membranes
- Placental abruption
- Placenta previa
- Manual removal of the placenta
- Cesarean delivery

In a study in which the effect of threat of abortion on pregnancy outcomes was examined and 24,835 pregnant women were analyzed retrospectively, pregnant women were divided into two groups according to whether there was a threatened miscarriage in the first trimester or not. The rates of cesarean section delivery were found to be statistically significantly higher in the low threat group. The rates of hyperemesis gravidarum, gestational diabetes mellitus and placenta previa were found to be statistically significant and more frequent in pregnancies with low threat

than in the control group. It was found that the birth weight of newborns was significantly lower in pregnancies with low threat (Kanmaz et al., 2019). In addition, complications such as preterm labor and intrauterine growth retardation may occur in these pregnancies in the later weeks of pregnancy (Breeze, 2016).

MISCARRIAGES

Abortion is defined as spontaneous or induced termination of pregnancy before fetal viability occurs (Cunningham et al., 2013). Not all pregnancies result in a live birth. About half of spontaneous pregnancies are lost before the first trimester is completed, usually before implantation or on the expected menstrual period (Jauniaux et al., 2006). After clinical diagnosis, usually 10 to 12% of pregnancies are lost before 8 weeks.

The World Health Organization defines the birth of a fetus before the 20th week of pregnancy or weighing less than 500 grams as miscarriage. The average weight of the 20-week fetus is 320 grams, and for the 22-23 week-old fetuses this average weight is 500 grams (Moore, 1977). These criteria are therefore partially inconsistent. Termination of pregnancy before fetal viability is achieved would be a more accurate term for abortion.

Abortion can be abortus incipient, missed abortion, incomplete abortion or complete abortion. The characteristics of these four conditions are different. Cervical effacement and patency, severity of pain and amount of bleeding vary.

Abortus incipient has severe pain in the groin, excessive vaginal bleeding, and cervical dilation. The amount of bleeding is often greater than other causes of miscarriage. Fetal tissue has not yet been excreted. Cervical dilation and rupture of membranes are likely to have an increasing effect on uterine contractions (Vink et al., 2016). Abortion is considered inevitable in case of bleeding and fever with increased uterine contractions. In these cases, miscarriage cannot be prevented and curettage is performed.

In missed abortion, there is no sonographic intrauterine fetal cardiac activity and fetal tissue is not excreted despite a certain period of time. The cervix is closed. There is no pain or bleeding and very little. They may cause disseminated intravascular coagulation (DIC).

Incomplete abortion is a condition in which the fetus and placental attachments are partially expelled from the uterine cavity, cervical opening and vaginal bleeding. The gestational sac is often irregular in shape. Fetus

and placenta attachments are usually excreted together before the 10th gestational week, but separately after this week.

In complete abortion, the fetus and placental appendages are completely thrown out of the uterine cavity. The cervical os is closed during the examination. Differential diagnosis with ectopic pregnancy is important. Initial sonographies may be important for differential diagnosis. Serum Beta HCG levels are helpful in diagnosis. Beta HCG levels drop rapidly in complete abortion.

Septic abortion is a serious febrile condition. Endometritis is the most common clinical finding. There may be parametritis, peritonitis, septicemia and shock. There are fever, foul-smelling vaginal discharge and bleeding, tenderness on abdominal examination, severe pain in cervical movements (Torres et al., 2012). Disseminated intravascular coagulation (DIC) may develop.

Anembryonic pregnancies account for approximately half of first trimester pregnancy losses. Diagnosis of anembryonic pregnancy is made when the gestational sac diameter is >20 mm in transvaginal ultrasonography, but the structures of the embryo cannot be shown (Morin et al., 2016). The remaining half consists of embryonic losses. Chromosomal anomalies are observed in half of the embryonic losses (Eiben et al., 1990). The most common chromosomal abnormalities are autosomal trisomies, among which trisomy 16 is the most common (Simpson et al., 2007).

The exact cause of the miscarriages is not clearly understood. Environmental, genetic and various medical conditions are held responsible. Maternal infections, advanced maternal age, medical conditions such as diabetes mellitus and thyroid diseases, maternal drug use, intrauterine device pregnancy, previous abortion history, cancer treatments, surgical procedures and trauma, nutritional disorders, use of smoking and other substances, immunological factors, uterine disorders and short interpregnancy periods are conditions that increase the risk of miscarriage in the first trimester.

In many cases, miscarriage does not recur. While the risk of miscarriage in the next pregnancy is about 20% in a woman who has had a miscarriage once, this risk reaches 35% in a woman who has had three miscarriages (Garrido-Gimenez et al., 2015). If fetal cardiac activity is observed and under the age of 35, the risk of miscarriage is around 4%, above the age of 40 this risk rises to 30%.

ECTOPIC PREGNANCY

It is defined as the implantation of the fertilized ovum outside the uterine cavity and the incidence is monitored to be approximately 2% (Moonen-Delarue et al., 1996). It is commonly seen in the 35-44 age group. Ectopic pregnancies constitute 9% of pregnancy-related maternal deaths. Ectopic pregnancies are the most commonly observed causes of maternal death during the first trimester (Sharma et al., 2020). Pain, vaginal bleeding and delayed menstruation are the most common findings. The details of this topic are described in another section.

OTHER CAUSES

Various vaginal and cervical infections, genital tumors, lacerations, cervical polyps, ectropion, uterine anomalies and fibroids, molar pregnancies cause bleeding in the first trimester. The details of this topic are described in another section.

ADMINISTRATION OF FIRST TRIMESTER BLEEDING

Vaginal bleeding in early pregnancy requires emergency intervention in some cases. The aim of the evaluation is to make the diagnosis as definitively as possible, but the exact etiology of first trimester vaginal bleeding often cannot be determined. Review of previous ultrasonography; It can help determine gestational age and pregnancy location. Patients should be asked about the amount of pain and bleeding. Bleeding equal to or heavier than the menstrual period and accompanied by pain are associated with an increased risk of early pregnancy loss (Johns et al., 2006). Patients should be evaluated for signs and symptoms of hypovolemia. Vital signs or peritoneal findings suggesting hemodynamic instability on physical examination require urgent evaluation.

In a hemodynamically unstable patient, intra-abdominal bleeding due to ectopic pregnancy rupture, massive vaginal bleeding due to incomplete abortion caused by incomplete expulsion of pregnancy products from the uterine cavity, and cervical shock as a result of parasympathetic stimulation due to abortion material remaining in the cervix should be considered in the differential diagnosis (Güler, 2020). In hemodynamically unstable patients, first of all, it is necessary to stabilize the patient. For this, intravenous fluid treatments and blood replacement can be done. Abdominal examination should be evaluated. The uterine cavity and adnexa are evaluated by

ultrasonography and the presence of intra-abdominal bleeding is investigated. Management is planned in line with these findings. If there is no intra-abdominal bleeding and the patient is hemodynamically stable, a detailed history is taken and a physical examination is performed. Complete blood count, serum Beta HCG, blood group test are requested and ultrasonographic examination is performed.

The first measurable finding in pregnancy is the high level of Beta HCG produced by the placenta after blastocyst implantation (Deutchman et al., 2009). This level of Beta HCG occurs approximately on the 23rd day of the last menstrual period, or eight days after conception. Therefore, it is possible to diagnose pregnancy before a missed period.

Quantitative serum Beta HCG levels predictably rise during the first four to eight weeks of normal pregnancy, increasing by at least 66% every 48 hours (Breeze, 2016). This rate of increase in Beta HCG levels is reassuring, but not indicative of a normal pregnancy (Deutchman et al., 2009). Insufficiently elevated Beta HCG levels do not differentiate between ectopic and failed intrauterine pregnancy. Unexpectedly high levels of Beta HCG warrant evaluation of gestational trophoblastic disease.

Serum progesterone levels are measured >25 ng/ml for 70% of intrauterine pregnancies (Gracia et al., 2001). Approximately 2% of serum progesterone levels in ectopic pregnancies are >25 ng/ml. High progesterone levels >25 ng/ml largely rule out ectopic pregnancies. When the progesterone level is <5 ng/ml, the probability of normal intrauterine pregnancy is 1/1500, and this value may lead to a dead fetus or ectopic pregnancy (Rausch et al., 2012).

Early detection of pregnancy is possible using transvaginal ultrasonography with a frequency of 5 MHz or higher (Deutchman et al., 2009). A 15 mm long sonolucent gestational sac is expected to be visible in the endometrium by the end of 5. week of gestation. The central blastocyst surrounded by a double echogenic chorionic villi and a ring of decidua separates the normal sac of an intrauterine pregnancy from a pseudogestational sac associated with an ectopic pregnancy (Gupta et al., 2007).

Yolk sac can be seen using transvaginal ultrasonography at 6 weeks of gestation. This confirms intrauterine pregnancy. By the end of the sixth week, a 2 to 5 mm embryo or fetal pole becomes visible (Deutchman et al., 2009). Measurement of embryonic crown-rump length (CRL) is

acknowledged as the most accurate method to determine gestational age. Fetal cardiac activity should be present when the length of the embryo exceeds 5 mm (Rhodes et al., 2002). The transabdominal scan is less sensitive and will show these highlights approximately one week after they appear transvaginally. When intrauterine pregnancy is detected on ultrasonography but fetal cardiac activity is uncertain, repeat ultrasonography should be performed within seven to ten days to confirm viability (Doubilet et al., 2013). A normal increase in the beta HCG level or a normal progesterone level may be reassuring in these situations.

Embryological events in early pregnancy occur in a predictable, gradual fashion. Early pregnancy loss or ectopic pregnancy may be raised as suspicion in case of a deviation from this established pattern (Rodgers et al., 2015). Intrauterine gestational sac at serum Beta HCG 1500-2000 IU/L levels should be seen by transvaginal ultrasonography (Paspulati et al., 2004). If the gestational sac or other pregnancy products are not monitored in these values, the possibility of ectopic pregnancy is high.

Since ectopic pregnancy is a life-threatening condition, it is important to evaluate it immediately. The first step in evaluating an ectopic pregnancy is to determine whether the patient has had an ultrasound examination and the results of this examination. Prior documentation of pregnancy in a normal intrauterine location immediately narrows the differential diagnosis. Adnexal tenderness and the presence of a mass may indicate an ectopic pregnancy (Deutchman et al., 2009). Hypotension, along with other symptoms of hemoperitoneum, may indicate a ruptured ectopic pregnancy and require urgent hospitalization for evaluation. The details of this issue are described in another section.

Examination with a vaginal speculum may reveal non-obstetric causes of bleeding such as cervicitis, vaginitis, cystitis, trauma, cervical cancer or polyps, or non-vaginal causes of bleeding such as hemorrhoids.

In threatened abortion, management is in the form of monitoring. Bed rest is recommended but has not been shown to improve pregnancy outcomes. The results of progesterone therapy are controversial. In a study that included 913 pregnant women in which 51 studies were meta-analyzed, it was shown that progesterone treatment reduced the risk of miscarriage in case of threat of miscarriage (Lee et al., 2017). In a meta-analysis of nine randomized control studies, which included 4907 pregnant women, a decrease in miscarriage rates was demonstrated when progesterone treatment

was compared with placebo, and no significant difference was observed in terms of preterm birth and live birth (Yan et al., 2021).

According to the amount of bleeding, pain status and the patient's wishes, one from the expectant, medical and surgical treatment options can be selected in complete, incomplete and delayed abortions. Patient satisfaction, psychological outcomes, infection rates, and future fertility are similar between these treatments (Neilson et al., 2013). Surgical methods are dilatation and curettage (D&C), dilatation and evacuation (D&E), hysterotomy or hysterectomy. Vacuum curettage is the most effective and safest method for terminating pregnancies less than 14 weeks of gestation. Sharp curettage 14-15. It can be applied if there is no vacuum curette in pregnancies less than the gestational week. D&E are applied in pregnancies older than 16 weeks of gestation. The complication rate is high. Hysterotomy or hysterectomy are not used as the first method. Mifepristone (antiprogestone), misoprostol (prostaglandin E1 analogue) and methotrexate (antimetabolite) are used as medical abortion methods (Paul et al., 2009). In the case of massive bleeding, severe pain or fever in abortus incipient, miscarriage is inevitable and the pregnancy is terminated. Curettage in incomplete abortion, medical abortion or waiting treatment in clinically stable patients can be applied. In surgical treatment, the remaining pregnancy product can be removed by vacuum curettage. In complete abortion, follow-up is sufficient and may not require surgical intervention. In missed abortion, one of the medical treatment or surgical methods may be preferred. Uterine aspiration is the procedure of choice for the surgical treatment of early pregnancy loss. Compared to sharp curettage, vacuum aspiration is associated with reduced pain, shorter procedure time, and less blood loss (Tunçalp et al., 2010).

Anti-D immunoglobulin should be administered to pregnant women who are Rh negative following abortions, bleeding or curettage (Coppola et al., 2003).

REFERENCES

- Abortion. Cunningham F, & Leveno K.J., & Bloom S.L., & Spong C.Y., & Dashe J.S., & Hoffman B.L., & Casey B.M., & Sheffield J.S.(Eds.), (2013). *Williams Obstetrics*, Twenty-Fourth Edition. McGraw Hill.
- Breeze, C. (2016). Early pregnancy bleeding. *Australian family physician*, 45(5), 283-286.
- Chung, T. K. H., Sahota, D. S., Lau, T. K., Mongelli, J. M., Spencer, J. A. D., & Haines, C. J. (1999). Threatened abortion: prediction of viability based on signs and symptoms. *Australian and New Zealand journal of obstetrics and gynaecology*, 39(4), 443-447.
- Coppola, P. T., & Coppola, M. (2003). Vaginal bleeding in the first 20 weeks of pregnancy. *Emergency Medicine Clinics*, 21(3), 667-677.
- Deutchman, M., Tubay, A. T., & Turok, D. K. (2009). First trimester bleeding. *American family physician*, 79(11), 985-992.
- Doubilet, P. M., Benson, C. B., Bourne, T., Blaivas, M., Barnhart, K. T., Benacerraf, B. R., ... & Goldstein, S. R. (2013). Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy. Barnhart KT, Benacerraf BR, Brown DL, Filly RA, Fox JC, Goldstein SR, Kendall JL, Lyons EA, Porter MB, Pretorius DH, Timor-Tritsch IE. Diagnostic criteria for nonviable pregnancy early in the first trimester. *N Engl J Med*, 369(15), 1443-51.
- Eiben, B., Bartels, I., Bähr-Porsch, S., Borgmann, S., Gatz, G., Gellert, G., ... & Hansmann, I. (1990). Cytogenetic analysis of 750 spontaneous abortions with the direct-preparation method of chorionic villi and its implications for studying genetic causes of pregnancy wastage. *American journal of human genetics*, 47(4), 656.
- Garrido-Gimenez, C., & Alijotas-Reig, J. (2015). Recurrent miscarriage: causes, evaluation and management. *Postgraduate medical journal*, 91(1073), 151-162.
- Gracia, C. R., & Barnhart, K. T. (2001). Diagnosing ectopic pregnancy: decision analysis comparing six strategies. *Obstetrics & Gynecology*, 97(3), 464-470.
- Gupta, N., & Angtuaco, T. L. (2007). Embryosonology in the first trimester of pregnancy. *Ultrasound Clinics*, 2(2), 175-185.
- Güler B. (2020). *Birinci Trimester Kanamaları ve Yönetimi:Obstetrik Kanamalar*. Akademisyen Kitabevi. Ankara, 87.
- Harville, E. W., Wilcox, A. J., Baird, D. D., & Weinberg, C. R. (2003). Vaginal bleeding in very early pregnancy. *Human Reproduction*, 18(9), 1944-1947.
- Hendriks, E., MacNaughton, H., & MacKenzie, M. C. (2019). First trimester bleeding: evaluation and management. *American family physician*, 99(3), 166-174.
- Jauniaux, E., Poston, L., & Burton, G. J. (2006). Placental-related diseases of pregnancy: involvement of oxidative stress and implications in human evolution. *Human reproduction update*, 12(6), 747-755.
- Johns, J., & Jauniaux, E. (2006). Threatened miscarriage as a predictor of obstetric outcome. *Obstetrics & Gynecology*, 107(4), 845-850.

- Kanmaz, A. G., Inan, A. H., Beyan, E., & Budak, A. (2019). The effects of threatened abortions on pregnancy outcomes. *Ginekologia polska*, 90(4), 195-200.
- Krause, S. A., & Graves, B. W. (1999). Midwifery triage of first trimester bleeding. *Journal of nurse-midwifery*, 44(6), 537-548.
- Lee, H. J., Park, T. C., Kim, J. H., Norwitz, E., & Lee, B. (2017). The influence of oral dydrogesterone and vaginal progesterone on threatened abortion: a systematic review and meta-analysis. *BioMed research international*, 2017.
- McKennett, M., & Fullerton, J. T. (1995). Vaginal bleeding in pregnancy. *American family physician*, 51(3), 639-646.
- Moonen-Delarue, M. W. G., & Haest, J. W. G. (1996). Ectopic pregnancy three times in line of which two advanced abdominal pregnancies. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 66(1), 87-88.
- Moore, K. L., & Persaud, T. V. N. (1993). *The Developing Human: Clinically Oriented Embryology [slides]*. Saunders.
- Morin, L., Cargill, Y. M., & Glanc, P. (2016). Ultrasound evaluation of first trimester complications of pregnancy. *Journal of Obstetrics and Gynaecology Canada*, 38(10), 982-988.
- Neilson, J. P., Gyte, G. M., Hickey, M., Vazquez, J. C., & Dou, L. (2013). Medical treatments for incomplete miscarriage. *Cochrane Database of Systematic Reviews*, (3).
- Paspulati, R. M., Bhatt, S., & Nour, S. (2004). Sonographic evaluation of first-trimester bleeding. *Radiologic Clinics*, 42(2), 297-314.
- Paul, M., Lichtenberg, E. S., Borgatta, L., Grimes, D. A., Stubblefield, P. G., & Creinin, M. D. (2009). Management of unintended and abnormal pregnancy. *Comprehensive abortion care*.
- Rausch, M. E., & Barnhart, K. (2012). Serum biomarkers for detecting ectopic pregnancy. *Clinical obstetrics and gynecology*, 55(2), 418.
- Rhodes, E., Kasales, C., Porter, M. B., Kupesic, S., & Harris, R. D. (2002). First-trimester sonographic findings associated with poor intrauterine outcome. *Radiologist*, 9(6), 309-315.
- Rodgers, S. K., Chang, C., DeBardeleben, J. T., & Horrow, M. M. (2015). Normal and abnormal US findings in early first-trimester pregnancy: review of the society of radiologists in ultrasound 2012 consensus panel recommendations. *Radiographics*, 35(7), 2135-2148.
- Sharma, S., Moudgil, S., Kapoor, V., & Devi, A. (2020). Primary ovarian ectopic pregnancy: an unusual case study. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 9(4), 1741-1743.
- Simpson, J. L., & Jauniaux, E. R. M. (2007). *Pregnancy loss. Obstetrics: Normal and Problem Pregnancies*. 5th ed. Philadelphia, Pa: Elsevier Churchill Livingstone.
- Snell, B. J. (2009). Assessment and management of bleeding in the first trimester of pregnancy. *Journal of midwifery & women's health*, 54(6), 483-491.
- Tannirandorn, Y., Sangsawang, S., Manotaya, S., Uerpairojkit, B., Samritpradit, P., & Charoenvidhya, D. (2003). Fetal loss in threatened abortion after

- embryonic/fetal heart activity. *International Journal of Gynecology & Obstetrics*, 81(3), 263-266.
- Tongsong, T., Srisomboon, J., Wanapirak, C., Sirichotiyakul, S., Pongsatha, S., & Polsrisuthikul, T. (1995). Pregnancy outcome of threatened abortion with demonstrable fetal cardiac activity: a cohort study. *Journal of obstetrics and gynaecology (Tokyo, Japan)*, 21(4), 331–335.
- Torres, M., & Moayed, S. (2012). Gynecologic and other infections in pregnancy. *Emergency Medicine Clinics*, 30(4), 869-884.
- Tunçalp, Ö., Gülmezoglu, A. M., & Souza, J. P. (2010). Surgical procedures for evacuating incomplete miscarriage. *Cochrane Database of Systematic Reviews*, (9).
- Vink, J., & Feltovich, H. (2016). Cervical etiology of spontaneous preterm birth. In *Seminars in Fetal and Neonatal Medicine* (Vol. 21, No. 2, pp. 106-112). WB Saunders.
- Wittels, K. A., Pelletier, A. J., Brown, D. F., & Camargo Jr, C. A. (2008). United States emergency department visits for vaginal bleeding during early pregnancy, 1993-2003. *American journal of obstetrics and gynecology*, 198(5), 523-e1.
- Yan, Y., Chen, Z., Yang, Y., Zheng, X., Zou, M., Cheng, G., & Yuan, Z. (2021). Efficacy of progesterone on threatened miscarriage: an updated meta-analysis of randomized trials. *Archives of Gynecology and Obstetrics*, 303(1), 27-36.
- Zhou, J., Huang, Z., Pan, X., Leung, W. T., Li, C., Chen, L., ... & Wang, L. (2019). New thoughts in exploring the pathogenesis, diagnosis, and treatment of threatened abortion. *BioScience Trends*, 13(3), 284-285.0

CHAPTER 6

2nd AND 3rd TRIMESTER BLEEDING AND ADMINISTRATION

Dr. Ahu KORKUT¹

¹ Eskişehir Osmangazi University, Medical School of Department of Obstetric and Gynecology, Orcid ID: 0000-0002-1693-6212, E-mail: ahuorta@hotmail.com

1. INTRODUCTION

Vaginal bleeding is a common occurrence in all stages of pregnancy. Vaginal bleeding occurring in the 2nd trimester (14+0-27+6 weeks) and 3rd trimester (28+0-42 weeks), although less common, are conditions that can cause maternal and fetal morbidity and mortality. First of all, maternal hemodynamics and fetal well-being are evaluated in a pregnant woman who applies with the complaint of bleeding. Etiology is tried to be determined based on gestational age, severity of bleeding and accompanying symptoms. The diagnosis is confirmed using imaging methods and laboratory tests. We can evaluate the bleeding seen in the 2nd and 3rd trimesters as the bleeding detected before and after the 20th gestational week.

First of all, the severity of bleeding (light or heavy) and pain (painful or non-painful, intermittent or constant) are evaluated in pregnant women who apply with bleeding complaints before the 20th week of pregnancy. In mild and painless bleeding, small placental detachment is suggestive of cervical insufficiency, vaginal and cervical lesions. Heavier and more painful bleeding may be associated with early pregnancy loss and large placental separations. Laboratory tests (hemoglobin/hematocrit) may be useful in heavy bleeding due to hemodynamic disturbance. Abdominal pain and uterine size are evaluated by physical examination of the patient. The patient is placed in the lithotomy position and the external genital organs and speculum are examined. By means of speculum examination, non-pregnant bleeding causes such as vaginal lesions, cervical polyps, cervical ectropion, amount of bleeding and vaginal infections are evaluated. In addition, early pregnancy loss or cervical insufficiency can be diagnosed by monitoring the cervical dilation and fetal membranes seen in the speculum, depending on whether it is accompanied by pain. Ultrasonography is very precious in obstetric hemorrhages. Fetal cardiac activity is evaluated. It is evaluated whether the placenta covers the cervical os (placenta previa), or there is a bleeding image compatible with placental separation. In addition, when a short cervix, open internal cervical os and prolapse of fetal membranes are detected in ultrasonography, the diagnosis of cervical insufficiency can be considered.

The term antepartum hemorrhage is used for genital system bleeding after the 20th week of pregnancy. It occurs in 4-5% of all pregnancies. In the evaluation of antepartum bleeding, vaginal manual examination should be avoided until placenta previa is excluded by ultrasonography.

2. CAUSES AND ADMINISTRATION OF BLEEDING BEFORE 20TH WEEK OF PREGNANCY

The primary reasons of vaginal bleeding before the 20th week of pregnancy are:

- Early pregnancy losses
- Ectopic pregnancy
- Cervical insufficiency
- Subchorionic hemorrhages
- Cervical, vaginal or uterine pathologies

2.a. Second Trimester Early Pregnancy Losses

These early pregnancy losses stand for pregnancy losses between 13-20 weeks (ACOG Practice Bulletin No. 135, 2013). The incidence of early pregnancy loss in the 2nd trimester is less than 1% (Wyatt et al., 2005). Pregnancy losses up to the 20th week of gestation are called fetal death, and losses above the 20th week of gestation are called stillbirth (McPherson, 2016). There may be more than one cause of pregnancy loss in the 2nd trimester, so the etiology has not been clearly defined (McNamee et al., 2014). These patients are a heterogeneous group. The underlying pathology is associated with obstetric complications such as preterm delivery and premature rupture of membranes before viability. Symptoms and signs seen in patients are frequently vaginal bleeding, pain, signs of infection or delivery. The diagnosis of 2nd trimester pregnancy loss is made by the absence of fetal cardiac activity by ultrasonography or spontaneous delivery. Known probable causes of pregnancy loss between these weeks are as follows:

- Infections (chorioamnionitis and maternal infections) (Allanson et al., 2010)
- Preterm delivery
- Premature rupture of membranes before viability
- Stress factors (Frazier et al., 2018)
- Cervical insufficiency
- Uterine anomalies
- Thrombophilias

- Fetal malformation and syndromes

Misoprostol and mifepristone can be applied in medical treatment of second trimester early pregnancy loss (Borgatta et al., 2011). Antibiotic prophylaxis is recommended before surgical treatment. (ACOG Practice Bulletin No. 200, 2018). Dilatation and curettage (D&C) can be performed as surgical treatment. Hysterotomy and hysterectomy are rarely performed in some necessary situations (placental invasion, preventing passage from the cervix to the uterus, etc.). In order to prevent alloimmunization in Rh D-negative patients, anti-D immunoglobulin should be administered (Wiebe et al., 2019)

2.b. Ectopic Pregnancy

While 96% of ectopic pregnancies were located in the fallopian tube, 3.2% ovarian, 2.4% cornual and 1.3% abdominal pregnancies were observed (Bouyer et al., 2002). Although ectopic pregnancy is rare in the second trimester, it can be either non tubal (abdominal, cervical, incision scar or cornual pregnancy) or heterotopic pregnancy when diagnosed. Heterotopic pregnancy is seen with a frequency of 1/30000 and frequently the reason is the increase in the use of assisted reproductive techniques (Tal et al., 1996; Seeber et al., 2006). Abdominal and pelvic pain and vaginal bleeding are common symptoms in ectopic pregnancy. 2. Trimester ectopic pregnancies can continue until later weeks, so the risk of rupture is high. There is a risk of maternal mortality. These patients may be admitted to hospital because of acute abdomen, severe vaginal bleeding, hypotension, tachycardia and shock. In case a ruptured ectopic pregnancy is suspected, it requires immediate surgical intervention. Treatment of second trimester ectopic pregnancies should be administered as medical (with methotrexate...) and as surgical (like laparotomy, laparoscopy, hysteroscopy) according to the gestational week, location, and patient's clinic.

2.c. Cervical Insufficiency

We can define it as painless cervical dilatation that causes recurrent pregnancy loss and preterm deliveries in the second trimester. The cervix consists primarily of fibrous tissue and some smooth muscle cells. Although the pathophysiology of cervical insufficiency is not known for sure, trauma to the cervix and congenital anomalies are risk factors. Cervical damage during

labor (vacuum, forceps, spontaneous or cesarean section) and surgical procedures applied to the cervix (dilation curettage, dilatation evacuation, conization, LEEP, cauterization, hysteroscopy) are defined as cervical trauma (Vyas et al., 2006). Collagen tissue diseases (Ehler Danlos syndrome), congenital uterine malformations, in utero exposure to diethylstilbestrol (DES) can be listed among the risk factors for congenital cervical insufficiency (Muragaki et al., 2003).

In addition, decidual inflammation, infection (maternal, fetal), subchorionic hemorrhages and uterine over-distension (polyhydramnios, multiple pregnancy) may cause shortening and opening of the cervix, leading to pregnancy loss and preterm delivery in the second trimester. The difference from cervical insufficiency is that it does not repeat, it is valid only for that particular pregnancy.

Recurrent pregnancy loss or preterm live birth is observed in the obstetric history of the patients, and painless cervical dilation is observed in the physical examination. Patients are usually asymptomatic or typically show mild symptoms (such as pelvic pressure, Braxton hick-like contractions, cramps, back pain, change in color and consistency of vaginal discharge) between 14-20 weeks.

In the physical examination of pregnant women who have a history suggestive of cervical insufficiency and have symptoms, the cervix should be visualized using a speculum and palpated manually. The cervix may be closed and minimally effaced (Oláh et al., 1992). Prolapse of fetal membranes can be observed from the cervical canal by speculum examination by applying Valsalva maneuver, suprapubic or uterine fundus pressure to the pregnant. In transvaginal ultrasonography, cervical length is monitored <25 mm. Sludge may be observed in the amniotic fluid. There is no specific finding for cervical insufficiency in the laboratory.

History-based diagnosis of cervical insufficiency concerns pregnant women with a history of >2 recurrent second trimester pregnancy loss or early preterm birth (mostly <24 weeks gestation) with asymptomatic or minimal symptoms. Cervical insufficiency is diagnosed when asymptomatic patients with a history of premature preterm birth with mild symptoms in their previous pregnancies and patients whose diagnosis is uncertain due to obstetric history have a cervical length (CL) <25 mm by ultrasonography. Cervical dilatation and effacement without pain in the physical examination of pregnant women between 14-27 weeks also makes the diagnosis of cervical insufficiency.

Intraamniotic infection is found in approximately 20-50% of pregnant women with cervical dilatation of 2 cm or more in physical examination (Romero et al., 1992). Amniocentesis is administered in these patients, and cerclage is not recommended since the risk of preterm delivery and pregnancy complications will rise in case infection is detected (Kusanovic et al., 2007).

Elective cerclage is recommended between 12-14 weeks in patients with a history-based diagnosis of cervical insufficiency (MRC/RCOG 1993). In addition, vaginal progesterone treatment can be started, but no significant difference was found in the studies performed when comparing cerclage alone or cerclage + progesterone (Eke et al., 2019).

We can also recommend cerclage in patients diagnosed with cervical insufficiency for which ultrasonography is indicated (history of early preterm delivery and CL < 25 mm in transvaginal ultrasonography). In addition, vaginal progesterone therapy can be started. Another alternative may be to administer only vaginal progesterone therapy. In a meta-analysis of randomized studies, it was determined that the success of cerclage was more effective in preventing preterm delivery than vaginal progesterone treatment alone (Berghella et al., 2011). In another indirect comparative meta-analysis, no significant difference was found between cerclage and vaginal progesterone treatment, but it was observed that the cerclage group was at higher risk for preterm delivery between the groups (Conde-Agudelo et al., 2018).

Cerclage is recommended for patients before the 24th gestational week who are diagnosed with cervical insufficiency based on physical examination. In the meta-analyses, it was found that cerclage was more successful in preventing premature preterm delivery in patients (Chatzakis et al., 2020).

Vaginal progesterone therapy is administered to patients whose CL is found to be 25 mm or less in anatomical obstetric ultrasonography scanning (between 18-24 weeks of gestation) performed in patients who have no history of preterm delivery and recurrent pregnancy loss or who are nulliparous. Cervical length follow-up with transvaginal ultrasonography is recommended. If the CL is less than 10 mm, cerclage is recommended.

2.d. Subchorionic Bleeding

In general, the first trimester and the early second trimester is monitored. The most common symptom is vaginal bleeding. Retroplacental hematoma can be seen on ultrasonography. Detachment may be part of the spectrum of the abruptio placenta. Although there were slightly increased

adverse pregnancy outcomes (detachment of the placenta, preterm delivery, premature rupture of membranes) in these pregnant women, the majority of them resulted in healthy delivery (Hull et al., 2019).

2.e. Vaginal, Cervical and Uterine Pathologies

Vaginal pathologies (infection, malignancy, laceration and papilloma), cervical pathologies (often ectropion, infection, polyp, malignancy and myoma) and uterine pathologies (such as malignancy and myoma) can be listed among the causes of 2nd and 3rd trimester vaginal bleeding that are not related pregnancy. It is treated for etiology. Cervical ectropions are formed by eversion of columnar epithelium. It is a normal finding in pregnancy and is frequently observed. It is prone to bleeding when touched during coitus and vaginal examinations which does not require treatment.

3. REASONS AND ADMINISTRATION OF BLEEDING AFTER 20th WEEK OF PREGNANCY

Major causes of vaginal bleeding after 20 weeks of gestation:

- Bloody show
- Placenta previa
- Ablatio placenta
- Uterine rupture
- Vasa previa
- Choriocarcinoma

3.a. Bloody Show

It is used to describe a small amount of bloody mucus vaginal discharge that can be observed 72 hours before the beginning of labor.

3.b. Placenta Previa

Definition and Epidemiology

The closure of the internal cervical os by the placental tissue is defined as placenta previa. In the previous definition, it was classified as complete, partial, marginal and low-lying placenta according to the closure of the placenta, while placenta previa (placenta closes the cervical os) and low-lying placenta (placenta does not close the internal os, but ends at 2 cm or closer)

by the "National Institute of Child Health and Human Development panel on fetal imaging". (Figure 1) (Hull et al., 2019). Digital and speculum examination of the cervix should be avoided without excluding the diagnosis of placenta previa by ultrasonography in unfollowed patients admitted to hospital with bleeding at the twentieth gestational week and above.

Placenta previa is seen in approximately 0.4% of births (Faiz et al., 2003; Cresswell et al., 2013). Its incidence is 2% higher at the 20th gestational week, and in the vast majority of these cases, this risk disappears until delivery (Hull et al., 2019). Major risk factors for placenta previa are as follows:

- Previous history of placenta previa: There is a 4-8% risk of recurrence (Rosenberg et al., 2011).
- Multiple pregnancy: Its incidence is 40% higher than singleton pregnancies (Ananth et al., 2003).
- History of previous cesarean section: The risk increases as the number of cesarean sections increases (Gilliam et al., 2002).
- Other risk factors can be listed as previous uterine surgery, increased parity, advanced maternal age, smoking, cocaine use, infertility treatment, previous curettage, male fetus and non-white race.



Figure 1: (A) Transabdominal ultrasound shows that the placenta completely covers the cervix. (B) Transabdominal ultrasound shows an apparent low-lying placenta.

Pathogenesis

Although the underlying cause is unknown in placenta previa, previous uterine surgical procedures and multiple pregnancies have increased the implantation and growth of trophoblasts into the lower uterine cavity (Faiz et

al., 2003). In addition, in multiple pregnancies, the placental surface size increases the extension of the placenta to the lower uterine segment and the possibility of covering the cervical os. 90% of placenta previa detected before the 20th gestational week disappears in the third trimester (Oyelese et al., 2006). Since placental growth and uterine growth are different, the part in the fundus with high blood supply to the placenta enlarges and the part in the lower uterine segment regresses and atrophies. Thus, the distance between the cervical os and the lower end of the placenta increases. This process is known as trophotropism. If the extension of the placenta on the internal cervical os at 18-24 weeks is <14 mm, the probability of placenta previa at term is close to zero, if it is >14 mm -<25mm, the probability of placenta previa at term is 20%, and if it is >25 mm and above, the probability of placenta previa is 40% -100% (Jansen et al., 2020). Posterior located placenta previa cases are less likely to move away from the cervical os at term than anterior located cases (Jansen et al., 2020). As the placental margin thickness increases, the probability of placenta previa increases at term (Hull et al., 2019).

Diagnosis

The most common symptom is painless vaginal bleeding (Fan et al., 2017). 10-20% of pregnant women seek medical advice for complaints of uterine contraction, pain and vaginal bleeding (Silver et al., 1984). One third of the patients are before the 30th week of pregnancy, one third is in 30.-36. gestational week and bleeding become symptomatic by experiencing the first bleeding episode after 36 weeks of gestation in the other third of the patients (Silver et al., 1984; Crane et al., 1999). 10% of the patients may not have any bleeding complaints until the term. The onset and number of early bleeding episodes increase the need for blood transfusion and the likelihood of emergency cesarean delivery (Ruiter et al., 2016). Bleeding in placenta previa can be caused by coitus, digital examination of the cervix, and contractions observed before delivery at term.

Transabdominal ultrasonography is the first approach to screen for placenta previa. If the placenta is closer to the cervical os than 20 mm in the transabdominal ultrasonography and the bladder is empty, we perform transvaginal ultrasonography to confirm the diagnosis and make a better evaluation. The false positive rate of transabdominal ultrasonography is 25% (Quant et al., 2014). It can be considered as an alternative imaging method in transperineal ultrasonography. Transvaginal ultrasonography is superior for

the diagnosis of placenta previa (Sunna et al., 1999). Color doppler is used in cases where placenta accreta spectrum is suspected and the umbilical cord is in the lower uterine segment (vasa previa). Image findings that increase the risk of antepartum hemorrhage can be counted as the placenta completely extending to the cervical os, placental margin thickness over 10 mm, and cervical length less than 30 mm (Zaitoun et al., 2011).

Magnetic resonance imaging (MRI) is a suitable method since the magnetic resonance properties of the cervix and placenta are different. Because of the reliability and accuracy of transvaginal ultrasonography and the high cost and limited use of MRI, it is not used in the diagnosis of placenta previa (Thurmond et al., 2010). It is used in cases of placenta accreta spectrum (PAS) complicated by placenta previa (Warshak et al., 2006).

Placenta accreta spectrum is the attachment of trophoblasts to the myometrium without decidua in between, the absence of the Nitabuch fibrinoid layer. PAS should definitely be considered in cases of placenta previa. It is especially observed in anterior placenta previa cases in the incision line. The frequency of PAS increased with the increase in the number of cesarean sections (Silver et al., 2006) (figure 2).

Other associated conditions with placenta previa can be listed as malpresentation, fetal growth restriction, congenital anomalies, vasa previa and velamentous umbilical cord (Weiner et al., 2016).

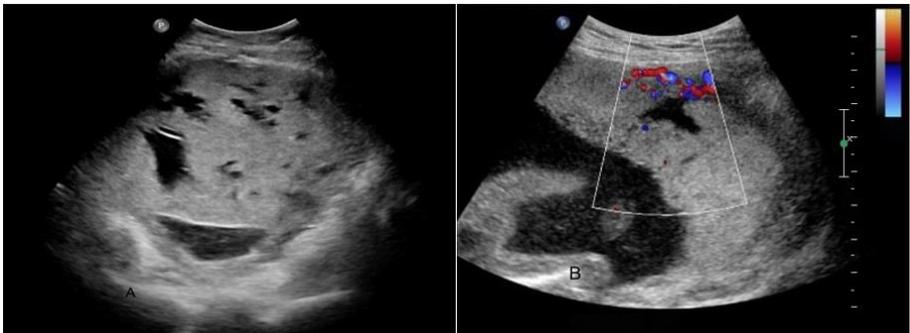


Figure 2: (A) Characteristic ultrasound appearance of placenta accreta. (B) Color flow Doppler study bridging of vessel into the placental tissue.

Administration

Placenta previa is a cause of maternal morbidity by causing antepartum and postpartum hemorrhage (Crane et al., 2000). The need for blood transfusion and the rate of hysterectomy are high in these patients (Fan et al., 2017). The main cause of neonatal mortality and morbidity is preterm delivery (Salihu et al., 2003). Adverse neonatal outcomes are more common in patients with recurrent bleeding episodes (Huang et al., 2021). Neonatal anemia is increased in placenta previa infants (Schneiderman et al., 2013). The need for blood transfusion and hysterectomy is higher in cases with the spectrum of placenta accreta. Morbidity in low-lying placenta is less than in cases with placenta previa. As the placenta closes to the cervical os, the rate of antepartum and postpartum hemorrhage, preterm delivery and cesarean delivery increases (Vergani et al., 2009).

Asymptomatic placenta previa or low-lying placenta cases detected by ultrasonography at 18-22 weeks of gestation are re-evaluated at 32 weeks of gestation. In cases where placenta previa or low-lying placenta is not detected in the evaluation, routine antenatal follow-up is continued. Placenta previa or low-lying placenta without PAS at 32 weeks of gestation is evaluated by ultrasonography at 36 weeks of gestation. Cesarean section is planned between 34+0-35+6 gestational weeks for pregnant women with PAS at 32nd gestational week and it is prepared for blood transfusion and hysterectomy. In the evaluation of placenta previa or low-lying placenta without PAS by ultrasonography at 36 weeks of gestation;

- Routine antenatal follow-up is recommended if there is no placenta previa or low-lying placenta.
- Cesarean section is planned at 36+0-37+6 weeks in cases with placenta previa (SMFM, 2018; ACOG Number. 831, 2021).
- In cases with low-lying placenta, if the distance of the placenta to the internal os is 10 mm or closer, cesarean section is planned at 36+0-37+6 weeks. If the distance is between 11-20 mm, vaginal delivery can be expected (Jansen et al., 2019).

Asymptomatic patients can be followed on an outpatient basis (Ononeze et al., 2006). All risks should be explained to patients and emergency information should be given to patients who need to contact the

hospital immediately. However, hospitalization is important in cases with short cervix findings on ultrasonography, rapid cervical shortening, inability to reach the hospital on time, and in cases where home care is not available (Shin et al., 2016). In order to reduce the risk of bleeding in cases of placenta previa, we recommend that they avoid sexual activity, moderate and heavy exercise, standing for long periods and heavy lifting (Palmer et al., 2013). Cerclage and tocolytic agents have been tried to reduce the risk of bleeding, but sufficient evidence has not been found to reduce it (Verspyck et al., 2017). The study with patients treated with Pessier and progesterone showed promising results, but the study was interrupted due to high cost (Stafford et al., 2019).

We first evaluate maternal and fetal well-being in placenta previa cases presenting with vaginal bleeding and determine whether emergency cesarean delivery is necessary.

- Maternal hemodynamics is evaluated. Vascular access is established.
- Although there is no consensus on laboratory tests, 2-4 U red blood cell suspension should be prepared for hemogram, blood group, blood transfusion and coagulopathy (fibrinogen level, activated partial thromboplastin time, prothrombin time) is evaluated. (Goodnough et al., 2011).
- Fetal heart rate is evaluated.
- The amount of blood loss is evaluated by some quantitative measurement techniques (Al Kadri et., 2011). Images that correlate the size and appearance of blood on certain surfaces (such as pads, vomit cups, bed linens) are helpful.
- Intravenous transfusion of crystalloid, blood and blood products may be required for hemodynamic stabilization of the patient. Many patients respond to supportive therapy and do not require emergency delivery, administration should be by means of follow-up in these patients (ACOG Number. 266, 2002). Antenatal corticosteroid treatment is applied to patients between 23+0-33+6 weeks of gestation if delivery is anticipated within one week. Correction of

the patient's anemia is necessary. Rh D-negative patients are administered anti-D immunoglobulin (Fung et al., 2003).

- Cesarean delivery is planned for patients with stable hemodynamics during 36+0-37+6 weeks of gestation.
- Cesarean delivery can be considered in patients with unstable hemodynamics, active bleeding, category 3 fetal heart rate, and significant vaginal bleeding over 34 weeks, regardless of gestational week. (SMFM, 2018). If delivery is planned within 24 hours in pregnant women under 32 weeks, magnesium sulfate treatment is planned.

Regional anesthesia is planned for planned cesarean deliveries. General anesthesia is preferred for emergency cesarean deliveries with active vaginal bleeding. Because of the high risk of intraoperative bleeding in placenta previa, a multidisciplinary approach is required. In cases without PAS, transverse incision to the uterus is mostly preferred. Vertical incision is preferred in fetal premature, transverse presentations and placenta accreta spectrum. The umbilical cord is clamped immediately. Severe postpartum hemorrhage may be observed after separation of the placenta. In the treatment of postpartum bleeding, uterotonic drugs (oxytocin, prostaglandin F₂ alpha, methylergonovine) and tranexamic acid are used first. A tourniquet can be applied until the drugs take effect. In the second stage, local surgical treatment (hemostatic sutures, local vasopressin application, Monsel solution, fibrin adhesive patches and local removal of that area in PAS cases) is applied. In the third stage, uterine artery ligation, hypogastric artery ligation, intrauterine balloon tamponade and/or uterine compression sutures (B-Lynch) are applied. Arterial embolization and hysterectomy are preferred in the last step.

3.c. Ablation Placenta

Definition and Epidemiology

It is defined as complete or partial separation of the placenta later the 20th gestational week, before the third stage of labor. It significantly increases maternal and neonatal morbidity and mortality. Ablation placenta complicates 3-10 out of 1000 births (Maeland et al., 2021; Lueth et al., 2021). It is an obstetric emergency. Most of them are observed in pregnancies of 32 weeks and above (Tikkanen et al., 2011). The etiology is a chronic process that leads to decidual necrosis, placental infection, and bleeding by vascular disruption,

largely due to abnormalities in the development of spiral arteries (Ananth et al., 2006; Avagliano et al., 2011). A small portion of the ablation placenta is caused by mechanical trauma and sudden uterine decompression (such as the birth of twins, premature rupture of membranes in polyhydramnios, etc.) (Melamed et al., 2012). The most important risk factor is the history of ablation placenta in the previous pregnancy, which increases the risk 10-15 times (Ananth et al., 1996). Other risk factors (Ananth et al., 2001):

- Obstetric causes, chronic hypertension, preeclampsia, preterm premature rupture of membranes, eclampsia, chorioamnionitis and placental ischemic diseases (fetal growth retardation)
- Sociodemographic; maternal age, smoking and high parity
- Acute causes; polyhydramnios, mechanical trauma and cocaine use
- Congenital uterine anomalies, fibroid and synechiae (Jenabi et al., 2017)
- Other rare causes: asthma, thrombophilias, fetal congenital anomalies, pregnancy-related acute kidney failure, polluted air, previous cesarean delivery and assisted reproductive techniques.

Pathogenesis

The cause of bleeding in abruptio placenta is premature rupture of maternal vessels in the decidua basalis. The ruptured vessel may be arterial or venous. Arterial hemorrhages cause acute and severe hemorrhages due to large placental separations, resulting in maternal disseminated intravascular coagulation (DIC), and category III fetal heart rate pattern. Venous hemorrhages may lead to smaller and self-limiting placental separations, resulting in fetal oligohydramnios and fetal growth restriction over time (Morales-Roselló et al., 2017). Bleeding may be occult or overt bleeding. Thrombin plays an important role in the pathogenesis and clinical outcomes of ablation placenta (Mackenzie et al., 2004). The impacts are as follows:

- It is a potent uterotonic agent and causes uterine contractions and hypertonus (Mackenzie et al., 2004)
- They cause tissue necrosis and disruption of the extracellular matrix, causing preterm birth and premature rupture of membranes (Bączkowska et al., 2021).

- They cause maternal disseminated intravascular coagulation by triggering the coagulation system (Thachil et al., 2009)
- Functional progesterone withdrawal occurs with decreased expression of progesterone receptors due to decidual cell necrosis (Lockwood et al., 2012)

Diagnosis

Clinical findings are vaginal bleeding, abdominal pain, low back pain and uterine tenderness accompanying severe uterine contractions. Its diagnosis is clinical. Detection of fetal heart rate disorders, fetal death and maternal DIC in patients with classical symptoms confirms the clinical diagnosis. Imaging methods, laboratory tests and histopathological evaluation of the postpartum placenta support the diagnosis. The size of the separated placenta does not correlate with the amount of vaginal bleeding. In acute and severe ablation placenta, the patient has severe abdominal pain, hypotension, and fetal heart rate abnormalities (Mei et al., 2018). DIC and fetal death are common if placental separation is more than 50% (Oyelese et al., 2006). In 10-20% of cases, patients present with the complaint of preterm labor without vaginal bleeding or with very little bleeding. In these cases, most of the blood accumulates between the fetal membranes and the decidua. Abdominal pain is caused by the irritating effect of blood extravasating into the myometrium and may lead to a Couvelaire uterus. Abruption placenta should be considered in patients with abdominal pain and severe uterine contraction. Bleeding is small and intermittent in cases of chronic ablation placenta. Over time, the fetus develops oligohydramnios and fetal growth restriction (Ananth et al., 2004).

While laboratory findings do not change in mild placental abruptions, DIC develops in acute and severe placental abruptions, the fibrinogen level decreases, and the rate of blood and blood products transfusion increases (Wang et al., 2016). If fibrinogen is <200 , the incidence of postpartum bleeding is 100%, and if it is >400 , the rate of not having postpartum bleeding is 79% (Charbit et al., 2007). The Kleihauer-Betke test may be an alternative, but its sensitivity is 4% (Atkinson et al., 2015).

Retroplacental hematoma can be seen with ultrasonography (USG), and these hematomas can be detected as isoechoic, hypoechoic and hyperechoic. The sensitivity of ultrasound in ablatio placenta is 25-60% (Shinde et al.,

2016). In acute detachment cases, there may be no USG findings or hyperechoic or isoechoic may be observed. USG findings are present in patients with symptoms, its positive predictive value is 88% (Shinde et al., 2016). Identification of USG findings is associated with worse maternal and perinatal outcomes. However, the absence of findings does not exclude the possibility of detachment.

Although MRI is not helpful in detecting cases that cannot be visualized, it is not used because of its high cost and does not change administration (Masselli et al., 2011).

Computed Tomography (CT) is used to detect visceral injury in patients with mechanical trauma. It has high sensitivity and low specificity (Jha et al., 2017).

While maternal outcomes are primarily related to the severity of placenta abruption, fetal and neonatal outcomes are related to both severity and week of gestation (Oyelese et al., 2006). Maternal outcomes may include hypovolemic shock requiring blood transfusion, acute renal failure, adult respiratory distress syndrome, multiple organ failure, peripartum hysterectomy, DIC, and death (Oyelese et al., 2006; Tikkanen et al., 2011). There is an increased risk of maternal cardiovascular disease in the long term (Grandi et al., 2019; Ananth et al., 2021).

Fetal and neonatal outcomes are hypoxia, asphyxia, low birth weight, and increased perinatal morbidity and mortality due to preterm delivery (Tikkanen et al., 2013; Downes et al., 2017). Fetal growth restriction is observed in cases of chronic ablation placenta (Sheiner et al., 2002). Perinatal mortality rate is between 3-12% (Ananth et al., 2011; Downes et al., 2017). The cause of postnatal death is preterm delivery. Ablatio placenta is responsible for 10% of preterm deliveries (Sheiner et al., 2002; Oyelese et al., 2006).

Histological examination of the placenta has findings only in 50% of acute and severe cases, and the most common finding is indentation on the maternal placental surface and intravillous hemorrhage (Chen et al., 2017). Chronic deciduitis, decidual necrosis, decidual vasculopathy, villitis, intervillous thrombosis, and hemosiderin deposition can be observed in the histopathological examination of chronic ablatio placenta (Elsasser et al., 2010).

Administration

Prompt diagnosis and administration are required to reduce the risks of maternal and neonatal morbidity and mortality. The prognosis may be poor in high-risk groups such as preeclampsia, cocaine uses and trauma.

In the first stage, the hemodynamic of the mother is evaluated. Intravenous vascular access is established and laboratory tests (hemogram, crossmatch, coagulation tests, liver enzymes, kidney function tests and toxicology tests if suspected in substance use) are performed. Crystalloid fluid is inserted, and urine output is kept above 30 ml/hour. Fetal heart rate monitoring is performed. Blood loss is tried to be estimated by measurement techniques. Maternal vital signs and urine output are monitored. The blood center should be informed about the need for blood and blood products, as the coagulation tests, which were normal at the beginning, may deteriorate. The anesthesia team should be notified. After these steps are completed, placenta previa should be ruled out by USG (Table 1). Neuroprotective magnesium sulfate should be started for pregnant women <32 weeks who are planned to give birth within 24-48 hours. Antenatal corticosteroids are administered for lung maturation to pregnant women <34 weeks who are likely to give birth within one week.

The most important factors affecting the administration of ablatio placenta are maternal and fetal well-being and gestational age. In case of severe detachment (DIC, acute renal failure, hypovolemic shock, need for blood transfusion, unreliable fetal heart rate, fetal growth restriction and fetal death) delivery should be performed.

Cesarean section is a good option for patients with unstable maternal hemodynamics and reactive fetal heart rate, since vaginal delivery is not imminent, there is a significant risk of coagulopathy and bleeding can be controlled quickly.

In cases where maternal hemodynamics is unstable and fetus is dead, the optimal delivery method should be chosen by considering maternal mortality and morbidity. Cesarean section should be chosen in patients who are not close to vaginal delivery and in patients with a history of hysterotomy.

In patients with stable maternal hemodynamics and a viable fetus but with an unreliable heart rate pattern (biophysical profile 0-4) the risk of fetal acidemia increases, so delivery should be performed immediately. If vaginal delivery will occur immediately, it can be considered, but if it will not happen immediately, cesarean delivery should be chosen.

Vaginal delivery is preferred when maternal hemodynamics is stable, and the fetus is dead. Morbidity is less than cesarean section. Vaginal delivery is a relative contraindication for those with a history of hysterotomy, and cesarean section is preferred.

Conservative administration should be chosen for pregnant women under <34 weeks with stable maternal hemodynamics and reactive fetal heart rate (Oyelese et al., 2006). Antenatal corticosteroid is administered for lung maturation and tocolytic therapy (nifedipine) can be given for 48 hours. Tocolytics prevent further contraction by breaking the bleeding and contraction cycle of thrombin (İncebiyık et al., 2017). However, among tocolytic agents, especially sympathomimetic agents such as terbutaline may cause hypotension and tachycardia, increasing the risk of ablation and masking hypovolemic symptoms (Towers et al., 1999). Ablation of indomethacin in the placenta; It should be avoided due to the risks of severe intraventricular bleeding, necrotizing enterocolitis and periventricular leukomalacia. During the hospitalization, nonstress test (NST) and biophysical profile are evaluated twice a day. Since growth retardation will develop in these fetuses over time, growth is followed by USG (Ananth et al., 1999). In cases where patients are asymptomatic, they are discharged, and biophysics is evaluated twice a week and fetal growth is evaluated every four weeks. Due to the increased risk of stillbirth, the delivery is planned between 37+0-38+0 weeks. In the presence of complications (fetal growth restriction, preeclampsia, premature rupture of membranes, unreliable NST or biophysical profile, maternal instability), delivery can be planned before 37 weeks. The placenta is absolutely sent to pathology and blood gas from the umbilical cord is sent for testing.

We plan delivery for pregnant women between 34-36 weeks with stable maternal hemodynamics and reactive fetal heart rate, since acute ablation placenta may be progressive, and the risk of neonatal morbidity is somewhat less. In patients with minimal vaginal bleeding and symptoms, conservative administration may be preferred if they have a reactive NST and a good biophysical profile score. It can be expected in asymptomatic patients, but delivery is planned at 37+0-38+0 weeks at the latest.

In pregnant women over 36 weeks with stable maternal hemodynamics and reactive fetal heart rate, delivery is planned in acute ablation placenta (Oyelese et al., 2006). If there is no obstetric indication (malpresentation, previous uterine incision) for cesarean delivery, vaginal delivery is planned.

Patients not in active labor can be treated with amniotomy and induction with oxytocin.

Postpartum patients are first administered oxytocin utero. The status of bleeding is evaluated by monitoring maternal vital signs, amount of bleeding, uterine tone, and urine output. Coagulation panel and hemogram are followed up with laboratory tests. Preparations for fluid replacement and blood transfusion should be made when necessary.

Table 1: Comparison of Clinical Features of Placenta Previa and Abruption Placenta

CLINICAL FEATURES	PLACENTA PREVIA	ABRUPTIO PLACENTA
BEGINNING	Third trimester, often over 30 weeks	Third trimester
BLEEDING	Mostly external, small or large amount of light red and coagulating blood	May be occult, external dark red or bloody amniotic fluid, non-clotting blood
PAIN, UTERINE TENDERNESS	Usually absent, uterus soft	Usually present; high uterine tone, tetanic uterus
FETAL HEART RATE	Usually normal	May be irregular or absent
FETAL PRESENTATION	Often not engaged, but may be non-vertex presentation	May be engaged
SHOCK	Usually not seen unless the bleeding is massive	Depending on the severity of occult or external bleeding, it may be moderate or severe.
BIRTH	Parallel to the condition of the baby and the state of bleeding, the baby can be monitored in the womb. Birth by cesarean section	Emergency delivery, usually by cesarean section

3.d. Uterine Rupture

Definition and Risk Factors

It is defined as the complete separation of all layers of the uterus. It is a pregnancy complication that increases the risk of maternal and fetal mortality. Dehiscence is a condition that is observed incidentally in cesarean section, does not cause serious maternal and fetal consequences and cannot be easily diagnosed with signs and symptoms. While the incidence of uterine rupture after cesarean section is 0.3% in general, this rate is higher in patients who have tried vaginal delivery after cesarean section (Guise et al., 2010).

The primary risk factor for uterine rupture is a previous cesarean section. Other risk factors are:

- History of previous rupture: In studies conducted on these patients, the rate of dehiscence in cesarean section during the current pregnancy is 19% (Fox, 2020).
- The risk of rupture is 1-12% in patients with previous fundal or vertical hysterotomy (Landon et al., 2011). In the National Institutes of Health (NIH) Maternal-Fetal Medicine Units Network Study, vaginal delivery after cesarean section was attempted for pregnant women. As a result, the rate of rupture after fundal, reverse T, and J incision was 1.9%, while the rate of rupture in lower segment transverse incision was 0.7% (Landon et al., 2004).
- Spontaneous and post-induction rupture rates in patients scheduled for vaginal delivery after induction cesarean section were reported by the NIH as 0.8%-1.5%, respectively. (NIH, 2010). In another systematic review conducted in 2015, the rupture/dehiscence rate was reported as 1.62-2.3 (Rossi et al., 2015). In the study of the American College of Obstetricians and Gynecologists (ACOG), the risk of rupture increases 5-10% with misoprostol (Plaut et al., 1999). Oxytocin administration alone increases the risk of rupture by 1.1% (Lin et al., 2004).
- The risk of uterine rupture increases in vaginal delivery after cesarean section (NIH 2010).
- Other risk factors are advanced maternal age, pregnancy over 40 weeks, fetal birth weight over 4000 g, less than 18 months between pregnancies, closure of the uterus with a single layer of suture,

multiple previous cesarean section and second trimester cesarean section (Lannon et al., 2015).

A small portion of uterine ruptures are also seen in patients who have not undergone uterine surgery. Its incidence is seen between 1/5700-1/20000 (Al-Zirqi et al., 2020). The incidence of rupture with and without a scar has increased in recent years (Al-Zirqi et al., 2016). Trauma, obstetric maneuvers (such as internal and external cephalic version, fundal pressure, etc.) and myometrial weakness (congenital muscle diseases such as Ehler-Danlos, uterotonic agents) can be counted in its etiology (Sakr et al., 2007). Risk factors are uterotonic agents, high parity, multiparity, macrosomia, dystocia, multiple pregnancy, placental anomalies, previous cerclage pregnancy and short two-pregnancy intervals (Al-Zirqi et al., 2020).

Clinical Signs and Symptoms

Uterine rupture signs and symptoms, respectively are as follows (Guiliano et al., 2014):

- It is the deterioration of fetal heart rate (FHR). There is no rupture-specific FHR pattern, but fetal bradycardia is the most common (Ridgeway et al., 2004). It can be observed one hour before rupture (Desseauve et al., 2016). Therefore, continued FHR monitoring is recommended for patients scheduled for vaginal delivery after cesarean section. (ACOG Practice Bulletin No. 205, 2019).
- Abdominal pain is in the form of acute onset uterine pain. Care should be taken (Markou et al., 2017).
- Vaginal bleeding
- Loss of level of the presenting part of the fetus
- If the rupture extends to the bladder, hematuria is observed.
- Disruption of maternal hemodynamics
- When the uterus ruptures, its tone is decreased despite increased uterine contractility (Craver Pryor et al., 2007). The amplitude of uterine contractions, called the ladder sign, gradually decreased (Matsuo et al., 2008).

Postpartum occult uterine rupture should be considered if pain and vaginal bleeding persist despite uterotonic agents.

Uterine rupture is an obstetric emergency. If maternal hemodynamics is stable and fetal heart rate is reactive, USG evaluation can be used to detect hemoperitoneum. Other findings on imaging may include hematoma in the incision scar, anhydramnios, empty uterus, fetus outside the uterus, and fetal death.

CT and MRI can be used in traumatized pregnant women.

Diagnosis

Definitive diagnosis is made by laparotomy. Hemoperitoneum and fetal parts and membranes are observed in the abdomen. It is observed that the uterus is completely separated. Differential diagnosis is made with ablatio placenta, preeclampsia, HELLP syndrome and sympathetic blockade due to neuroaxial anesthesia.

Administration

In the administration of patients with suspected uterine rupture before delivery, primarily maternal hemodynamics is stabilized. Required fluid and blood transfusion is done. Preparations are made for emergency cesarean section and the anesthesia team and neonatology team are informed. The choice of anesthesia is decided according to the urgency of delivery. Regional anesthesia is not preferred in emergencies and coagulation disorders. The choice of incision in laparotomy is preferred for diagnosis and other etiologies. A better abdominal evaluation can be made by choosing a midline incision instead of a Pfannenstiel incision.

The first decision in the treatment of patients with uterine rupture at laparotomy should be decided whether to repair the prime. Primary repair should be performed in patients with stable hemodynamics, low bleeding, small uterine defect, young patients and patients with fertility desire. If adequate hemostasis and repair cannot be achieved, hysterectomy is performed.

Complications such as atony (uterotonic, balloon catheter, hemostatic sutures, arterial ligation), bladder injury (intraoperative urology consultation), pelvic organ injuries (intraoperative general surgery and cardiovascular surgery consultation) and placenta accreta spectrum should be managed.

Two morbidities associated with uterine rupture are the increased need for blood transfusions and hysterectomy. The perinatal mortality rate from uterine rupture has been reported as 5-26% (Al-Zirqi et al., 2018). In a study conducted by the NIH, the rate of neonatal hypoxic ischemic encephalopathy in newborns after uterine rupture was 6% (Landon et al., 2004). If the time from fetal heart rate deterioration to delivery is >18 minutes, neonatal morbidity increases (Holmgren et al., 2012). Rapid intervention does not always prevent neonatal mortality and morbidity (Bujold et al., 2002).

American College of Obstetricians and Gynecologists recommends delivery at 36+0-37+0 gestational weeks for patients with a history of rupture in previous pregnancy. (ACOG Practice Bulletin No. 205, 2019). In patients with uterine dehiscence, delivery is planned at 37+0-38+0 weeks.

3.e. Vasa Previa

Definition, Epidemiology and Pathogenesis

The extension of fetal vessels in the membranes above the internal cervical os is defined as vasa previa. It is a rare complication that may result in rupture of membranes, fetal blood loss and fetal mortality. Its prevalence is approximately 1/1300-1/2500, but the prevalence is 1/202 in pregnancies with assisted reproductive techniques. (Zhang et al., 2020). Three types of vasa previa have been described.

1. Type: They are vasa previa cases associated with velamentous umbilical cord insertion (umbilical vessels run in the membrane before reaching the placental edge) or marginal cord insertion (umbilical vessels are connected from the placental edge) (Catanzarite et al., 2001).
2. Type: In the presence of a placenta containing a bilobed or succenturiate lobe, fetal vessels extending in the membrane between the placental lobes are associated with the internal cervical os (Catanzarite et al., 2001).
3. Type: In cases of placenta previa or low-lying placenta, one or more boomerang vessels pass through the membrane along the placental margin, despite normal umbilical cord insertion (Suekane et al., 2020).

No definitive criteria have been defined between the proximity of fetal vessels to the internal os and the risk of rupture. In some studies, the results of fetal vessels with <2 cm internal os distance and fetal vessels with internal os were considered to be similar (Oyelese et al., 2006). However, data are limited (Rebarber et al., 2014).

Risk factors are velamentous cord insertion, placenta with bilobed or succenturiate lobe, multiple pregnancy, assisted reproductive techniques (invitro fertilization), and placenta previa or low-lying placenta detected in second trimester USG scan (Zhang et al., 2020). Risk factors are not independent from each other and in a systematic review; 83% of cases have one or more risk factors together (Ruiter et al., 2016).

Although the pathogenesis is not clearly known, velamentous cord insertion is similar. Common hypothesis: The umbilical cord enters the center of the normal placental disc, but its location remains more peripheral because placental trophotropism cannot follow (Kouyoumdjian, 1980). Its association with placenta previa supports the hypothesis.

Diagnosis

Diagnosis can be made by observing fetal vessels on and near the internal os (<2 cm) using transvaginal ultrasonography and color doppler. The sensitivity of the combined use of ultrasonography and color doppler is high (Figure 3). MRI is used to clarify the diagnosis when there is uncertainty in the diagnosis and if it will change our administration (Nguyen et al., 2012). Although there are case reports suggesting the use of three-dimensional (3D) ultrasonography technology for the diagnosis of vasa previa and determining the appropriate location of the uterine incision at birth, its superiority over two-dimensional (2D) technology has not been proven (Oyelese et al., 2004; Mabuchi et al., 2010). In cases without an ultrasonographic diagnosis, Apt test, Kleihauer-Betke test or electrophoresis can be used for fetal or maternal differentiation of sudden vaginal bleeding that starts with membrane rupture (Odunsi et al., 1996). However, there is no time for these tests because fetal heart rate abnormalities such as fetal bradycardia and preterminal sinusoidal rhythm develop. If vasa previa is suspected, emergency cesarean delivery should be performed.

In the differential diagnosis, free umbilical cord in the cervix, cervico-uterine vessels, cervical varices, amniotic band and chorioamniotic separation are considered.

Although placenta location and image are part of the routine anatomic obstetric ultrasonography examination between 18-22 weeks, vasa previa screening is not routinely performed. (SMFM, 2015; Silver, 2015). Transvaginal USG and color doppler are common in pregnant women with risk factors (placenta previa, low-lying placenta, bilobed or succenturiate placenta containing placenta) and suspected vasa previa. Pregnant women with placenta previa and low-lying placenta in the 2nd trimester are at risk for vasa previa, even if placenta placement improves in the future. Therefore, The Society for Maternal-Fetal Medicine (SMFM) recommends transvaginal USG follow-up at 32 weeks of gestation for these patients. (SMFM, 2015). In a meta-analysis comparing the pregnancy outcomes of vasa previa cases with and without prenatal diagnosis, perinatal survival increased in those with prenatal diagnosis (Zhang et al., 2021). Although pregnancy outcomes improved significantly in patients with a prenatal diagnosis, the rate of preterm delivery increased in one review (38% of 122 cases planned for preterm delivery) (Westcott et al., 2020).

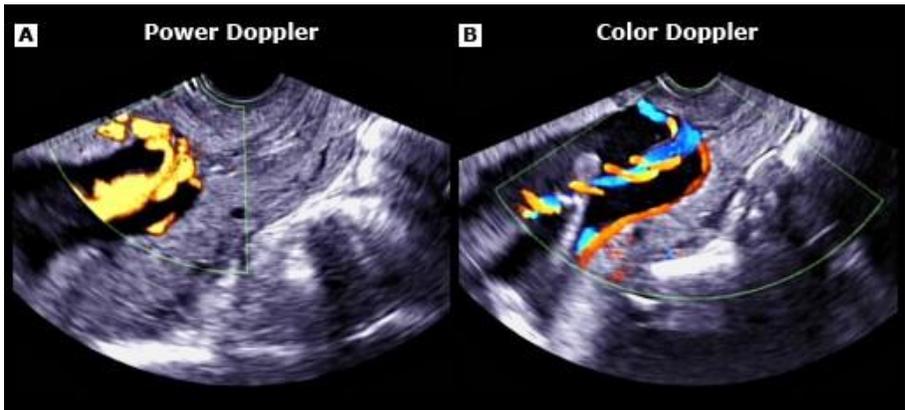


Figure 3: Succenturiate lobe placenta complicated by vasa previa on transvaginal ultrasonography

Administration

Although there is insufficient data for an optimal administration method, several recommendations are available. Patients who are found to have placenta previa or low-lying placenta in the ultrasonographic examination performed in the 2nd trimester are re-evaluated at the 32nd

gestational week. If placenta previa or low-lying placenta is detected in this week, it is evaluated for vasa previa by transvaginal USG.

In the administration of 3rd trimester pregnant women with prenatal diagnosis of vasa previa, they should preferably be hospitalized between 30-34 weeks, maternal and fetal well-being (at least once a day NST) should be performed, and antenatal corticosteroid treatment should be applied in pregnant women under 34 weeks. Outpatient follow-up may be an alternative approach for patients between 30-34 weeks with a cervical length >25 mm, no complaints of uterine contraction and vaginal bleeding, no history of preterm delivery and a hospitalization time of <15 minutes (Fishel Bartal et al., 2019). During outpatient and inpatient follow-up, emergency cesarean delivery is planned in the presence of any of the following:

- Persistent variable deceleration in NST
- Non-reactive NST
- Premature rupture of membranes
- Suspected preterm delivery
- Vaginal bleeding accompanied by fetal heart rate abnormalities (fetal tachycardia, sinusoidal heart rate pattern)
- Fetal blood detection by Apt and Kleihauer-Betke test

According to some authors, cesarean delivery is recommended between 34+0-35+6 weeks (Robinson et al., 2011). ACOG and SMSF recommended planned cesarean delivery at 34+0-37+0 weeks. (SMFM, 2015; ACOG Number 831, 2021).

Aberrant vessels should be avoided during uterine incision in cesarean section and emergency cord clamping is required if fetal vessels are damaged. (SMFM, 2015). Cesarean section should be performed in the center where emergency newborn blood transfusion can be performed.

There is no evidence for a different approach to the administration of twin pregnancies.

3.f. Choriocarcinoma

Choriocarcinoma is a rare cause of antepartum hemorrhage and can be observed in any trimester. The most common risk factor is a history of molar pregnancy. It can be observed after abortion, postpartum and rarely with existing intrauterine pregnancy. Bleeding may result from vaginal metastasis

or from a primary intrauterine tumor. It may cause respiratory distress, neurological symptoms and acute abdomen by metastasizing to the lung, brain and retro-abdominal (Jorgensen et al., 2019). In the presence of respiratory and neurological symptoms accompanying vaginal bleeding, it should be considered after excluding other causes of antepartum bleeding.

REFERENCES

- ACOG Practice Bulletin No. 135. (2013). Second-trimester abortion. *Obstetrics Gynecology*; 121:1394.
- ACOG Practice Bulletin No. 205. (2019). Vaginal Birth After Cesarean Delivery. *Obstetrics Gynecology*; 133:e110.
- Al Kadri H.M., Al Anazi B.K., Tamim H.M. (2011). Visual estimation versus gravimetric measurement of postpartum blood loss: a prospective cohort study. *Archives of Gynecology and Obstetrics*; 283:1207
- Allanson B., Jennings B., Jacques A., et al.(2010). Infection and fetal loss in the mid-second trimester of pregnancy. *The Australian and New Zealand Journal of Obstetrics and Gynaecology*; 50:221.
- Al-Zirqi I., Daltveit A.K., Vangen S. (2018). Infant outcome after complete uterine rupture. *American Journal of Obstetrics and Gynecology*; 219:109.e1.
- Al-Zirqi I., Stray-Pedersen B., Forsén L., et al. (2016). Uterine rupture: trends over 40 years. *BJOG*; 123:780.
- Al-Zirqi I., Vangen S. (2020). Prelabour uterine rupture: characteristics and outcomes. *BJOG*; 127:1637.
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200. (2018). Early Pregnancy Loss. *Obstetrics Gynecology*; 132:e197.
- American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, Society for Maternal-Fetal Medicine. (2021). Medically Indicated Late-Preterm and Early-Term Deliveries: ACOG Committee Opinion, Number 831. *Obstetrics Gynecology*; 138:e35.
- Ananth C.V., Berkowitz G.S., Savitz D.A., Lapinski R.H. (1999). Placental abruption and adverse perinatal outcomes. *JAMA*; 282:1646.
- Ananth C.V., Demissie K., Smulian J.C., Vintzileos A.M. (2003). Placenta previa in singleton and twin births in the United States, 1989 through 1998: a comparison of risk factor profiles and associated conditions. *American Journal of Obstetrics & Gynecology*; 188:275
- Ananth C.V., Getahun D., Peltier M.R., Smulian J.C. (2006). Placental abruption in term and preterm gestations: evidence for heterogeneity in clinical pathways. *Obstetrics Gynecology*; 107:785.
- Ananth C.V., Oyelese Y., Prasad V., et al. (2006). Evidence of placental abruption as a chronic process: associations with vaginal bleeding early in pregnancy and placental lesions. *European Journal of Obstetrics & Gynecology and Reproductive Biology*; 128:15.
- Ananth C.V., Oyelese Y., Srinivas N., et al. (2004). Preterm premature rupture of membranes, intrauterine infection, and oligohydramnios: risk factors for placental abruption. *Obstetrics Gynecology*; 104:71.
- Ananth C.V., Patrick H.S., Ananth S., et al. (2021). Maternal Cardiovascular and Cerebrovascular Health After Placental Abruption: A Systematic Review and Meta-Analysis (CHAP-SR). *American Journal of Epidemiology*; 190:2718.
- Ananth C.V., Savitz D.A., Williams M.A. (1996). Placental abruption and its association with hypertension and prolonged rupture of membranes: a methodologic review and meta-analysis. *Obstetrics Gynecology*; 88:309.

- Ananth C.V., Smulian J.C., Demissie K., et al. (2001). Placental abruption among singleton and twin births in the United States: risk factor profiles. *American Journal of Epidemiology*; 153:771.
- Ananth C.V., VanderWeele T.J. (2011). Placental abruption and perinatal mortality with preterm delivery as a mediator: disentangling direct and indirect effects. *American Journal of Epidemiology*; 174:99.
- Ananth C.V., Wilcox A.J. (2001). Placental abruption and perinatal mortality in the United States. *American Journal of Epidemiology*; 153:332.
- Atkinson A.L., Santolaya-Forgas J., Matta P., et al. (2015). The sensitivity of the Kleihauer-Betke test for placental abruption. *Journal of Obstetrics and Gynaecology*; 35:139.
- Avagliano L., Bulfamante G.P., Morabito A., Marconi A.M. (2011). Abnormal spiral artery remodelling in the decidual segment during pregnancy: from histology to clinical correlation. *Journal of Clinical Pathology*; 64:1064.
- Bączkowska M., Zgliczyńska M., Faryna J., et al. (2021). Molecular Changes on Maternal-Fetal Interface in Placental Abruption-A Systematic Review. *International Journal of Molecular Sciences*; 22.
- Berghella V., Rafael T.J., Szychowski J.M., et al. (2011). Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. *Obstetrics Gynecology*; 117:663.
- Borgatta L., Kapp N., Society of Family Planning. Clinical guidelines. (2011). Labor induction abortion in the second trimester. *Contraception*; 84:4.
- Bouyer J., Coste J., Fernandez H., et al. (2002). Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases. *Human Reproduction*; 17:3224.
- Bujold E., Gauthier R.J. (2002). Neonatal morbidity associated with uterine rupture: what are the risk factors? . *American Journal of Obstetrics and Gynecology*; 186:311.
- Catanzarite V., Maida C., Thomas W., et al. (2001). Prenatal sonographic diagnosis of vasa previa: ultrasound findings and obstetric outcome in ten cases. *Ultrasound Obstetrics Gynecology*; 18:109.
- Charbit B., Mandelbrot L., Samain E., et al. (2007). The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *Journal of Thrombosis and Haemostasis*; 5:266.
- Chatzakis C., Efthymiou A., Sotiriadis A., Makrydimas G. (2020). Emergency cerclage in singleton pregnancies with painless cervical dilatation: A meta-analysis. *Acta Obstetrica et Gynecologica Scandinavica*; 99:1444.
- Chen A.L., Goldfarb I.T., Scourtas A.O., Roberts D.J. (2017). The histologic evolution of revealed, acute abruptions. *Human Pathology*; 67:187.
- Committee on Obstetric Practice. (2002). ACOG committee opinion. Placenta accreta. Number 266, January 2002. *American College of Obstetricians and Gynecologists. The International Journal of Gynecology & Obstetrics*; 77:77.
- Conde-Agudelo A., Romero R., Da Fonseca E., et al. (2018). Vaginal progesterone is as effective as cervical cerclage to prevent preterm birth in women with a singleton gestation, previous spontaneous preterm birth, and a short cervix: updated indirect comparison meta-analysis. *Am J Obstetrics Gynecology*; 219:10.

- Crane J.M., van den Hof M.C., Dodds L., et al. (1999). Neonatal outcomes with placenta previa. *Obstetrics Gynecology*; 93:541.
- Crane JM, Van den Hof MC, Dodds L, et al. (2000). Maternal complications with placenta previa. *American Journal of Perinatology*; 17:101.
- Craver Pryor E., Mertz H.L., Beaver B.W., et al.(2007). Intrapartum predictors of uterine rupture. *American Journal of Perinatology*; 24:317.
- Cresswell J.A., Ronsmans C., Calvert C., Filippi V. (2013). Prevalence of placenta praevia by world region: a systematic review and meta-analysis. *Tropical Medicine and International Health*; 18:712.
- Desseauve D., Bonifazi-Grenouilleau M., Fritel X., et al. (2016). Fetal heart rate abnormalities associated with uterine rupture: a case-control study: A new time-lapse approach using a standardized classification. *European Journal of Obstetrics & Gynecology and Reproductive Biology*; 197:16.
- Downes K.L., Shenassa E.D., Grantz K.L. (2017). Neonatal Outcomes Associated With Placental Abruption. *American Journal of Epidemiology*; 186:1319.
- Eke A.C., Sheffield J., Graham E.M. (2019). Adjuvant 17-hydroxyprogesterone caproate in women with history-indicated cerclage: A systematic review and meta-analysis. *Acta Obstetrica et Gynecologica Scandinavica*; 98:139.
- Elovitz M.A., Ascher-Landsberg J., Saunders T., Phillippe M. (2000). The mechanisms underlying the stimulatory effects of thrombin on myometrial smooth muscle. *American Journal of Obstetrics & Gynecology*; 183:674.
- Elsasser D.A., Ananth C.V., Prasad V., et al. (2010). Diagnosis of placental abruption: relationship between clinical and histopathological findings. *European Journal of Obstetrics & Gynecology and Reproductive Biology*; 148:125
- Faiz A.S. Ananth C.V. (2003). Etiology and risk factors for placenta previa: an overview and meta-analysis of observational studies. *The Journal of Maternal-Fetal & Neonatal Medicine*; 13:175.
- Fan D., Wu S., Liu L., et al. (2017). Prevalence of antepartum hemorrhage in women with placenta previa: a systematic review and meta-analysis. *Scientific Reports*; 7:40320.
- Fan D., Xia Q., Liu L., et al. (2017). The Incidence of Postpartum Hemorrhage in Pregnant Women with Placenta Previa: A Systematic Review and Meta-Analysis. *PLoS One*; 12:e0170194.
- Final report of the Medical Research Council/Royal College of Obstetricians and Gynaecologists multicentre randomised trial of cervical cerclage. (1993). MRC/RCOG Working Party on Cervical Cerclage. *An International Journal of Obstetrics & Gynaecology*; 100:516.
- Fishel Bartal M., Sibai B.M., Ilan H., et al. (2019). Prenatal Diagnosis of Vasa Previa: Outpatient versus Inpatient Management. *American Journal of Perinatology*; 36:422.
- Fox N.S. (2020). Pregnancy Outcomes in Patients With Prior Uterine Rupture or Dehiscence: A 5-Year Update. *Obstetrics Gynecology*; 135:211.
- Frazier T., Hogue C.J.R., Bonney E.A., et al. (2018). The storm; a review of pre-pregnancy stress and risk of spontaneous abortion. *Psychoneuroendocrinology*; 92:142.

- Fung Kee Fung K, Eason E, Crane J, et al. (2003). Prevention of Rh alloimmunization. *Journal of Obstetrics and Gynaecology Canada*; 25:765.
- Gilliam M., Rosenberg D., Davis F. (2002) The likelihood of placenta previa with greater number of cesarean deliveries and higher parity. *Obstetrics Gynecology*; 99:976.
- Goodnough L.T., Daniels K., Wong A.E., et al. (2011). How we treat: transfusion medicine support of obstetric services. *Transfusion*; 51:2540.
- Grandi S.M., Fillion K.B., Yoon S., et al. (2019). Cardiovascular Disease-Related Morbidity and Mortality in Women With a History of Pregnancy Complications. *Circulation*; 139:1069.
- Guiliano M., Closset E., Therby D., et al. (2014). Signs, symptoms and complications of complete and partial uterine ruptures during pregnancy and delivery. *European Journal of Obstetrics & Gynecology and Reproductive Biology*; 179:130.
- Guise J.M., Eden K., Emeis C., et al. (2010). Vaginal birth after cesarean: new insights. *Evid Rep Technol Assess (Full Rep)*; :1.
- Holmgren C., Scott J.R., Porter T.F., et al. (2012). Uterine rupture with attempted vaginal birth after cesarean delivery: decision-to-delivery time and neonatal outcome. *Obstetrics Gynecology*; 119:725.
- Huang S., Zuo Q., Wang T., et al. (2021). Maternal and neonatal outcomes of repeated antepartum bleeding in 493 placenta previa cases: a retrospective study. *The Journal of Maternal-Fetal & Neonatal Medicine*; :1.
- Hull A.D., Resnik R. Silver M.R. (2019). Placenta previa and Accreta, vasa previa, subchorionic hemorrhage and abruptio placenta. In Resnik R., Lockwood C.J., Greene M.F., Copel JA, Silver RM (eds) *Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice*, Eighth Edition. Philadelphia, Elsevier pp 786- 797
- Iwahashi M., Muragaki Y., Ooshima A., Umesaki N.(2003). Decreased type I collagen expression in human uterine cervix during pregnancy. *Journal of Clinical Endocrinology and Metabolism*; 88:2231.
- Jang D.G., Jo Y.S., Lee S.J., Lee G.S. (2011). Risk factors of neonatal anemia in placenta previa. *Journal of Health and Medical Sciences*; 8:554.
- Jansen C., de Mooij Y.M., Blomaard C.M., et al. (2019). Vaginal delivery in women with a low-lying placenta: a systematic review and meta-analysis. *BJOG* 2019; 126:1118.
- Jansen C.H.J.R., Kleinrouweler C.E., Kastelein A.W., et al. (2020). Follow-up ultrasound in second-trimester low-positioned anterior and posterior placentae: prospective cohort study. *Ultrasound Obstetrics Gynecology*; 56:725.
- Jansen C.H.J.R., Kleinrouweler C.E., van Leeuwen L., et al. (2020). Which second trimester placenta previa remains a placenta previa in the third trimester: A prospective cohort study. *European Journal of Obstetrics & Gynecology and Reproductive Biology*; 254:119.
- Jenabi E., Ebrahimzadeh Zagami S. (2017). The association between uterine leiomyoma and placenta abruptio: A meta-analysis. *The Journal of Maternal-Fetal & Neonatal Medicine*; 30:2742.

- Jha P., Melendres G., Bijan B., et al. (2017). Trauma in pregnant women: assessing detection of post-traumatic placental abruption on contrast-enhanced CT versus ultrasound. *Abdominal Radiology*; 42:1062.
- Jorgensen K., Roychowdhury M., da Cunha G., et al. (2019). Stage IV Gestational Choriocarcinoma Diagnosed in the Third Trimester. *Obstetrics Gynaecology*; 133:163.
- Kouyoumdjian A. (1980). Velamentous insertion of the umbilical cord. *Obstetrics and gynaecology*; 56:737.
- Kusanovic J.P., Espinoza J., Romero R., et al. (2007). Clinical significance of the presence of amniotic fluid 'sludge' in asymptomatic patients at high risk for spontaneous preterm delivery. *Ultrasound Obstetrics Gynecology*; 30:706.
- Landon M.B., Hauth J.C., Leveno K.J., et al. (2004). Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. *The New England Journal of Medicine*; 351:2581.
- Landon M.B., Lynch C.D. (2011). Optimal timing and mode of delivery after cesarean with previous classical incision or myomectomy: a review of the data. *Seminars in Perinatology*; 35:257.
- Lannon S.M., Guthrie K.A., Vanderhoeven J.P., Gammill H.S. (2015). Uterine rupture risk after periviable cesarean delivery. *Obstetrics Gynecology*; 125:1095.
- Leung AS, Leung EK, Paul RH. (1993) Uterine rupture after previous cesarean delivery: maternal and fetal consequences. *American Journal of Obstetrics and Gynecology*; 169:945.
- Lin C., Raynor B.D. (2004). Risk of uterine rupture in labor induction of patients with prior cesarean section: an inner city hospital experience. *American Journal of Obstetrics & Gynecology*; 190:1476.
- Lockwood C.J., Kayisli U.A., Stocco C., et al. (2012). Abruption-induced preterm delivery is associated with thrombin-mediated functional progesterone withdrawal in decidual cells. *American Journal of Pathology*; 181:2138.
- Lueth A., Blue N., Silver R.M., et al. (2021). Prospective evaluation of placental abruption in nulliparous women. *The Journal of Maternal-Fetal & Neonatal Medicine*; :1.
- Mabuchi Y., Yamoto M., Minami S., et al. (2010). Two cases of vasa previa diagnosed prenatally using three-dimensional ultrasonography. *Journal of Clinical Ultrasound*; 38:389.
- Mackenzie A.P., Schatz F., Krikun G., et al. (2004). Mechanisms of abruption-induced premature rupture of the fetal membranes: Thrombin enhanced decidual matrix metalloproteinase-3 (stromelysin-1) expression. *American Journal of Obstetrics & Gynecology*; 191:1996.
- Maeland K.S., Morken N.H., Schytt E., et al. (2021). Placental abruption in immigrant women in Norway: A population-based study. *Acta Obstetrica et Gynecologica Scandinavica*; 100:658.
- Markou G.A, Muray J.M, Poncelet C. (2017).Risk factors and symptoms associated with maternal and neonatal complications in women with uterine rupture. A 16 years multicentric experience. *European Journal of Obstetrics & Gynecology and Reproductive Biology*; 217:126.

- Masselli G., Brunelli R., Di Tola M., et al. (2011). MR imaging in the evaluation of placental abruption: correlation with sonographic findings. *Radiology*; 259:222.
- Matsuo K., Scanlon J.T., Atlas R.O., Kopelman J.N. (2008). Staircase sign: a newly described uterine contraction pattern seen in rupture of unscarred gravid uterus. *Journal of Obstetrics and Gynaecology Research*; 34:100.
- McNamee K.M, Dawood F., Farquharson R.G. (2014). Mid-trimester pregnancy loss. *Obstetrics and Gynecology Clinics of North America*; 41:87.
- McPherson E. (2016). Recurrence of stillbirth and second trimester pregnancy loss. *The American Journal of Medical Genetics Part A*; 170A:1174.
- Mei Y., Lin Y. (2018). Clinical significance of primary symptoms in women with placental abruption. *The Journal of Maternal-Fetal & Neonatal Medicine*; 31:2446.
- Melamed N., Aviram A., Silver M., et al. (2012). Pregnancy course and outcome following blunt trauma. *The Journal of Maternal-Fetal & Neonatal Medicine*; 25:1612.
- Morales-Roselló J., Khalil A., Akhoundova F., et al. (2017). Fetal cerebral and umbilical Doppler in pregnancies complicated by late-onset placental abruption. *The Journal of Maternal-Fetal & Neonatal Medicine*; 30:1320.
- National Institutes of Health Consensus Development Conference Panel. (2010). National Institutes of Health Consensus Development conference statement: vaginal birth after cesarean: new insights March 8-10, 2010. *Obstetrics Gynecology*; 115:1279.
- Nguyen D., Nguyen C., Yacobozzi M., et al. (2012). Imaging of the placenta with pathologic correlation. 50. *Semin Ultrasound CT MR*; 33:65.
- Odunsi K., Bullough C.H., Henzel J., Polanska A. (1996). Evaluation of chemical tests for fetal bleeding from vasa previa. *International Journal of Gynecology & Obstetrics*; 55:207.
- Oláh K.S., Gee H. (1992). The prevention of preterm delivery--can we afford to continue to ignore the cervix? *An International Journal of Obstetrics & Gynaecology*; 99:278.
- Ononeze B.O., Ononeze V.N., Holohan M. (2006). Management of women with major placenta praevia without haemorrhage: a questionnaire-based survey of Irish obstetricians. *Journal of Obstetrics and Gynaecology*; 26:620.
- Oyelese Y., Ananth C.V. (2006). Placental abruption. *Obstetrics Gynecology*; 108:1005.
- Oyelese Y., Chavez M.R., Yeo L., et al. (2004). Three-dimensional sonographic diagnosis of vasa previa. *Ultrasound Obstetrics Gynaecology*; 24:211.
- Oyelese Y., Smulian J.C. (2006). Placenta previa, placenta accreta, and vasa previa. *Obstetrics Gynecology*; 107:927.
- Palmer K.T., Bonzini M., Harris E.C., et al. (2013). Work activities and risk of prematurity, low birth weight and pre-eclampsia: an updated review with meta-analysis. *Occupational & Environmental Medicine*; 70:213.
- Plaut M.M., Schwartz M.L., Lubarsky S.L. (1999). Uterine rupture associated with the use of misoprostol in the gravid patient with a previous cesarean section. *American Journal of Obstetrics & Gynecology*; 180:1535.

- Quant H.S., Friedman A.M., Wang E., et al. (2014). Transabdominal ultrasonography as a screening test for second-trimester placenta previa. *Obstetrics Gynecology*; 123:628.
- Raymond E.G., Mills J.L. (1993). Placental abruption. Maternal risk factors and associated fetal conditions. *Acta Obstetrica et Gynecologica Scandinavica*; 72:633.
- Rebarber A., Dolin C., Fox N.S., et al. (2014). Natural history of vasa previa across gestation using a screening protocol. *Journal of Ultrasound in Medicine*; 33:141.
- Ridgeway J.J., Weyrich D.L., Benedetti T.J. (2004). Fetal heart rate changes associated with uterine rupture. *Obstetrics Gynecology*; 103:506.
- Robinson B.K., Grobman W.A. (2011). Effectiveness of timing strategies for delivery of individuals with vasa previa. *Obstetrics Gynaecology*; 117:542.
- Romero R., Gonzalez R., Sepulveda W., et al. (1992). Infection and labor. VIII. Microbial invasion of the amniotic cavity in patients with suspected cervical incompetence: prevalence and clinical significance. *The American Journal of Obstetrics and Gynecology*; 167:1086.
- Rosenberg T., Pariente G., Sergienko R., et al. (2011). Critical analysis of risk factors and outcome of placenta previa. *Archives of gynecology and obstetrics*; 284:47.
- Rossi A.C., Prefumo F. (2015). Pregnancy outcomes of induced labor in women with previous cesarean section: a systematic review and meta-analysis. *Archives of Gynecology and Obstetrics*; 291:273.
- Ruiter L., Eschbach S.J., Burgers M., et al. (2016). Predictors for Emergency Cesarean Delivery in Women with Placenta Previa. *American Journal of Perinatology*; 33:1407.
- Ruiter L., Kok N., Limpens J., et al. (2016). Incidence of and risk indicators for vasa praevia: a systematic review. *BJOG*; 123:1278.
- Sakr R., Berkane N., Barranger E., et al. (2007). Unscarred uterine rupture--case report and literature review. *Clinical and Experimental Obstetrics & Gynecology*; 34:190.
- Salihu H.M., Li Q., Rouse D.J., Alexander G.R. (2003). Placenta previa: neonatal death after live births in the United States. *American Journal of Obstetrics and Gynecology*; 188:1305.
- Schneiderman M., Balayla J. (2013). A comparative study of neonatal outcomes in placenta previa versus cesarean for other indication at term. *The Journal of Maternal-Fetal & Neonatal Medicine*; 26:1121.
- Seeber B.E., Barnhart K.T. (2006). Suspected ectopic pregnancy. *Obstetrics Gynecology*; 107:399.
- Sheiner E, Shoham-Vardi I, Hallak M, et al.(2001). Placenta previa: obstetric risk factors and pregnancy outcome. *The Journal of Maternal-Fetal Medicine*; 10:414.
- Sheiner E., Shoham-Vardi I., Hadar A., et al. (2002). Incidence, obstetric risk factors and pregnancy outcome of preterm placental abruption: a retrospective analysis. *The Journal of Maternal-Fetal & Neonatal Medicine*; 11:34.

- Shin J.E., Shin J.C., Lee Y., Kim S.J. (2016). Serial Change in Cervical Length for the Prediction of Emergency Cesarean Section in Placenta Previa. *PLoS One*; 11:e0149036.
- Shinde G.R., Vaswani B.P., Patange R.P., et al. (2016). Diagnostic Performance of Ultrasonography for Detection of Abruptio and Its Clinical Correlation and Maternal and Foetal Outcome. *Journal of Clinical and Diagnostic Research*; 10:QC04.
- Silver R., Depp R., Sabbagha R.E., et al. (1984). Placenta previa: aggressive expectant management. *American Journal of Obstetrics & Gynecology*; 150:15.
- Silver R.M. (2015). Abnormal Placentation: Placenta Previa, Vasa Previa, and Placenta Accreta. *Obstetrics Gynaecology*; 126:654.
- Silver R.M., Landon M.B., Rouse D.J., et al.(2006). Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstetrics Gynecology*; 107:1226.
- Society for Maternal-Fetal Medicine (SMFM). (2018). Electronic address: pubs@smfm.org, Gyamfi-Bannerman C. Society for Maternal-Fetal Medicine (SMFM) Consult Series #44: Management of bleeding in the late preterm period. *American Journal of Obstetrics & Gynecology*; 218:B2.
- Society of Maternal-Fetal (SMFM) Publications Committee, Sinkey R.G., Odibo A.O., Dashe JS. (2015). Diagnosis and management of vasa previa. *American Journal of Obstetrics and Gynecology*; 213:615.
- Stafford I.A., Garite T.J., Maurel K., (2019). et al. Cervical Pessary versus Expectant Management for the Prevention of Delivery Prior to 36 Weeks in Women with Placenta Previa: A Randomized Controlled Trial. *American Journal of Perinatology Reports*; 9:e160.
- Suekane T., Tachibana D, Pooh R.K., et al. (2020). Type-3 vasa previa: normal umbilical cord insertion cannot exclude vasa previa in cases with abnormal placental location. *Ultrasound Obstetrics Gynecology*; 55:556.
- Sunna E., Ziadeh S. (1999). Transvaginal and transabdominal ultrasound for the diagnosis of placenta praevia. *Journal of Obstetrics and Gynaecology*; 19:152.
- Tal J., Haddad S., Gordon N., Timor-Tritsch I. (1996). Heterotopic pregnancy after ovulation induction and assisted reproductive technologies: a literature review from 1971 to 1993. *Fertil Steril*; 66:1.
- Thachil J., Toh C.H. (2009). Disseminated intravascular coagulation in obstetric disorders and its acute haematological management. *Blood Reviews*; 23:167.
- Thurmond A., Mendelson E., Böhm-Vélez M., et al. (2000). Role of imaging in second and third trimester bleeding. *American College of Radiology. ACR Appropriateness Criteria. Radiology*; 215 Suppl:895.
- Tikkanen M. (2011). Placental abruptio: epidemiology, risk factors and consequences. *Acta Obstetrica et Gynecologica Scandinavica*; 90:140.
- Tikkanen M., Luukkaala T., Gissler M., et al. (2013). Decreasing perinatal mortality in placental abruptio. *Acta Obstetrica et Gynecologica Scandinavica*; 92:298.
- Towers C.V., Pircon R.A., Heppard M. (1999). Is tocolysis safe in the management of third-trimester bleeding? *American Journal of Obstetrics & Gynecology*; 180:1572.

- Vergani P., Ornaghi S., Pozzi I., et al. (2009). Placenta previa: distance to internal os and mode of delivery. *The state of the American Journal of Obstetrics & Gynecology*; 201:266.e1.
- Verspyck E., de Vienne C., Muszynski C., et al. (2017). Maintenance nifedipine therapy for preterm symptomatic placenta previa: A randomized, multicenter, double-blind, placebo-controlled trial. *PLoS One*; 12:e0173717.
- Vyas N.A., Vink J.S., Ghidini A., et al. (2006). Risk factors for cervical insufficiency after term delivery. *The American Journal of Obstetrics and Gynecology*; 195:787.
- Wang L, Matsunaga S, Mikami Y, et al. (2016). Pre-delivery fibrinogen predicts adverse maternal or neonatal outcomes in patients with placental abruption. *Journal of Obstetrics and Gynaecology*; 42:796.
- Warshak C.R., Eskander R., Hull A.D., et al. (2006). Accuracy of ultrasonography and magnetic resonance imaging in the diagnosis of placenta accreta. *Obstetrics Gynecology*; 108:573.
- Weiner E., Miremberg H., Grinstein E., et al. (2016). The effect of placenta previa on fetal growth and pregnancy outcome, in correlation with placental pathology. *Journal of perinatology*; 36:1073.
- Westcott J.M., Simpson S., Chasen S., et al. (2020). Prenatally diagnosed vasa previa: association with adverse obstetrical and neonatal outcomes. *American Journal of Obstetrics & Gynecology MFM*; 2:100206.
- Wiebe E.R., Campbell M., Aiken A.R.A, Albert A. (2019). Can we safely stop testing for Rh status and immunizing Rh-negative women having early abortions? A comparison of Rh alloimmunization in Canada and the Netherlands. *Contraception*; 1:100001.
- Wyatt P.R., Owolabi T., Meier C., Huang T. (2005). Age-specific risk of fetal loss observed in a second trimester serum screening population. *The American Journal of Obstetrics and Gynecology*; 192:240.
- Zaitoun M.M., El Behery M.M., Abd El Hameed A.A., Soliman B.S. (2011). Does cervical length and the lower placental edge thickness measurement correlates with clinical outcome in cases of complete placenta previa? *Archives of Gynecology and Obstetrics*; 284:867.
- Zhang W., Geris S., Al-Emara N., et al. (2021). Perinatal outcome of pregnancies with prenatal diagnosis of vasa previa: systematic review and meta-analysis. *Ultrasound in Obstetrics & Gynecology*; 57:710.
- Zhang W., Geris S., Beta J., et al. (2020). Prevention of stillbirth: impact of two-stage screening for vasa previa. *Ultrasound Obstetrics Gynaecology*; 55:605.

CHAPTER 7

BLEEDING DUE TO ECTOPIC PREGNANCY

Dr. Aysun ALPARSLAN ÇULHA¹

Dr. Fatih AKKUŞ²

¹ Baskent University Hospital Konya Department Of Obstetric And Gynecology
ORCID ID: 0000-0002-3262-4286 / aysunalparslan@gmail.com

² Necmettin Erbakan University, Meram Faculty of Medicine, Department of
Obstetrics and Gynecology / Perinatology Department ORCID ID: 0000-0001-7037-
9165 / fakkus1987@gmail.com

BLEEDING DUE TO ECTOPIC PREGNANCY

INTRODUCTION

An ectopic pregnancy refers to a pregnancy located outside the endometrial cavity("ACOG Practice Bulletin No. 191: Tubal Ectopic Pregnancy," 2018; Elson et al., 2016). The most common site of ectopic pregnancies is the fallopian tubes, accounting for 90% of the cases. However, it can also be seen in abdominal cavity (1%), cervical (1%), ovarian (1-3%) and cesarean section scar (1-3%). In rare cases, when an ectopic pregnancy is accompanied by an intrauterine pregnancy, it is called a heterotopic pregnancy. Heterotopic pregnancies, which are estimated to occur in 1 in 30,000 pregnancies, are seen between 1-2 in 1000 ART(Assisted Reproductive Techniques) pregnancies due to the increase in the use of ART in recent years(Clayton et al., 2007; Reece et al., 1983).

RISK FACTORS

Tubal ectopic pregnancy is caused by infection, tubal surgery, congenital anomalies or tumors. The mechanism is usually dependent on damaged ciliary activity. The highest risk is associated with a previous history of ectopic pregnancy or tubal surgery(Bouyer et al., 2003; Murray et al., 2005)

Having a previous ectopic pregnancy increases the risk of repeat ectopic pregnancy approximately 3-8 times. A history of salpingostomy for ectopic pregnancy is a risk factor for recurrent ectopic pregnancy(Li et al., 2015; Zhang et al., 2016). The incidence of ectopic pregnancy is strongly associated with the incidence of pelvic inflammatory disease (PID). The risk of ectopic pregnancy increased approximately 3 times in patients with a history of PID(Bouyer et al., 2003; Kamwendo et al., 2000; Li et al., 2015). Pelvic tuberculosis is associated with infertility rather than ectopic pregnancy. The incidence of ectopic pregnancy is higher in patients with infertility. In vitro fertilization (IVF) increases the risk of both tubal ectopic and heterotopic pregnancy(Du et al., 2017). Patients with previous tubal ligation may prefer tubal reconstructive surgery instead of IVF. Reconstructive surgery ectopic pregnancy rates range from 3 to 30 percent(Audebert et al., 2014). The use of oral contraceptives or intrauterine devices (IUD) reduces the risk of having both an intrauterine and ectopic pregnancy. But if they do get pregnant, they can increase the chance of an ectopic pregnancy(Schultheis et al., 2021). However, smoking(x2-3), exposure to DES in utero(x3,7), vaginal douching(x3), increasing age and endometriosis increase the risk of ectopic pregnancy(Alataş et al., 2008; Bouyer et al., 2003; Hoover et al., 2011; Nybo Andersen et al., 2000).

Ectopic pregnancy can be asymptomatic as well as presenting most commonly with first trimester vaginal bleeding or abdominal pain(Alkatout et

al., 2013). If a patient is admitted to the hospital with vaginal bleeding and abdominal pain, ectopic pregnancy should be excluded firstly. Some symptoms (breast tenderness, frequent urination, nausea) seen in normal pregnant women are less common. Since progesterone and human chorionic gonadotropin (HCG) levels are lower than normal pregnancy, such symptoms are less common in ectopic pregnancy. This can make early diagnosis even more difficult (Feng et al., 2013; Wu et al., 2014). Rupture of the tube or ectopic pregnancy material can cause life-threatening intra-abdominal bleeding. Rupture may present with severe abdominal pain or symptoms resulting from excessive blood loss, such as fainting, loss of consciousness. Many studies have shown that the risk of rupture due to ectopic pregnancy is 18-20% (Casanova et al., 2009; Job-Spira et al., 1999).

There is no pathognomonic form of vaginal bleeding for ectopic pregnancy. It can range from light brown spotting to severe vaginal bleeding. Likewise, there is no pathognomonic abdominal pain pattern for ectopic pregnancy. Patients can often describe widespread or localized pain. However, if rupture occurs, they feel sharper and stronger pain.

DIAGNOSIS

Diagnosis is made if intrauterine pregnancy could not be detected in transvaginal ultrasound (TVUS) despite a HCG level of 1500 mIU/mL and an ectopic pregnancy focus was seen in the right or left adnex.

An abnormally elevated serum hCG level provides a clue for diagnosis. The hcg value, which is expected to double after two days until today, does not actually rise that much (Barnhart et al., 2004).

The actual expected rate of increase depends on the initial hCG level. The expected rate of increase is 49 percent for a baseline hCG level of <1500 mIU/mL, 40 percent for a baseline hCG level of 1500 to 3000 mIU/mL, and 33 percent for a baseline hCG level of >3000 mIU/mL (Barnhart et al., 2016).

DIFFERENTIAL DIAGNOSIS

The classic signs of an ectopic pregnancy are vaginal bleeding and/or abdominal pain in the setting of a positive pregnancy test. In the differential diagnosis of bleeding in early pregnancy, implantation bleeding, spontaneous curettage, abortion imminens, gestational trophoblastic disease, and uterus, vagina, cervix pathologies come to mind. Vaginal ultrasound should definitely be done (Tulandi et al., 2015). Differential diagnosis of lower abdominal pain in pregnant patients includes urinary tract infection, kidney stones, diverticulitis, appendicitis, ovarian neoplasms, ovarian cyst rupture, large size or bleeding in ovarian cyst, ovarian torsion, leiomyomas, and round ligament pain (Tulandi et al., 2015).

COMPLICATIONS

Since the most common type of ectopic pregnancy is tubal ectopic pregnancy, the most common complication is rupture with internal bleeding, which can lead to hypovolemic shock. The most common cause of first trimester maternal death is ectopic pregnancy bleeding. Approximately 10% of maternal deaths are due to ectopic pregnancy. Depending on the location of the ectopic pregnancy, bleeding can be intra-abdominal or vaginal. Since the most common place of ectopic pregnancy is the tuba uterina, tubal ectopic pregnancy should be considered when we refer to it as ectopic pregnancy in this section. But in recent years, we have started to see cesarean scar (CSP) pregnancy very often. Bleeding due to CSP is also mentioned.

Tubal Ectopic Pregnancies

Ectopic pregnancy accounts for 1% of all pregnancies. Up to 98% of ectopic pregnancies occur in the fallopian tube. All ectopic pregnancies require treatment, although conservative treatments are also available. Treatment options for ectopic pregnancy include medical treatment or surgery in today's medicine. Pharmacological therapy with methotrexate can be used in early ectopic pregnancy when there is no imminent risk of rupture. If the ectopic pregnancy has ruptured, surgery is required. If the tube is not ruptured, methotrexate treatment can be started. However, surgery can also be performed in an unruptured ectopic pregnancy. The patient's stable, beta hcg value <5000, no fetal cardiac activity, and an ectopic focus smaller than 3-4 cm are the eligibility criteria for methotrexate therapy (Hajenius et al., 2007; Mol et al., 2008). However, if the patient is hemodynamically unstable, has a heterotopic pregnancy, and has a high risk of rupture, surgery may be a more appropriate option. If the patient has a hematological, renal or hepatic disease, in the presence of a condition that limits the use of methotrexate such as immune deficiency, active lung disease and peptic ulcer, the use of methotrexate is not appropriate.

Patients with an ectopic pregnancy may become hemodynamically unstable if there is a rupture and bleeding in the structure in which the pregnancy is implanted, usually the fallopian tube (Bouyer et al., 2002). However, in young healthy patients, vital signs may be normal in the early stages of bleeding, as compensatory mechanisms work better (Parks et al., 2006). Physical examination is usually unremarkable or may reveal lower abdominal tenderness. If the bleeding is excessive, the abdomen may swell and the patient may have widespread rebound tenderness. If the ectopic pregnancy has ruptured, we can talk about a real emergency. Ectopic pregnancy should be considered in women of reproductive age with sudden onset of abdominal pain and impaired hemodynamics. When we encounter such a patient, urgent surgical intervention should be performed without

waiting for the tests we have taken to confirm the pregnancy. If a patient with intra-abdominal bleeding comes to the emergency room, a large-diameter venous catheter should be inserted and fluid resuscitation should be started immediately, while vitals are quickly evaluated. For blood transfusion, the blood center should be contacted immediately and blood preparation should be done urgently. A Foley catheter should be placed to monitor the patient for fluid balance before starting the surgical procedure. Emergency laparotomy is performed in patients with very poor hemodynamics and in whom laparoscopic surgery cannot be performed. Salpingosomy or salpingectomy can be performed depending on the patient's fertility status and preferences. In addition to the advancement in laparoscopic surgical technique, better management of hemodynamic status by anesthesiologists has facilitated the laparoscopic treatment of women with ectopic pregnancy with massive hemoperitoneum(Soriano et al., 1997). There are two surgical approach options for tubal pregnancy. These are salpingectomy and salpingostomy. These two approaches appear to have similar fertility outcomes(Hajenius et al., 2007). Salpingectomy is the standard procedure if the fallopian tube is severely damaged, bleeding cannot be controlled, or the pregnancy seems too large to be removed with a salpingostomy.

Cesarean Scar Pregnancy (CSP)

Refers to a pregnancy implanted on or into a scar from a previous cesarean delivery. A pregnancy implanted in or within the myomectomy scar may occur. If unrecognized or poorly managed, CSP can lead to serious fetal and maternal morbidity and mortality. CSP is probably the precursor of the placenta accreta spectrum (PAS). There are two types of CSPs. One of them is CSP (type 1) located on a well healed scar, and the other is CSP (type 2) located on an incompletely healed scar (in a niche)(Rotas et al., 2006).

CSPs bleeding in early pregnancy, uterine rupture; In the late period, it is associated with complications such as PAS, high morbidity and maternal death. However, the cause is not clear, but some CSPs may continue to have a viable pregnancy(Cali et al., 2018). About one-third of patients with CSP are asymptomatic when diagnosed with ultrasound(Gonzalez & Tulandi, 2017). Vaginal bleeding is the most common symptom in patients with symptoms. However, symptoms can range from vaginal bleeding with or without abdominal/pelvic pain to uterine rupture with hypovolemic shock(Vial et al., 2000).

Cervical pregnancy is a rare form of ectopic pregnancy and can be distinguished from CSP by the presence of a gestational sac or placenta in the cervix (TVUS). Most of the time, the patient does not have a previous cesarean section history.

Hemodynamically unstable patients (a patient with bleeding and current or impending hemodynamic instability) require immediate surgical intervention, such as emergency wedge resection or hysterectomy. Bilateral uterine artery embolization can also be tried in appropriate centers.

In haemodynamically stable patients, optimal management is uncertain as the number of reported cases to base a specific treatment recommendation is insufficient. Treatment options include termination of pregnancy (medical or surgical) or continuation of the pregnancy. Surgical treatment is more successful than medical treatment. In a study of 3127 patients, patients undergoing surgery (hysterectomy, surgical resection, or dilatation and curettage) had higher success rates (83 percent versus 60 percent) compared to medical (ie, intragestational methotrexate) treatment(Maheux-Lacroix et al., 2017).

Interstitial Or Cornual Pregnancy

Interstitial and cornual ectopic pregnancy can be used interchangeably. However, they actually refer to different situations. Cornual implantation describes those in the upper and lateral uterine cavity, while interstitial refers to those implanted in the proximal intramural portion of the tube. Rudimentary horn pregnancy is intrauterine pregnancy located in the rudimentary uterine horn of the unicornuate uterus. There is a high risk of uterine rupture in such pregnancies. There is a mortality risk of 2-2.5% in interstitial and cornual pregnancies. This accounts for 20% of all deaths due to ectopic pregnancies(Molinario & Barnhart, 2007; Tang et al., 2006). Both can be treated with cornual resection via laparotomy. In recent years, uterine-sparing laparoscopic surgery or treatment with methotrexate has been described in the literature(Soriano et al., 2008).

REFERENCES

- ACOG Practice Bulletin No. 191: Tubal Ectopic Pregnancy. (2018). *Obstet Gynecol*, 131(2), e65-e77. <https://doi.org/10.1097/aog.0000000000002464>
- Alataş, E., Yildirim, B., Oztekin, O., & Gezgin, T. (2008). Laparoscopic management of a primary ectopic ovarian pregnancy and vaginal douching as a possible cause. *Arch Gynecol Obstet*, 277(4), 363-365. <https://doi.org/10.1007/s00404-007-0464-8>
- Alkatout, I., Honemeyer, U., Strauss, A., Tinelli, A., Malvasi, A., Jonat, W., Mettler, L., & Schollmeyer, T. (2013). Clinical diagnosis and treatment of ectopic pregnancy. *Obstet Gynecol Surv*, 68(8), 571-581. <https://doi.org/10.1097/OGX.0b013e31829cdebb>
- Audebert, A., Pouly, J. L., Bonifacie, B., & Yazbeck, C. (2014). Laparoscopic surgery for distal tubal occlusions: lessons learned from a historical series of 434 cases. *Fertil Steril*, 102(4), 1203-1208. <https://doi.org/10.1016/j.fertnstert.2014.06.047>
- Barnhart, K. T., Guo, W., Cary, M. S., Morse, C. B., Chung, K., Takacs, P., Senapati, S., & Sammel, M. D. (2016). Differences in Serum Human Chorionic Gonadotropin Rise in Early Pregnancy by Race and Value at Presentation. *Obstet Gynecol*, 128(3), 504-511. <https://doi.org/10.1097/aog.0000000000001568>
- Barnhart, K. T., Sammel, M. D., Rinaudo, P. F., Zhou, L., Hummel, A. C., & Guo, W. (2004). Symptomatic patients with an early viable intrauterine pregnancy: HCG curves redefined. *Obstet Gynecol*, 104(1), 50-55. <https://doi.org/10.1097/01.Aog.0000128174.48843.12>
- Bouyer, J., Coste, J., Fernandez, H., Pouly, J. L., & Job-Spira, N. (2002). Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases. *Hum Reprod*, 17(12), 3224-3230. <https://doi.org/10.1093/humrep/17.12.3224>
- Bouyer, J., Coste, J., Shojaei, T., Pouly, J. L., Fernandez, H., Gerbaud, L., & Job-Spira, N. (2003). Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. *Am J Epidemiol*, 157(3), 185-194. <https://doi.org/10.1093/aje/kwf190>
- Calì, G., Timor-Tritsch, I. E., Palacios-Jaraquemada, J., Monteagudo, A., Buca, D., Forlani, F., Familiari, A., Scambia, G., Acharya, G., & D'Antonio, F. (2018). Outcome of Cesarean scar pregnancy managed expectantly: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*, 51(2), 169-175. <https://doi.org/10.1002/uog.17568>
- Casanova, B. C., Sammel, M. D., Chittams, J., Timbers, K., Kulp, J. L., & Barnhart, K. T. (2009). Prediction of outcome in women with symptomatic first-trimester pregnancy: focus on intrauterine rather than ectopic gestation. *J Womens Health (Larchmt)*, 18(2), 195-200. <https://doi.org/10.1089/jwh.2008.0896>
- Clayton, H. B., Schieve, L. A., Peterson, H. B., Jamieson, D. J., Reynolds, M. A., & Wright, V. C. (2007). A comparison of heterotopic and intrauterine-only pregnancy outcomes after assisted reproductive technologies in the United States from 1999 to 2002. *Fertil Steril*, 87(2), 303-309. <https://doi.org/10.1016/j.fertnstert.2006.06.037>

- Du, T., Chen, H., Fu, R., Chen, Q., Wang, Y., Mol, B. W., Kuang, Y., & Lyu, Q. (2017). Comparison of ectopic pregnancy risk among transfers of embryos vitrified on day 3, day 5, and day 6. *Fertil Steril*, *108*(1), 108-116.e101. <https://doi.org/10.1016/j.fertnstert.2017.05.027>
- Elson, C., Salim, R., Potdar, N., Chetty, M., Ross, J., & Kirk, E. (2016). Diagnosis and management of ectopic pregnancy. *BJOG: an international journal of obstetrics and gynaecology*, *123*(13), e15-e55.
- Feng, C., Chen, Z. Y., Zhang, J., Xu, H., Zhang, X. M., & Huang, X. F. (2013). Clinical utility of serum reproductive hormones for the early diagnosis of ectopic pregnancy in the first trimester. *J Obstet Gynaecol Res*, *39*(2), 528-535. <https://doi.org/10.1111/j.1447-0756.2012.02001.x>
- Gonzalez, N., & Tulandi, T. (2017). Cesarean Scar Pregnancy: A Systematic Review. *J Minim Invasive Gynecol*, *24*(5), 731-738. <https://doi.org/10.1016/j.jmig.2017.02.020>
- Hajenius, P. J., Mol, F., Mol, B. W., Bossuyt, P. M., Ankum, W. M., & van der Veen, F. (2007). Interventions for tubal ectopic pregnancy. *Cochrane Database Syst Rev*, *2007*(1), Cd000324. <https://doi.org/10.1002/14651858.CD000324.pub2>
- Hoover, R. N., Hyer, M., Pfeiffer, R. M., Adam, E., Bond, B., Cheville, A. L., Colton, T., Hartge, P., Hatch, E. E., Herbst, A. L., Karlan, B. Y., Kaufman, R., Noller, K. L., Palmer, J. R., Robboy, S. J., Saal, R. C., Strohsnitter, W., Titus-Ernstoff, L., & Troisi, R. (2011). Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med*, *365*(14), 1304-1314. <https://doi.org/10.1056/NEJMoa1013961>
- Job-Spira, N., Fernandez, H., Bouyer, J., Pouly, J. L., Germain, E., & Coste, J. (1999). Ruptured tubal ectopic pregnancy: risk factors and reproductive outcome: results of a population-based study in France. *Am J Obstet Gynecol*, *180*(4), 938-944. [https://doi.org/10.1016/s0002-9378\(99\)70665-4](https://doi.org/10.1016/s0002-9378(99)70665-4)
- Kamwendo, F., Forslin, L., Bodin, L., & Danielsson, D. (2000). Epidemiology of ectopic pregnancy during a 28 year period and the role of pelvic inflammatory disease. *Sex Transm Infect*, *76*(1), 28-32. <https://doi.org/10.1136/sti.76.1.28>
- Li, C., Zhao, W. H., Zhu, Q., Cao, S. J., Ping, H., Xi, X., Qin, G. J., Yan, M. X., Zhang, D., Qiu, J., & Zhang, J. (2015). Risk factors for ectopic pregnancy: a multi-center case-control study. *BMC Pregnancy Childbirth*, *15*, 187. <https://doi.org/10.1186/s12884-015-0613-1>
- Maheux-Lacroix, S., Li, F., Bujold, E., Nesbitt-Hawes, E., Deans, R., & Abbott, J. (2017). Cesarean Scar Pregnancies: A Systematic Review of Treatment Options. *J Minim Invasive Gynecol*, *24*(6), 915-925. <https://doi.org/10.1016/j.jmig.2017.05.019>
- Mol, F., Mol, B. W., Ankum, W. M., van der Veen, F., & Hajenius, P. J. (2008). Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis. *Hum Reprod Update*, *14*(4), 309-319. <https://doi.org/10.1093/humupd/dmn012>
- Molinaro, T. A., & Barnhart, K. T. (2007). Ectopic pregnancies in unusual locations. *Semin Reprod Med*, *25*(2), 123-130. <https://doi.org/10.1055/s-2007-970051>

- Murray, H., Baakdah, H., Bardell, T., & Tulandi, T. (2005). Diagnosis and treatment of ectopic pregnancy. *Cmaj*, 173(8), 905-912. <https://doi.org/10.1503/cmaj.050222>
- Nybo Andersen, A. M., Wohlfahrt, J., Christens, P., Olsen, J., & Melbye, M. (2000). Maternal age and fetal loss: population based register linkage study. *Bmj*, 320(7251), 1708-1712. <https://doi.org/10.1136/bmj.320.7251.1708>
- Parks, J. K., Elliott, A. C., Gentilello, L. M., & Shafi, S. (2006). Systemic hypotension is a late marker of shock after trauma: a validation study of Advanced Trauma Life Support principles in a large national sample. *Am J Surg*, 192(6), 727-731. <https://doi.org/10.1016/j.amjsurg.2006.08.034>
- Reece, E. A., Petrie, R. H., Sirmans, M. F., Finster, M., & Todd, W. D. (1983). Combined intrauterine and extrauterine gestations: a review. *Am J Obstet Gynecol*, 146(3), 323-330. [https://doi.org/10.1016/0002-9378\(83\)90755-x](https://doi.org/10.1016/0002-9378(83)90755-x)
- Rotas, M. A., Haberman, S., & Levгур, M. (2006). Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. *Obstet Gynecol*, 107(6), 1373-1381. <https://doi.org/10.1097/01.AOG.0000218690.24494.ce>
- Schultheis, P., Montoya, M. N., Zhao, Q., Archer, J., Madden, T., & Peipert, J. F. (2021). Contraception and ectopic pregnancy risk: a prospective observational analysis. *Am J Obstet Gynecol*, 224(2), 228-229. <https://doi.org/10.1016/j.ajog.2020.10.013>
- Soriano, D., Vicus, D., Mashiach, R., Schiff, E., Seidman, D., & Goldenberg, M. (2008). Laparoscopic treatment of cornual pregnancy: a series of 20 consecutive cases. *Fertil Steril*, 90(3), 839-843. <https://doi.org/10.1016/j.fertnstert.2007.07.1288>
- Soriano, D., Yefet, Y., Oelsner, G., Goldenberg, M., Mashiach, S., & Seidman, D. S. (1997). Operative laparoscopy for management of ectopic pregnancy in patients with hypovolemic shock. *J Am Assoc Gynecol Laparosc*, 4(3), 363-367. [https://doi.org/10.1016/s1074-3804\(05\)80229-4](https://doi.org/10.1016/s1074-3804(05)80229-4)
- Tang, A., Baartz, D., & Khoo, S. K. (2006). A medical management of interstitial ectopic pregnancy: a 5-year clinical study. *Aust NZ J Obstet Gynaecol*, 46(2), 107-111. <https://doi.org/10.1111/j.1479-828X.2006.00537.x>
- Tulandi, T., Barbieri, R., & Falk, S. (2015). Ectopic pregnancy: Clinical manifestations and diagnosis. *Up to date*.
- Vial, Y., Petignat, P., & Hohlfeld, P. (2000). Pregnancy in a cesarean scar. *Ultrasound Obstet Gynecol*, 16(6), 592-593. <https://doi.org/10.1046/j.1469-0705.2000.00300-2.x>
- Wu, G., Yang, J., Xu, W., Yin, T., Zou, Y., & Wang, Y. (2014). Serum beta human chorionic gonadotropin levels on day 12 after in vitro fertilization in predicting final type of clinical pregnancy. *J Reprod Med*, 59(3-4), 161-166.
- Zhang, D., Shi, W., Li, C., Yuan, J. J., Xia, W., Xue, R. H., Sun, J., & Zhang, J. (2016). Risk factors for recurrent ectopic pregnancy: a case-control study. *Bjog*, 123 Suppl 3, 82-89. <https://doi.org/10.1111/1471-0528.14011>

CHAPTER 8

GESTATIONAL TROPHOBLASTIC DISEASE AND VAGINAL BLEEDING

Dr. Şebnem KARAGÜN¹

¹ Mersin University, Faculty of Medicine, Department of Perinatology, Mersin, Orchid No: 0000-0003-2339-1609, E-mail: karagunsebnem@gmail.com

Gestational Trophoblastic Disease And Bleeding

Introduction

Gestational trophoblastic diseases (GTD) include a group of heterogeneous diseases originating from abnormal placental tissues. It was first described as dropsy of uterus by Hippocrates in 400 BC.(Ober,1961) Gestational trophoblastic diseases are currently defined as a wide group of diseases with different histological patterns. In this group, Gestational Trophoblastic Neoplasia (GTN) represent the subgroup resulting in the development of malignancy. Although GTNs are rare tumors, they have a good prognosis even in the presence of extensive metastases.(Lurain J. R,2010). All forms of gestational trophoblastic disease can be successfully diagnosed and treated with preservation of reproductive function. GTD management has importance because of the high life expectancy, even with GTN. While vaginal bleeding may be the first symptom in gestational trophoblastic diseases (more than 90% of patients) (Lolar S. 2021), it is also an important complication in patients who are in the chemotherapy phase.(Ngan, H. Et all, 2018) This section was written to compile current approaches to the management of GTD-related vaginal bleeding.

Terminology

The first modern classification of trophic neoplasia types was made in 1910. (Ewing, 1910) In 2020, WHO published a revised classification for female genital tract tumors. (McCluggage et al, 2022) Table 1 includes the main headings of GTD classification.

Table 1. (McCluggage et al, 2022)

Trofoblast cell type	Gestational tropholastic disease	Immunohistochemistry (tumours only)
Chorionic villous trophoblast	<ul style="list-style-type: none"> •Hydatidiform mole •Atypical villous lesions 	
Villous intermediate trophoblast	Gestational choriocarcinoma	Syncytiotrophoblastic cells are diffusely positive for hCG, hPL, HSD3B1, and SALL4; Ki67 proliferative index of >90%
Implantation-site	Placental site	Diffusely positive for

intermediate trophoblast	trophoblastic tumour	hPL and MCAM; scattered giant cells positive for hCG; negative for SALL4; Ki67 proliferative index of 10–30%
Implantation-site intermediate trophoblast	Exaggerated implantation site reaction	
Chorionic-type intermediate trophoblast	Epithelioid trophoblastic tumour	Diffusely positive for p63
Chorionic-type intermediate trophoblast	Placental site nodule/atypical placental site nodule	
Mixed intermediate trophoblast	Mixed trophoblastic tumours	Mixture of cell types and corresponding immunohistochemical expression patterns

hCG, Human chorionic gonadotropin; hPL, human placental lactogen; MCAM, melanoma cell adhesion molecule (also known as Mel-CAM); SALL4, member of the spalt-like, sal-like family of transcription factors expressed during stem cell-like differentiation in a variety of tumours.

In the spectrum of GTD disease, the premalignant group includes complete and partial moles, while the malignant group invasive mole, choriocarcinoma and rare placental site and epithelioid trophoblastic tumours (PSTT/ETT) (Clark, J. Et all, 2021)

Hydatidiform moles

The terms mole and hydatidiform were defined by William Smellie (1752) as a bunch of grapes consisting of different sizes. (Slim, R. & Mehio, A. 2007) In humans, 5-6 days after conception, the zygote gradually transforms into a blastocyst. This blastocyst then invades the endometrium and uterine vasculature. When the proliferation/invasion phenomenon does not occur properly, trophoblast cells can lead to a rare pregnancy complication known as hydatidiform mole (complete or partial). (Candelier J. J. 2016). The moles exhibit diffuse trophoblastic hyperplasia where the structures of villousities are particularly aberrant and hydropic. Such dysregulation of the trophoblast may result from faulty formation of vascular

structures, increased level of apoptosis in precursor components of blood vessels, or defective recruitment of pericytes around villous stromal vessels.(Kim, K et al., 2015) This persistent faulty vascular organization of the villous stroma can lead to hydropic villi mainly in CHM. In partial hydatiform mole (PHM), these trophoblastic anomalies are less common and usually contain identifiable embryonic or fetal tissue. Differentiation of partial mole from abnormal villous structures accompanied by nonmolar hydropic degenerations and nonmolar aneuploidic pregnancies can be diagnostically challenging. (Han, L 2020) The distinctive pathological features and clinical presentations of CHM and PHM are summarized in Table 2.(Soper, J. Et all, 2004)

Table 2. (Soper, J. Et all, 2004)

Feature	Partial hydatiform mole	Compleat mole
Karyotype	Most commonly 69,XXX or 69,XX 2/3 paternal, 1/3 maternal origin	Most commonly 46,XX or 46,XY diandric diploidy
Fetus	Often present	Absent
Amnion, fetal red blood cells	Usually present	Absent
Villous edema	Focal	Diffuse
Diagnosis	Missed abortion	Molar gestation
Theca lutein cysts	Rare	% 15- 20
Postmolar malignant sequelae	<5%	6–32%

In the United States, hydatidiform moles are observed in approximately 1 in 600 therapeutic abortions and 1 in 1500 pregnancies.(Soper, J. et all, 2004) In the follow-up of molar pregnancies, malignant disease progression requiring chemotherapy is observed in approximately 20% of patients.

Patients with CHM are typically referred to an obstetrician because of signs and symptoms consistent with missed periods, early pregnancy or early

pregnancy complications. Table 3 summarizes the symptoms of molar pregnancy.(Soto-Wright et all, 1995)

Table 3 Clinical features of molar pregnancy

Common features	Less common or late features
Vaginal bleeding	Hyperthroidism
Pelvic pressure and pain	Theca lutein cyst
Uterin size greater than gestational age	Preeclampcia before 20 weeks of gestation
Hyperemesis gravidarum	Anemia

With the increasing access to ultrasonography and sensitive hCG measurement, the diagnosis of molar pregnancies can be easily made in the first trimester. It has been reported that complications such as excessive vaginal bleeding have decreased with the early diagnosis of CHM. (Joneborg, U. & Marions, L., 2014)

Maternal age is a well-known risk factor for CHM: women over 40 are 10 times more likely to develop HM compared to younger women. In a one study investigating the effect of age on the course of molar pregnancy, it was shown that abnormal vaginal bleeding, hyperemesis gravidarum, and termination of pregnancy after 12 weeks were more common in women over 40 years of age. In addition, the increase in uterine size was greater in this group. (Mangili, G.et all, 2014) A delayed diagnosis with increasing age in molar pregnancy not only causes life-threatening vaginal bleeding, but also cause to have a larger trophoblastic mass. (Mangili, G.et all, 2014) Although GTD often presents with vaginal bleeding, it can also rarely cause hemoperitoneum due to uterine rupture. (Maheut, C. et al, 2021) Repair of uterine rupture by laparoscopy without the need for hysterectomy in a case of hemoperitoneum due to molar pregnancy also offered a conservative option in the management of bleeding.(Grin, L. et all, 2017)

Uterine evacuation of HM is the cornerstone of treatment. The use of iv oxytocin during evacuation is recommended to reduce bleeding that may occur during the procedure. Rh immune globulin should be given to Rh-negative women at the time of molar evacuation as RhD factor is expressed on the trophoblast.(Soper J. T., 2021). Induction or hysterotomy have no place in the management of molar pregnancy, as they increase maternal morbidity and the risk of postmolar GTN requiring chemotherapy. (Ngan, H.

Et al, 2018) Hysterectomy is a reasonable management method in HM in women over 40 who have completed their fertility. (Lurain, J. R et al, 1983) The risk of GTN, which is 15-20% after evacuation, has been reported as 3-5% if hysterectomy is performed instead of evacuation. (Ngan, H. Et al, 2018)

Postmolar Gestational Trophoblastic Neoplasia

Postmolar GTN is typically diagnosed using hCG monitoring after molar pregnancy termination. The NCCN Guidelines use FIGO staging criteria for postmolar GTN as specified by the hCG monitor as it meets one of the following criteria after HM therapy. (FIGO Oncology Committee 2002).

- hCG levels plateau for 4 consecutive values over ≥ 3 weeks
- hCG levels rise $\geq 10\%$ for 3 values over ≥ 2 weeks
- hCG persistence 6 months or more after molar evacuation

Second curettage or hysterectomy can be considered for persistent postmolar GTN. (Pezeshki, M et al, 2004) In a recent randomized controlled trial, second uterine curettage did not significantly reduce the number of chemotherapy courses among postmolar gestational trophoblastic neoplasia patients. Postmolar GTN may also present with excessive vaginal bleeding that may require surgery. (Hemida R.,2019)

Gestational Trophoblastic Neoplasia

Gestational trophoblastic neoplasia (GTN) consists of a group of malignant neoplasms that can follow a hydatidiform or non-molar pregnancy. GTN is divided into the following histological types:

- Invasive mole
- Choriocarcinoma
- Placental site trophoblastic tumor (PSTT)
- Epithelioid trophoblastic tumor (ETT)

Clinical Presentation of GTN

The presentation of GTN may differ depending on the previous pregnancy event, disease extent and condition of the patient.. Postmolar GTN, including invasive mole or choriocarcinoma, presents with increased

irregular vaginal bleeding, uterine subinvolution, and adnexal mass after initial treatment of a molar pregnancy. (Abu-Rustum et al, 2019) Rarely, vaginal metastatic trophoblastic lesion observed during curettage may cause uncontrolled excessive bleeding.(Lurain J. R., 2010).

Uterine perforation due to increased tumoral mass and bleeding due to immature angiogenesis of metastatic lesions can manifest themselves in many different ways. Increased intracranial pressure as a result of bleeding from brain metastases may cause headache, seizures, and neurological deficits, while dyspnea, hemoptysis, and chest pain may be observed in pulmonary metastases.(Lurain J. R., 2010). ETT and PSTT typically present with irregular uterine bleeding that occurs after a previous pregnancy. Apart from bleeding, ETT may present with small bowel obstruction, a mass protruding into the cervix in routine gynecological examination, and an incidental lung mass on x-ray examination. (Shih, I. M. & Kurman, R. J. 1998). Although PSST presents with findings such as amenorrhea, back pain due to spinal metastases, nephrotic syndrome, headache due to brain metastases, the most common symptom is irregular vaginal bleeding. (Hyman, D. Et al, 2013)

Invasive mole

Invasive mole develops after a molar pregnancy when molar villi invade the myometrium. (Hyman, D. Et al, 2012) While 15% of CHMs will develop local invasion and 5% will usually metastasize to the lungs and vagina. In PHM, on the other hand, the development of metastases is different from CHM, the development of local invasion occurs in only 3% to 5% of patients, and metastatic disease is extremely rare.

Choriocarcinoma

Choriocarcinoma consists of invasive, highly vascular, and anaplastic trophoblastic tissue made up of cytotrophoblasts and syncytiotrophoblasts without villi. There are two major types of choriocarcinoma which are gestational and non-gestational. They have very different pathophysiology and prognosis. The former arises following a hydatidiform mole, normal pregnancy, or most commonly, spontaneous abortion, while non-gestational choriocarcinoma arises from pluripotent germ cells. (Stockton, L et al, 2018) Choriocarcinoma, which is the most aggressive histological type among GTN, metastasizes mostly to the lung, brain, liver and pelvis by

hematogenous route. It presents with bleeding where it metastasizes. (Lurain J. R. 2010)

Placental site trophoblastic tumor

PSTTs are malignancies that usually occur after a nonmolar abortion or pregnancy, in which the chorionic villi are not observed. (Osborne, R. & Dodge, J. 2012). PSTT exhibits different behavioral patterns than choriocarcinoma, such as lower hCG secretion, less vascular invasion, and a tendency to localize in the uterus for a longer period of time before metastasis. (Baergen, R. N. et al, 2006)

Epithelioid trophoblastic tumor

ETT is a neoplastic transformation of the chorionic terminal extravillous trophoblast that classically occurs in women of reproductive age, usually after a normal pregnancy. At diagnosis, these tumors detectable as roughly nodular infiltrates in the myometrium. (McGregor, S et al, 2020)

Pretherapy Evaluation of GTN

The first step after GTN diagnosis is staging and risk scoring. Along with the history and physical examinations, the following evaluation should be performed: complete blood count, clotting function studies, renal and liver function studies, blood type and determination of pretherapy hCG level. The hCG level that used to evaluate the GTN Risk scoring is obtained in the diagnosis of gestational trophoblastic neoplasia, not in the first evacuation of the molar pregnancy. Biopsy should not be performed due to the risk of excessive bleeding from visible lesions in the vagina and cervix. In the search for metastases for GTN, a contrast-enhanced chest/abdominal/pelvic CT scan is recommended, and if there is pulmonary metastases and neurological symptoms, a brain MRI (preferred) or a brain CT is recommended. (Abu-Rustum et al, 2019)

Staging of Gestational Trophoblastic Neoplasia

Currently, the 2000 FIGO staging system (Table 4) is the standard classification in the management of GTN, while a modified World Health Organization (WHO) prognostic index score (Table 5) also ranks patients as low risk and high risk. (Ngan, H. Y. Et al, 2003)

Table 4 FIGO 2000 Staging and Classification of GTN

Stage 1	Disease confined to the uterus
Stage 2	Direct extension or metastasis to other genital structures
Stage 3	Lung metastasis
Stage 4	Nonpulmonary distant metastasis

Table 5 Modified WHO Risk Scoring System as Adapted by FIGO

Prognostic Factor	0	1	2	4
Age	<40	≥40		
Previous pregnancy	Hydatidiform mole	Abortion	Term	
Months since last pregnancy	< 4	4-6	7-12	>12
Pretreatment hCG (IU/mL)	<10 ³	10 ³ to 10 ⁴	>10 ⁴ to 10 ⁵	>10 ⁵
Tumor size (cm)	<3	3-4	≥5	-
Site of metastases	Lung	Splen, kidney	Gastrointestinal Tract	Brain, liver
Number of metastases		1-4	5-8	>8
Previous Failed chemotherapy			Single Drug	≥2

Management of low risk GTN

All patients with low-risk gestational trophoblastic neoplasia can be treated with single agent chemotherapy, usually without the need for hysterectomy if fertility preservation is desired. The most frequently used

single-agent regimens with methotrexate and actinomycin D. (Lawrie, T. A. et al, 2016) Serum hCG levels are monitored during chemotherapy and when hCG values normalize, additional cycles of consolidation therapy are usually administered. The FIGO and National Comprehensive Cancer Network recommend two to three cycles of consolidation chemotherapy after hCG normalization. (Lybol, C. et al, 2012)

Management of high risk GTN

High-risk GTN patients are uniquely sensitive to chemotherapy, with the exception of PSST and ETTT.(Braga, A. et al, 2021) Since all high-risk GTN patients may develop resistance to single-agent chemotherapy, multi-agent regimens are preferred for treatment. (Ross, G.T. et al, 1965). The current regimen, which provides complete response rates of 71% to 78% and long-term survival rates of 85% and 94% for high-risk GTN patients, is the use of etoposide, methotrexate (MTX) and ActinomycinD (ActD) in alternation with cyclophosphamide and vincristine (EMA-CO). (Lurain, J. R. Et al) Treatment should be continued until the hCG level remains undetectable for 3 consecutive weeks. Finally, after the patient reaches undetectable hCG levels, we administer at least three courses of EMA-CO as consolidation therapy to reduce the risk of recurrence. (Braga, A. et al, 2021) Although there are no universally accepted guidelines, patients with PSTT or ETT should be treated with a combination of surgery and chemotherapy because of their poor prognosis. Multi-agent regimens are often used, including EMA/CO or EMA-EP. (Papadopoulos, A, et al, 2002)

Bleeding management in GTD

Gestational trophoblastic disease typically occurs in women with a desire to preserve fertility. The mean age at diagnosis for women from different ethnic groups ranges from 21,6 to 23,4. (Drake. R. D. et al, 2006) The mainstay of treatment for GTD in this group of young patients is uterine evacuation. (Ngan, H. et al, 2018) Uterine evacuation is more complicated in GTD than in other benign conditions. After uterine evacuation, persistent vaginal bleeding can be observed. This may be due to GTD disrupting the normal anatomical vasculature, vessel-invading trophoblastic tissues, and impaired hemostasis. While GTD causes excessive proliferation of trophoblastic tissue, it also leads to the development of many small vessels by invasion of the endometrium and myometrium. Therefore, GTD is highly

vascular and associated with massive hemorrhage. (Touhami O. et al, 2014) When repeat uterine evacuation fails to completely stop ongoing vaginal bleeding, more aggressive interventions are typically required, such as total abdominal hysterectomy, arterial ligation, or embolization to control bleeding. (Tse, K. Y. et al, 2007) Bacri balloon use instead of invasive procedures has been found to be successful in persistent vaginal bleeding after uterine evacuation. (Kolomeyevskaya, N. V et al, 2009)

Bleeding management in GTN

With successful chemotherapy methods, the mortality of GTN patients has been significantly reduced. In advanced disease, the prognosis may be compromised by other complications, such as vaginal or intraperitoneal bleeding, which can be life-threatening.

The incidence of vaginal metastases in GTN is 4%, and these lesions are usually located on the anterior vaginal wall. Excision, suturing and embolization are used in the management of those who are symptomatic to require blood transfusion. (Berry, E. et al, 2008) According to a recent case report, excessive vaginal bleeding was stopped with vaginal packing in a patient with vaginal metastasis due to invasive mole. (Mamede, R. et al, 2021)

One of the causes of vaginal bleeding that complicates the management in GTN is uterine arteriovenous malformations (AVM). Uterine AVM may cause chronic vaginal bleeding or life-threatening bleeding even if no residual tumor remains after chemotherapy. Even if there is complete resolution, the probability of uterine AVM in GTN is 10-15%, but only 3% of them cause chronic bleeding. (McGrath, S. et al, 2012) While ultrasound imaging with pulsed Doppler analysis and MRI are helpful for the diagnosis and localization of uterine AVM, angiography is essential for treatment planning. (Touhami, O. et al, 2014) Treatment of uterine AVM is based on the amount of vaginal bleeding, the location of the lesion, the extent of GTN, and the desire for future fertility. In a GTN study investigating the efficacy of angiographic embolization therapy, bilateral internal iliac arteries or bilateral uterine arteries embolization was performed according to the location of the lesion, and the success rate was found to be 85%. (Keepanasseril, A. et al, 2011) There is also a case study in which uterine AVM lesions causing vaginal bleeding were managed laparoscopically, not by embolization. (Corusic, A. et al, 2009) In patients with hemorrhagic GTN,

uterine AVM embolization has advantages such as prevention of operative hemorrhagic complications and rapid recovery time, in addition to its fertility-preserving effect. (Tsai, C. C. et al, 2006) In case of embolization failure, surgical uterine artery ligation may also be attempted before hysterectomy. (Milingos, D. et al, 2007)

Uterine rupture is a rare complication of GTN that presents with bleeding and requires urgent surgical intervention. In a study in which uterine resection was performed with a fertility-preserving approach in the presence of uterine rupture, the risk of recurrence was found to be similar to the general risk of GTN population. (Wang, X. et al, 2017)

In a study that analyzed situations requiring surgery in the management of GTN, it was observed that patients with hysterectomy had advanced-stage GTN with large tumor size that did not respond to chemotherapy. Also in this group, there were patients who had nephrectomy, craniotomy and partial lung resection due to bleeding due to a metastasis and chemotherapy resistance. (Fülöp, V. et al, 2016) In a study examining premature deaths caused by GTN, fatal tumor bleeding due to masses in the brain and lungs, such as vaginal bleeding, also caused the loss of patients. (Lybol, C. et al, 2012) In a retrospective study examining deaths due to GTN, it was found that 46% of all deaths were caused by vaginal bleeding and bleeding due to metastases. (Freitas, F. et al, 2020)

Conclusions

As a result, GTN is a disease group that has a high life expectancy and is mostly cured with chemotherapy with a fertility-preserving approach. Even in the presence of GTN, life extension has increased compared to the past with accurate staging, progressive imaging methods, effective chemotherapy and most importantly, follow-up of patients in referral centers. In a study on the reduction of mortality in patients treated in referral centers by nine times, this was attributed to more effective management of complications such as vaginal bleeding in these centers. (Brewer, J. et al, 1971) While vaginal bleeding can be the first sign of GTD, it can also be a complication that will cause death of the patient in GTN. Nowadays, with the use of non-invasive options such as angiography and embolization, these patients can be managed without the need for surgery. At this point, the important thing is to recognize high-risk patients at the right time and direct

them to referral centers that can treat them with a multidisciplinary approach.

REFERENCES

- Abu-Rustum, N. R., Yashar, C. M., Bean, S., Bradley, K., Campos, S. M., Chon, H. S., Chu, C., Cohn, D., Crispens, M. A., Damast, S., Dorigo, O., Eifel, P. J., Fisher, C. M., Frederick, P., Gaffney, D. K., Han, E., Huh, W. K., Lurain, J. R., Mariani, A., Mutch, D., ... Scavone, J. (2019). Gestational Trophoblastic Neoplasia, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN*, 17(11), 1374–1391.
- Baergen, R. N., Rutgers, J. L., Young, R. H., Osann, K., & Scully, R. E. (2006). Placental site trophoblastic tumor: A study of 55 cases and review of the literature emphasizing factors of prognostic significance. *Gynecologic oncology*, 100(3), 511–520.
- Berry, E., Hagopian, G. S., & Lurain, J. R. (2008). Vaginal metastases in gestational trophoblastic neoplasia. *The Journal of reproductive medicine*, 53
- Braga, A., Elias, K. M., Horowitz, N. S., & Berkowitz, R. S. (2021). Treatment of high-risk gestational trophoblastic neoplasia and chemoresistance/relapsed disease. *Best practice & research. Clinical obstetrics & gynaecology*, 74, 81–96.
- Brewer, J. I., Eckman, T. R., Dolkart, R. E., Torok, E. E., & Webster, A. (1971). Gestational trophoblastic disease. A comparative study of the results of therapy in patients with invasive mole and with choriocarcinoma. *American journal of obstetrics and gynecology*, 109(2), 335–340.
- Candelier J. J. (2016). The hydatidiform mole. *Cell adhesion & migration*, 10(1-2), 226–235.
- Clark, J. J., Slater, S., & Seckl, M. J. (2021). Treatment of gestational trophoblastic disease in the 2020s. *Current opinion in obstetrics & gynecology*, 33(1), 7–12.
- Corusic, A., Barisic, D., Lovric, H., Despot, A., & Planinic, P. (2009). Successful laparoscopic bipolar coagulation of a large arteriovenous malformation due

- to invasive trophoblastic disease: a case report. *Journal of minimally invasive gynecology*, 16(3), 368–371.
- Drake, R. D., Rao, G. G., McIntire, D. D., Miller, D. S., & Schorge, J. O. (2006). Gestational trophoblastic disease among Hispanic women: a 21-year hospital-based study. *Gynecologic oncology*, 103(1), 81–86.
- Ewing J. Chorioma: a clinical and pathological study. *Surg Gynecol Obstet* 1910;10:366e92.
- FIGO Oncology Committee (2002). FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Oncology Committee. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, 77(3), 285–287.
- Freitas, F., Braga, A., Viggiano, M., Velarde, L., Maesta, I., Uberti, E., Madi, J. M., Yela, D., Fernandes, K., Silveira, E., Leal, E., Sun, S. Y., Dos Santos Esteves, A., Filho, J. R., Junior, J. A., Elias, K. M., Horowitz, N. S., & Berkowitz, R. S. (2020). Gestational trophoblastic neoplasia lethality among Brazilian women: A retrospective national cohort study. *Gynecologic oncology*, 158(2), 452–459.
- Fülöp, V., Szigetvári, I., Szepesi, J., Végh, G., Zsirai, L., & Berkowitz, R. S. (2016). The Role of Surgery in the Management of Gestational Trophoblastic Neoplasia The Hungarian Experience. *The Journal of reproductive medicine*, 61(5-6), 197–204.
- Goldstein, D. P., & Berkowitz, R. S. (2012). Current management of gestational trophoblastic neoplasia. *Hematology/oncology clinics of North America*, 26(1), 111–131.
- Grin, L., Namazov, A., Volodarsky, M., Anteby, E., Lavie, O., & Gemer, O. (2017). Laparoscopic Management of an Invasive Mole Perforating the Uterus. *Journal of minimally invasive gynecology*, 24(2), 199–200.
- Han, L. M., Grenert, J. P., Wiita, A. P., Quinn, M., Fujimoto, V. Y., & Rabban, J. T. (2020). Prevalence of Partial Hydatidiform Mole in Products of Conception From Gestations With Fetal Triploidy Merits Reflex Genotype Testing

- Independent of the Morphologic Appearance of the Chorionic Villi. *The American journal of surgical pathology*, 44(6), 849–858.
- Hemida, R., Vos, E. L., El-Deek, B., Arafa, M., Toson, E., Burger, C. W., & van Doorn, H. C. (2019). Second Uterine Curettage and the Number of Chemotherapy Courses in Postmolar Gestational Trophoblastic Neoplasia: A Randomized Controlled Trial. *Obstetrics and gynecology*, 133(5), 1024–1031.
- Hyman, D. M., Bakios, L., Gualtiere, G., Carr, C., Grisham, R. N., Makker, V., Sonoda, Y., Aghajanian, C., & Jewell, E. L. (2013). Placental site trophoblastic tumor: analysis of presentation, treatment, and outcome. *Gynecologic oncology*, 129(1), 58–62.
- Joneborg, U., & Marions, L. (2014). Current clinical features of complete and partial hydatidiform mole in Sweden. *The Journal of reproductive medicine*, 59(1-2), 51–55.
- Keepanasseril, A., Suri, V., Prasad, G. R., Gupta, V., Bagga, R., Aggarwal, N., Dhaliwal, L. K., & Khandelwal, N. (2011). Management of massive hemorrhage in patients with gestational trophoblastic neoplasia by angiographic embolization: a safer alternative. *The Journal of reproductive medicine*, 56(5-6), 235–240.
- Kim, K. R., Sung, C. O., Kwon, T. J., Lee, J., & Robboy, S. J. (2015). Defective pericyte recruitment of villous stromal vessels as the possible etiologic cause of hydropic change in complete hydatidiform mole. *PloS one*, 10(4), e0122266.
- Kolomeyevskaya, N. V., Tanyi, J. L., Coleman, N. M., Beasley, A. D., Miller, H. J., & Anderson, M. L. (2009). Balloon tamponade of hemorrhage after uterine curettage for gestational trophoblastic disease. *Obstetrics and gynecology*, 113(2 Pt 2), 557–560.
- Lawrie, T. A., Alazzam, M., Tidy, J., Hancock, B. W., & Osborne, R. (2016). First-line chemotherapy in low-risk gestational trophoblastic neoplasia. *The Cochrane database of systematic reviews*, 2016(6), CD007102.

- Lolar S. (2021). Gestational trophoblastic disease. *JAAPA : official journal of the American Academy of Physician Assistants*, 34(4), 52–53. <https://doi.org/10.1097/01.JAA.0000735796.40503.de>
- Lurain J. R. (2010). Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *American journal of obstetrics and gynecology*, 203(6), 531–539.
- Lurain J. R. (2010). Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *American journal of obstetrics and gynecology*, 203(6), 531–539.
- Lurain, J. R., Brewer, J. I., Torok, E. E., & Halpern, B. (1983). Natural history of hydatidiform mole after primary evacuation. *American journal of obstetrics and gynecology*, 145(5), 591–595.
- Lurain, J. R., Singh, D. K., & Schink, J. C. (2006). Primary treatment of metastatic high-risk gestational trophoblastic neoplasia with EMA-CO chemotherapy. *The Journal of reproductive medicine*, 51(10), 767–772.
- Lybol, C., Centen, D. W., Thomas, C. M., ten Kate-Booij, M. J., Verheijen, R. H., Sweep, F. C., Ottevanger, P. B., & Massuger, L. F. (2012). Fatal cases of gestational trophoblastic neoplasia over four decades in the Netherlands: a retrospective cohort study. *BJOG : an international journal of obstetrics and gynaecology*, 119(12), 1465–1472.
- Lybol, C., Sweep, F. C., Harvey, R., Mitchell, H., Short, D., Thomas, C. M., Ottevanger, P. B., Savage, P. M., Massuger, L. F., & Seckl, M. J. (2012). Relapse rates after two versus three consolidation courses of methotrexate in the treatment of low-risk gestational trophoblastic neoplasia. *Gynecologic oncology*, 125(3), 576–579.
- Maheut, C., Rollin, I., Baissas, P., Panel, P., & Niro, J. (2021). Management of uterine rupture during molar pregnancy. *Journal of gynecology obstetrics and human reproduction*, 50(7), 102058.

- Mamede, R., Beja, M., Djokovic, D., & Costa, C. (2021). Invasive mole presenting as a heavily bleeding vaginal lesion 3 weeks after uterine evacuation. *BMJ case reports*, 14(6), e242208.
- Mangili, G., Giorgione, V., Gentile, C., Bergamini, A., Pella, F., Almirante, G., & Candiani, M. (2014). Hydatidiform mole: age-related clinical presentation and high rate of severe complications in older women. *Acta obstetrica et gynecologica Scandinavica*, 93(5), 503–507.
- McCluggage, W. G., Singh, N., & Gilks, C. B. (2022). Key changes to the World Health Organization (WHO) classification of female genital tumours introduced in the 5th edition (2020). *Histopathology*, 80(5), 762–778.
- McGrath, S., Harding, V., Lim, A. K., Burfitt, N., Seckl, M. J., & Savage, P. (2012). Embolization of uterine arteriovenous malformations in patients with gestational trophoblastic tumors: a review of patients at Charing Cross Hospital, 2000-2009. *The Journal of reproductive medicine*, 57(7-8), 319–324.
- McGregor, S. M., Furtado, L. V., Montag, A. G., Brooks, R., & Lastra, R. R. (2020). Epithelioid Trophoblastic Tumor: Expanding the Clinicopathologic Spectrum of a Rare Malignancy. *International journal of gynecological pathology : official journal of the International Society of Gynecological Pathologists*, 39(1), 8–18. Ngan, H. Y., Bender,
- Milingos, D., Doumplis, D., Sieunarine, K., Savage, P., Lawson, A. D., & Smith, J. R. (2007). Uterine arteriovenous malformation: fertility-sparing surgery using unilateral ligation of uterine artery and ovarian ligament. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*, 17(3), 735–737.
- Ngan, H. Y., Bender, H., Benedet, J. L., Jones, H., Montrucoli, G. C., Pecorelli, S., & FIGO Committee on Gynecologic Oncology (2003). Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, 83 Suppl 1, 175–177.

- Ngan, H., Seckl, M. J., Berkowitz, R. S., Xiang, Y., Golfier, F., Sekharan, P. K., Lurain, J. R., & Massuger, L. (2018). Update on the diagnosis and management of gestational trophoblastic disease. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, 143 Suppl 2, 79–85.
- Ober WB, Fass RO. The early history of choriocarcinoma. *Ann NY Acad Sci* 1961; 172: 299–426.
- Osborne, R., & Dodge, J. (2012). Gestational trophoblastic neoplasia. *Obstetrics and gynecology clinics of North America*, 39(2), 195–212.
- Papadopoulos, A. J., Foskett, M., Seckl, M. J., McNeish, I., Paradinas, F. J., Rees, H., & Newlands, E. S. (2002). Twenty-five years' clinical experience with placental site trophoblastic tumors. *The Journal of reproductive medicine*, 47(6), 460–464.
- Pezeshki, M., Hancock, B. W., Silcocks, P., Everard, J. E., Coleman, J., Gillespie, A. M., Tidy, J., & Coleman, R. E. (2004). The role of repeat uterine evacuation in the management of persistent gestational trophoblastic disease. *Gynecologic oncology*, 95(3), 423–429.
- Ross, G. T., Goldstein, D. P., Hertz, R., Lipsett, M. B., & Odell, W. D. (1965). Sequential use of methotexate and Actinomycin D in the Treatment of metastatic choriocarcinoma and related trophoblastic diseases in women. *American journal of obstetrics and gynecology*, 93, 223–229.
- Shih, I. M., & Kurman, R. J. (1998). Epithelioid trophoblastic tumor: a neoplasm distinct from choriocarcinoma and placental site trophoblastic tumor simulating carcinoma. *The American journal of surgical pathology*, 22(11), 1393–1403.
- Slim, R., & Mehio, A. (2007). The genetics of hydatidiform moles: new lights on an ancient disease. *Clinical genetics*, 71(1), 25–34.
- Soper J. T. (2021). Gestational Trophoblastic Disease: Current Evaluation and Management. *Obstetrics and gynecology*, 137(2), 355–370.
- Soper, J. T., Mutch, D. G., Schink, J. C., & American College of Obstetricians and Gynecologists (2004). Diagnosis and treatment of gestational trophoblastic

- disease: ACOG Practice Bulletin No. 53. *Gynecologic oncology*, 93(3), 575–585.
- Soto-Wright, V., Bernstein, M., Goldstein, D. P., & Berkowitz, R. S. (1995). The changing clinical presentation of complete molar pregnancy. *Obstetrics and gynecology*, 86(5), 775–779.
- Stockton, L., Green, E., Kaur, B., & De Winton, E. (2018). Non-Gestational Choriocarcinoma with Widespread Metastases Presenting with Type 1 Respiratory Failure in a 39-Year-Old Female: Case Report and Review of the Literature. *Case reports in oncology*, 11(1), 151–158.
- Touhami, O., Gregoire, J., Noel, P., Trinh, X. B., & Plante, M. (2014). Uterine arteriovenous malformations following gestational trophoblastic neoplasia: a systematic review. *European journal of obstetrics, gynecology, and reproductive biology*, 181, 54–59.
- Touhami, O., Gregoire, J., Noel, P., Trinh, X. B., & Plante, M. (2014). Uterine arteriovenous malformations following gestational trophoblastic neoplasia: a systematic review. *European journal of obstetrics, gynecology, and reproductive biology*, 181, 54–59.
- Tsai, C. C., Cheng, Y. F., Changchien, C. C., & Lin, H. (2006). Successful term pregnancy after selective embolization of a large postmolar uterine arteriovenous malformation. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*, 16 Suppl 1, 439–441.
- Tse, K. Y., Chan, K. K., Tam, K. F., & Ngan, H. Y. (2007). 20-year experience of managing profuse bleeding in gestational trophoblastic disease. *The Journal of reproductive medicine*, 52(5), 397–401.
- Wang, X., Yang, J., Li, J., Zhao, J., Ren, T., Feng, F., Wan, X., & Xiang, Y. (2017). Fertility-sparing uterine lesion resection for young women with gestational trophoblastic neoplasias: single institution experience. *Oncotarget*, 8(26), 43368–43375.

CHAPTER 9

GENITAL INFECTIONS IN PREGNANCY AND BLEEDING

Dr. Ayşe GÜLMEZ¹

¹ Selcuk University Faculty of Medicine, Department of Gynecological Oncology, Konya, Turkey orcid no; 0000-0002-3021-8655, ayseyilmazsoy@gmail.com

INTRODUCTION

The genital flora of healthy women consists of a wide variety of anaerobic and aerobic bacteria, predominantly lactobacilli, which are facultative, microaerophilic and anaerobic. Lactobacilli are the most well-known members of normal vaginal flora (Donati).

Genital microflora has an important role in the prevention of vaginal infections such as bacterial vaginosis (BV), viral infections and sexually transmitted diseases (Jayaram PM). During pregnancy, some differences occur in the female genital tract microbiome due to metabolic, endocrinological and immunological changes. These changes may cause infections in fetoplacental unit via the ascending road. These states lead to chronic inflammatory situations and may be associated with adverse maternal and neonatal outcome. Vulvovaginal Candidiasis (VVC), Bacterial Vaginosis (BV) and Trichomonas Vaginitis (TV) are the common vaginal infections in pregnancy (Bagga).

The prevalence of lower genital tract infections in healthy pregnant women is around 40-54%, which is quite a high rate. Specific pathogens that were isolated from the vagina and/or cervix of asymptomatic pregnant women include: *C. albicans* (14-42%), *T. vaginalis* (11-20%), *C. trachomatis* (7-31%), *N. gonorrhoea* (0.5-14%) and group B streptococcus (4-25%). Untreated, genital tract infections in pregnant women may result in: fetal loss, preterm labor, preterm birth, premature rupture of the membranes, low birthweight, eye and lung damage in the newborn. (Marai W. (2001).

Genital tract infections may result from disruption of the genital flora or from external pathogens, most of which are sexually transmitted diseases. (Brunham). Sexually transmitted infections (STIs), such as chlamydial, gonorrhea, and trichomonal infections, are common in pregnant women in many countries and there are many publications linking them with increased maternal and neonatal adverse outcomes. A successful pregnancy depends on both maternal tolerance of the fetal immune system and resistance to microorganisms. Infection with pathogenic microorganisms during pregnancy may cause premature delivery, miscarriage, growth restriction, neonatal morbidity, and other adverse outcomes. Moreover, the host also has an intact immune system to avoid these adverse outcomes.

Vaginal microbiota in pregnancy

Vaginal microbiota occurs predominantly in lactobacilli in both pregnant and non-pregnant women.

Bacterial vaginosis is a vaginal infection that consists of reduction of lactobacilli and multiplication of various anaerobic bacteria. (Jayaram PM).

Although there is microbial colonization in the cervicovaginal epithelium, the upper genital tract is considered sterile. Teisela K.1987, Goplerud).During pregnancy, the body undergoes hormonal, metabolic and immunological changes that are essential for normal fetal development. In addition to these changes, which are necessary for physiological adaptation, changes in the microbiota can affect maternal-fetal health. (Dobbler)

Although the occurrence and diagnosis of vulvovaginitis in pregnant women similar in nonpregnant women, the management of various vulvar and vaginal infections during pregnancy often presents a clinical dilemma. First, the effects of the medications sometimes may be teratogenic and should be avoided in pregnant women. Second, due to some changes in the microflora during pregnancy, it can cause some infections that are more resistant to treatment. (Sullivan C)

The vagina has a squamous epithelium and is adequate to bacterial vaginosis, trichomoniasis, and candidiasis. The endocervix has a columnar epithelium and is adequate to infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or less commonly, herpes simplex virus. (Wilson J.F.(2009)

Chlamydia trachomatis

Chlamydia trachomatis (*C. trachomatis*), a Gram-negative obligate intracellular bacterium and the most common sexually transmitted bacterial infection especially in young women.(He).

Chlamydia and gonorrhea are common infections that can affect pregnancy outcomes. Prevalence of chlamydia in pregnancy is 2% to 20% depending on the population. The risk of chlamydial conjunctivitis and pneumonia is increased in newborns born by normal vaginal delivery from women with genital *Chlamydia trachomatis* infection.(Leeper, C., (2018)

Genital *Chlamydia trachomatis* (*C.trachomatis*) infection may lead to pregnancy complications such as miscarriage, preterm labour, low birthweight, preterm rupture of membranes, increased perinatal mortality, postpartum endometritis, chlamydial conjunctivitis (in newborn) and *C.trachomatis* pneumonia (in newborn) (Cluver, C., 2017). Also, untreated chlamydial infections can lead to

intrapartum fever and late postpartum endometritis. Untreated puerperal chlamydial infection leads to approximately 20% of postpartum upper genital tract infection (especially late postpartum endometritis). While rare during pregnancy, persistent upper genital tract infection can lead to pelvic inflammatory disease and its sequelae, i.e. infertility, ectopic pregnancy and chronic pelvic pain beyond the peripartum period. Mother-to-infant transmission at the time of delivery also occurs. Pregnancy may increase susceptibility to chlamydial infections due to physiological immunosuppression.

Maternal antibodies to *C. trachomatis* do not provide adequate protection for the newborn. (Smith, J. R., (1993). Newborns born to mothers with chlamydia infection will develop conjunctivitis, and late-onset pneumonia.

Chlamydial infections of the female genital tract are often asymptomatic. Therefore, screening all pregnant women early during pregnancy and treating the infected ones has been the mainstay of intervention strategies focusing on obstetric populations (Genc M. R. 2002).

Diagnostic techniques include nucleic acid amplification testing (NAAT), culture, antigen detection, and genetic probes; microscopy is not useful for the diagnosis of chlamydia. Because of high sensitivity and specificity and wide availability, NAAT is the diagnostic technique of choice.

Nucleic acid amplification testing (test of choice) — Nucleic acid amplification testing (NAAT) methodology consists of amplifying *C. trachomatis* DNA or RNA sequences using polymerase chain reaction (PCR), transcription-mediated amplification (TMA), or strand displacement amplification (SDA). These sensitive, specific tests have become the "gold standard" and are the preferred diagnostic method, if available (Dize; Workowski).

Bacterial vaginosis

Bacterial vaginosis is the most common lower genital tract infection among women of reproductive age, and the most common cause of vaginitis in both pregnant and nonpregnant women (Yudin M. H., 2005). Bacterial vaginosis is caused by anaerobic bacteria (*Prevotella*, *Mobiluncus*, *Gardnerella vaginalis*, *Ureaplasma*, *Mycoplasma*), and does not cause inflammation. Symptoms are fishy odor; thin, homogenous discharge that

may worsen after intercourse; pelvic discomfort may be present (Paladine, H. L., 2018).

Vaginal discharge based on changes in a vaginal ecosystem (decreasing number of *Lactobacillus* and increasing number of *Mobiluncus* spp., *Gardnerella vaginalis*, *Prevotella* spp., *Mycoplasma hominis*, *Peptostreptococcus* spp) appears to be a major cause of bacterial vaginosis (Romanik).

Bacterial vaginosis was associated with recurrent late second trimester miscarriage and preterm labour. Observational studies showed an association between bacterial vaginosis and spontaneous miscarriages (Chiaffarino). Bacterial vaginosis was associated with pelvic inflammatory disease, bartholinitis, Bartholin's gland abscess and urethral syndrome (Kampan).

The authors recommend that all pregnant women be screened and treated with the Centers for Disease Control and Prevention (CDC-P) recommended oral regimens early in pregnancy. Each treated women should be evaluated for "test of cure" 1 month after treatment. Mothers likely to benefit from "screen and treat" approaches include 1) those with the highest concentrations of genital anaerobes and mycoplasmas, 2) women with prior preterm birth or who have low body mass (BMI < 19.8 kg/m²), 3) those with evidence of endometritis before pregnancy, and 4) those who are treated with oral agents effective for both presumed intrauterine mycoplasmas and other bacterial vaginosis flora (i.e., oral clindamycin or erythromycin and metronidazole) (McGregor).

Bacterial vaginosis (BV) is an imbalance of vaginal microbiota caused by a reduction in the normal lactobacillary bacteria, and a heavy over-growth of mixed anaerobic bacteria. Various clinical (Amsel's Criteria), laboratory (Nugent's score) and molecular diagnostic method (quantitative PCR) are used for diagnosis. BV in pregnancy is associated with increased risk of preterm birth, low birth weight, chorioamnionitis and postpartum endometritis, apart from bothersome vaginal discharge. Antibiotic treatment with metronidazole or clindamycin are effective in eradicating bacterial vaginosis and safe to use in pregnancy. Treatment of bacterial vaginosis has not been shown to improve obstetric outcomes in women at low risk of preterm birth, but may reduce the risk of preterm birth and low birth weight in women at increased risk of preterm birth. Routine screening and treatment is not recommended in low risk women (Jayaram).

The prevalence of symptomatic BV ranges from 10 to 40% depending on the population studied. The risk factors vary, as seen below:

- Black race
- Cigarette smoking
- Intrauterine device
- Early age of sexual intercourse
- Oral sex
- New or multiple sexual partners
- Frequent douching (more than once per week)
- Sex during menses
- Sexual activities with another woman (O'Brien R. F, 2005)

Vaginal discharge is common in pregnancy and may not always pathological, may be physiologic. In women with persistent discharge, screening for lower genital tract infections (vaginal and cervical) is recommended. If bacterial vaginosis is diagnosed in a symptomatic pregnant woman, treatment is indicated. The PHAC guidelines on STI recommend using

- Metronidazole 500 mg orally twice daily for 7 days or
 - Metronidazol 250mg orally 3 times a day x 7 days or
 - Clindamycin 300 mg orally twice daily for 7 days.
- (MacDonald N, 2006)

Patients should avoid alcohol during and for 24 hours after treatment with metronidazol (O'Brien R. F, 2005). For the diagnosis of BV, Amsel's criteria were followed. According to Amsel's criteria, if at least three of the following four criteria were fulfilled, it was confirmed to be a case of BV (Amsel).

- Grayish white, thin, and homogeneous vaginal discharge,
- Vaginal pH higher than 4.5,
- Release fishy or amine odor after adding 10% potassium hydroxide (KOH) solution to wet mount - also known as "whiff test."
- Presence of clue cell (> 20%) on microscopic examination.

1. Gram staining was done to determine the Nugent's score by a clinical microbiologist. Nugent's score system was based on the number of different morphotypes of bacteria, Lactobacillus-like (large uniform Gram-positive bacilli), Gardnerella vaginalis-like (small pleomorphic Gram-variable bacilli), or Prevotella/Bacteroides-like (small Gram-negative bacilli), and Mobiluncus-like (curved Gram-variable bacilli). A Nugent score

of 7–10 was interpreted as consistent with BV and a score of 4–6 as intermediate, while a score of 0–3 was interpreted as negative for BV (Nugent).

Nugent's scoring system for diagnosis of bacterial vaginosis

Score	<i>Lactobacillus</i> morphotypes	<i>Gardnerella</i> and <i>Bacteroides</i> morphotypes	Curved gram-variable rods
0	4+	0	0
1	3+	1+	1+ or 2+
2	2+	2+	3+ or 4+
3	1+	3+	
4	0	4+	

The score is determined by the average number of each morphotype seen per oil-immersion field but varies with the type of bacteria. Excluding *Lactobacillus* morphotypes, a score of 0 means no morphotypes are present; 1, 0 to 1 morphotype present per high-power field; 2, 1 to 4 morphotypes present; 3, 5 to 30 morphotypes present; 4, 30 or more morphotypes present. A total score of 7 to 10 is indicative of bacterial vaginosis infection, 4 to 6 is indeterminate, and 0 to 3 is normal. (Total score = *Lactobacilli* score and *Gardnerella vaginalis* score and *Bacteroides* species score and curved gram-variable rod score.)

(Nugent)

Cervicitis and pelvic inflammatory disease

Cervicitis is a clinical syndrome characterized by inflammation of primarily the columnar epithelium of the uterine endocervix. It can be acute or chronic. While acute cervicitis are usually caused by infections, chronic cervicitis having mostly non-infectious sources. The clinical spectrum of the disease varies widely, from asymptomatic cases to patients with mucopurulent cervical discharge and systemic signs. Any of these cases has the potential to develop devastating complications like pelvic inflammatory disease (PID). It is, therefore, very important for the clinician to recognize the symptoms, investigate and reach a diagnosis promptly, and initiate effective treatment immediately. (Wilson J. F. (2009). In the clinic. Vaginitis and cervicitis. Annals of internal medicine).

Infectious agents in cervicitis include *Neisseria gonorrhoea*, *Chlamydia trachomatis*, and less commonly, *Herpes simplex*, *Trichomonas vaginalis*, and *Mycoplasma genitalium*. *Neisseria* and *Chlamydia* primarily infect the columnar epithelium of endocervix, whereas *HSV* and *Trichomonas* affect the squamous epithelium of ectocervix (Marrazzo; Workowski). Bacterial vaginosis has also been associated with cervicitis (Iqbal).

Typical symptoms reported include purulent or mucopurulent vaginal discharge and intermenstrual or post-coital bleeding. Dyspareunia has also been reported.

All women with suspicion of cervicitis should undergo pelvic and vaginal examinations. The classic signs include yellow or mucoid discharge from the os and easy bleeding of the endocervix on touching with cotton applicator (also called friability). However, a normal physical exam does not rule out an infection. In addition, punctate hemorrhages (strawberry vagina) are suggestive of *Trichomonas*, while vesicles and ulcers are more suggestive of hsv infection.

Herpes Simplex

Genital herpes is the main cause of genital ulcers and a common sexually transmitted infection, which can be transmitted to the baby from the genital tract during birth. Neonatal herpes is a rare but serious infection.

HSV 2 causes ulcerative, erosive and hemorrhagic cervicitis, in which ulcers and vesicles located especially in the ectocervix are seen during pregnancy. (Tosh)

The incidence of new HSV-1 or HSV-2 infection during pregnancy is approximately 2 % .The goals for the management of genital herpes during pregnancy include the prevention of any spread of the virus from mother to neonate by suppressing viral replication in the genital tract in late pregnancy and planning a cesarean section for mothers with active genital tract infections and the rapid identification and treatment of infected neonates.

During pregnancy, antiviral prophylaxis with acyclovir is recommended from 36 weeks of gestation until delivery in women with a history of genital herpes. Elective cesarean delivery should be performed in laboring patients with active lesions to reduce the risk of neonatal herpes (Groves M. J.,2016)

Neonatal herpes is mainly caused by exposure to the virus in the genital tract during birth from the mother with active genital lesions. Inutero and postnatal infection may also develop, but is rare.

The management of the patient with prelabor rupture of membranes and active genital herpes lesions should be done by considering both the risks of prematurity and the risk of neonatal herpes separately (Major CA, Towers CV, 2003).

Since the classical presentation with multiple vesicles is not usually present in all patients, the diagnosis of genital herpes should be supported by laboratory tests. These tests are; viral culture (viral culture as the gold standard) polymerase chain reaction (PCR), direct fluorescence antibody, and type-specific serologic tests. The choice of test varies with the clinical presentation. Cell culture and PCR-based testing are the preferred tests for a patient presenting with active lesions, although PCR-based testing has the greatest overall sensitivity and specificity (Gupta R, 2007).

Tzanck smear is a point-of-care test to detect the cytopathic changes associated with HSV infection. It does not require expensive equipment, can be quickly done in the clinician's office, and yields rapid results, but is highly operator skill-dependant.

Routine screening of pregnant women for HSV is not recommended.

The recommended doses of acyclovir and valacyclovir for the treatment of first-episode or recurrent genital herpes in pregnant women is similar to that of non-pregnant women. Pregnant women with a clinical history of genital herpes should be offered suppressive viral therapy from 36 weeks of gestation. If a primary episode occurs in the third trimester, antiviral treatment should be continued until delivery. Acyclovir is the most well-studied antiviral in pregnancy. Acyclovir and Valacyclovir belong to pregnancy category B.

The doses of antiviral medication used for suppressive therapy in pregnancy are higher than the corresponding doses in non-pregnant women because of enhanced renal clearance. Caesarean section is recommended in women with active genital lesions at the time of delivery and in women with a first-episode genital HSV infection during the third trimester (Sindhuja T, Gupta V, 2021).

Mycoplasma cervicitis is asymptomatic in many patients; therefore, many cases remain undiagnosed (Tosh).

Mucopurulent cervicitis (MPC) is an inflammatory condition of the cervix that has been viewed primarily as the consequence of infection with sexually acquired pathogens, typically *Chlamydia trachomatis* or *Neisseria gonorrhoeae*, and occasionally, *Trichomonas vaginalis* or herpes simplex virus (HSV) . In practice, MPC is a clinically diagnosed made when mucopurulent discharge or easily induced bleeding (friability) is present at the endocervical os; more subtle signs include edema of the cervical ectropion (edematous ectopy) and the presence of an elevated number of

polymorphonuclear (PMN) white blood cells as detected by Gram stain of a smear of endocervical secretions (Holmes KK).

Improvement of symptoms is dependent on the etiology of cervicitis. According to the CDC guidelines, empiric treatment is recommended for women at higher risk of STIs, which include women <25, those with a new sexual partner, a partner with an STI, or multiple concurrent sexual partners. For these women, antimicrobials which is effective for both chlamydia and gonorrhea is given. Empiric treatment is also suggested for women with no identifiable pathogen on testing. Treatment can be delayed until the confirmatory tests are available for women at lower risk of STIs. According to the guidelines published by Institut national d'excellence en Sante et en services sociaux (INESSS), the empiric regimens are as follows:

1g single oral dose azithromycin PLUS either 800 mg cefixime in a single oral dose or 250 mg intramuscular ceftriaxone in a single dose.

For severe allergy to penicillins/cephalosporins: 2g oral azithromycin in For infectious agents identified by laboratory investigations, the treatment is as follows:

- 1.Chlamydia: A single oral dose of 1g azithromycin
 - 2.Mycoplasma: 1g oral azithromycin ,
 - 3.Trichomonas: A single oral 2g dose of metronidazole
 - 4.Bacterial vaginosis: Twice daily 500mg metronidazole for 7 days or intravaginal 0.75% metronidazole gel once daily for 5 days
 - 5.HSV: Oral 400mg acyclovir three times daily for 7 to 10 days
-
- a single dose (Marrazzo; Workowski; Young C).

The sexually transmitted infections *Neisseria gonorrhoea* and *Chlamydia trachomatis* are the two primary infectious agents for cervicitis. Chlamydial infections being the most prevalent. Other less common infectious causes are Herpes simplex viruses, *Mycoplasma genitalium*, Bacterial vaginosis, trichomonas, streptococcal infections (groups A and B), and rarely cytomegalovirus. In up to 50% of patients, clinical symptoms of cervicitis may not be noticeable. When symptomatic, clinical manifestations may include mucopurulent cervical discharge, cervical motion tenderness, cervical friability, postcoital bleeding, intermenstrual bleeding, dyspareunia, or concomitant external vaginal irritation and dysuria. Between 10% and 15% of gonorrhoea and chlamydial infections cause concomitant urinary tract infections also. If the patient has any other symptoms, such as fever and abdominal pain (especially in conjunction with cervical motion tenderness), PID should be suspected and treated empirically (Biggs). Pelvic inflammatory disease (PID) is a polymicrobial infection of the upper genital tract that primarily affects young, sexually active women (Brunham). PID is uncommon during pregnancy, although if it occurs, it is usually within the first 12 weeks before the mucous plug can act as an adequate barrier. Pregnant women with suspected PID should be hospitalized and given parenteral antibiotics. (Regimen A; Cefotetan IV 2g every 12 hours or Cefoxitin 2 g IV every six hours Regimen B; Clindamycin 900mg IV every eight hours plus Gentamicin (Loading dose IV or IM (2 mg per kg), followed by a maintenance dose (1.5 mg per kg) every eight hours; or a single daily dose (3 to 5 mg per kg). Alternative regimen; Ampicilline/sulbactam 3g IV every six hours.

PID during pregnancy increases the risk of preterm delivery and increases maternal morbidity (Zeger).

The diagnosis is made primarily with clinical suspicion. Clinically suspicious findings are:

- Cervical or vaginal mucopurulent discharge or cervical friability or tenderness cervical / uterin/ adnexal tenderness
- Elevated C-reactive protein
- Elevated erythrocyte sedimentation rate
- Presence of abundant numbers of white blood cells (WBCs) on saline microscopy of vaginal secretions (eg, >15 to 20 WBCs per high power field or more WBCs than epithelial cells)
- Oral temperature greater than 101°F (38.3°C)

- Testing positive for *Neisseria gonorrhoeae* or Chlamydia trachomatis.

The most specific criteria for the diagnosis of PID; Transvaginal sonography or magnetic resonance imaging techniques , or Doppler studies, or laparoscopy.

Neisseria gonorrhoeae

Neisseria gonorrhoeae infection is one of the most common bacterial sexually transmitted diseases (STD). Gonorrhoea may present cervicitis or urethritis in women. The aetiological agent of gonorrhoea, the bacterium *Neisseria gonorrhoeae* (the gonococcus), generally causes mucosal infections of the urogenital tract, predominantly infecting columnar and transitional epithelia, although it can also affect the stratified squamous epithelium of the ectocervix . *N. gonorrhoeae* is a diplococcal (that is, it is typically composed of two joined cells with the adjacent sides flattened, resulting in a characteristic kidney or coffee bean appearance on microscopy), Gram-negative microorganism.(Unemo, M., 2019).

Untreated gonococcal cervicitis during pregnancy has been reported to lead to miscarriage, premature labor associated with chorioamnionitis, and infections of the eyes and pharynx of neonates. Therefore, pregnant women with suspected infection should receive genetic testing for *Neisseria gonorrhoeae* in early pregnancy (Suzuki).

Neisseria gonorrhoeae can be contagious from the mother's genital tract to the newborn during birth and can cause gonococcal ophthalmia neonatorum as well as systemic neonatal infection. It can also cause endometritis and pelvic sepsis in the mother (Brocklehurst P. (2002). Antibiotics for gonorrhoea in pregnancy. The Cochrane database of systematic reviews).

N. gonorrhoeae mainly colonizes the genital mucosa but it can also colonize the ocular, nasopharyngeal and anal mucosa. Pathology largely results from damage that is caused by the activation of innate immune responses at the sites of colonization, as *N. gonorrhoeae* does not express potent exotoxins (Danby).

Risk factors and risk markers for gonorrhoea include a recent new sexual partner, multiple sexual partners, being unmarried, young age, of an under-represented ethnic population, low educational and socioeconomic levels, substance abuse, and a history of previous gonorrhoea (Hook).

Pregnant women infected with *N. gonorrhoeae* should be treated with ceftriaxone 500 mg in a single IM dose plus treatment for chlamydia if infection has not been excluded. When cephalosporin allergy or other considerations preclude treatment with this regimen, consultation with an infectious disease specialist or an STD clinical expert is recommended. It is also effective to use 400mg oral cefixime, treatment of gonococcal infection in pregnancy (Ramus RM, 2001). Although routine screening and treatment for *Chlamydia trachomatis*, *N. gonorrhoeae* and *Trichomonas vaginalis* for pregnant women is done in several high-income countries like the United States, screening is not routinely around the World (Bristow, 2017).

Vulvovaginal candidiasis

Vulvovaginal candidiasis is estimated to be the second most common cause of vaginitis after bacterial vaginosis. Vulvovaginal candidiasis is a symptomatic vaginitis (inflammation of the vagina and/or vulva) caused by infection with a *Candida* yeast. Asymptomatic prevalence has been reported in 10% of women (de Oliveira).

High hormone levels increase *Candida* adhesions and hyphae formation and decrease vaginal immun response in pregnant women (Gonçalves B, 2016).

Vulvovaginal candidiasis is characterised by vulval itching and may also present with abnormal 'cheese-like' or watery vaginal discharge. Vulvovaginal candidiasis is estimated to be the second most common cause of vaginitis after bacterial vaginosis. *Candida albicans* accounts for 85% to 90% of cases. Risk factors include pregnancy (and other situations where oestrogen levels are increased), diabetes mellitus, immunosuppression, and systemic antibiotics. Incidence increases with the onset of sexual activity, but associations with different types of contraceptives are unclear (Martin Lopez J. E. (2015).

Candida albicans accounts for 85% to 90% of cases of vulvovaginal candidiasis. (Horowitz; Sobel J. D, 1997) *Candida glabrata* accounts for almost all of the remaining cases, (Sobel J. D. (2007). Vulvovaginal candidosis. *Lancet* (London) and treatment failure with azoles is common (around 50%) in patients with *C. glabrata* vaginitis. (Sobel) Development of symptomatic vulvovaginal candidiasis probably represents increased growth of yeast that previously colonised the vagina without causing symptoms. Risk factors for vulvovaginal candidiasis include pregnancy and other

situations that increase oestrogen levels (e.g., contraceptive use and oestrogen therapy), diabetes mellitus, immunosuppression, (Duerr) and systemic antibiotics. The evidence that different types of contraceptives are associated with risk factors is contradictory. The incidence of vulvovaginal candidiasis rises with initiation of sexual activity, but we found no direct evidence that vulvovaginal candidiasis is sexually transmitted (Foxman B. (1990). The epidemiology of vulvovaginal candidiasis: risk factors. American journal of public health) (Geiger).

No studies reported an increased risk of birth defects with the use of a single, low dose of fluconazole (150 mg) for VVC in pregnancy, however, because of the potential risks of high-dose oral fluconazole therapy (400 to 800 mg/day) for VVC in pregnancy such as being teratogenic and was not recommended. It is an effective and safe option an application of vaginal miconazole for seven days for the treatment (Bender).

A large observational epidemiologic study found no association between moderate to heavy *Candida* vaginal colonization and adverse pregnancy outcome (Cotch).

Treatment of pregnant people is primarily indicated for relief of symptoms; vaginal candidiasis is not associated with adverse pregnancy outcomes (Cotch).

During pregnancy, the use of oral azole therapy should be avoided particularly during the first trimester, because it may increase the risk of miscarriage and its impact on birth defects is unclear (Bérard).

It is known that the vaginas of approximately 30% of women who are in the third trimester of pregnancy are colonised by *Candida* (Farr).

In pregnancy, VVC can be prolonged and associated with more severe symptoms, and resolution of symptoms typically requires longer courses of therapy. Only topical azoles are recommended in pregnancy. Treatment using external imidazole creams and intravaginal ovules for up to 14 days may be required. Repeat treatments may also be needed. Oral fluconazole should be avoided in pregnancy as it may increase the risk of tetralogy of Fallot (Mølgaard-Nielsen).

The safety of oral fluconazole in the second and third trimesters has not been investigated. Intravaginal boric acid has been associated with a greater than 2-fold increased risk of birth defects when used during the first 4 months of pregnancy (Acs), and should thus be avoided during this time.

Vulvovaginal candidiasis (VVC), also known as candidal vulvovaginitis, vaginal yeast infection, and vaginal thrush, is the infection of the vulva and vaginal wall caused primarily by *Candida albicans*

(Mtibaa;Sobel J.D.(2007). Epidemiological reviews demonstrate that approximately 75% of all women have more than one scene of VVC through their lifetime, while 40–45% encounter two or more episodes (Sobel J. D, 2007). Diabetes mellitus, use of broad-spectrum antibiotics, elevated estrogen levels (oral contraceptive use or pregnancy), immunosuppression, use of contraceptive devices, bad hygienic habits are some of the important risk factors for VVC. As the high estrogen levels increase the glycogen content in vaginal secretion, the incidence of VVC increases without any negative consequences during the pregnancy. Pregnancy is one of the criteria of complicated VVC, therefore, low dose oral fluconazole and vaginal miconazole are often used in combination (Bender; Forbes).

Trichomonas

Trichomonas vaginalis is the most common, non-viral sexually transmitted infection (STI) worldwide (Rowley). Although most infected women are asymptomatic, symptomatic women often have foul-smelling yellow or green vaginal discharge, dyspareunia, urinary frequency, dysuria, and/or vulvar pruritus or erythema (Schumann). Untreated or persistent *T. vaginalis* in women has been associated with infertility and poor pregnancy outcomes (Mielczarek; Silver).

Trichomonas is a motile organism and it has at least 4 flagella that provide undulating motility. It attaches to the genital tract epithelium and secretes cytotoxics that damage the epithelium. During an infection, the vaginal pH usually increases.

Low socioeconomic state, multiple sex partners, lifetime frequency of sexual activity, lack of barrier contraceptive use, illitis drug use and smoking are the risk factors for trichomonas infection. (Hainer, B. L., 2011).

The most common diagnostic testing performed is wet prep microscopy. Trichomonads are motile organisms with flagella and can be seen moving in the preparation when viewed with a microscope. This test has been shown to be only 40% - 60% sensitive but is typically the most common testing method used due to convenience and low cost (Kissinger P, 2015).

OSOM *Trichomonas* test This trichomonas rapid antigen test is an immunochromatographic capillary-flow enzyme immunoassay based on trichomonas membrane proteins, which can detect trichomonas in 10min. Compared with wet preparation and culture, OSOM *Trichomonas* test has a

much improved sensitivity, excellent specificity and compares favourability to NAAT assays with reported sensitivities of 83%–90% (Gaydos).

Nucleic acid amplification tests (NAATs) are gaining favor when testing for *Trichomonas vaginalis*. They have become the gold standard when testing for gonorrhea and chlamydia. Many of the NAATs available have been shown to have greater than 90% sensitivity and specificity when testing for *Trichomonas vaginalis* (Van Der Pol B, 2016).

Before NAATs and other point-of-care options were developed, the gold standard was a culture when testing for *Trichomonas vaginalis* with a negative wet prep and a symptomatic patient.

The vaginal pH is usually more than 4.5 in the presence of trichomoniasis, but this is not a specific finding. The whiff test is done by adding drops of potassium hydroxide to a sample of vaginal discharge. This leads to fishy smell. (Schumann JA).

Treatment and dosing options — Metronidazole 500 mg orally twice a day for seven days is the preferred treatment for pregnant individuals. While both single- and multiple-dose regimens are acceptable, we reserve the single-dose regimen for pregnant individuals who are unable to complete seven days of treatment or prefer single-dose therapy. There are no specific data comparing single-dose and multiple-dose regimens in pregnant individuals. However, there are no reasons to think that efficacy is different in pregnant patients, and, although tolerance may be diminished because many pregnant women have significant nausea or vomiting, some clinicians have historically preferred metronidazole 500 mg twice daily orally for five to seven days to lessen medication-induced nausea and vomiting.

There is limited information on the safety of tinidazole or secnidazole in pregnancy; therefore, we avoid their use, especially in the first trimester. Although clotrimazole 1% cream inserted vaginally often results in symptomatic relief, it does not eradicate the organisms and therefore is not advised. For these reasons, oral metronidazole therapy is preferred.

References

- ACOG Committee on Practice Bulletins--Gynecology (2006). ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists, N., May 2006: Vaginitis. *Obstetrics and gynecology*, 107(5), 1195–1206.
- Acs, N., Bánhidly, F., Puhó, E., & Czeizel, A. E. (2006). Teratogenic effects of vaginal boric acid treatment during pregnancy. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, 93(1), 55–56.
- Amsel, R., Totten, P. A., Spiegel, C. A., Chen, K. C., Eschenbach, D., & Holmes, K. K. (1983). Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. *The American journal of medicine*, 74(1), 14–22.
- Bagga, R., & Arora, P. (2020). Genital Micro-Organisms in Pregnancy. *Frontiers in public health*, 8, 225. <https://doi.org/10.3389/fpubh.2020.00225>.
- Bender, R. A., Çalışkan, Ş., Önal, B., Aslancan, R., & Çalışkan, E. (2021). Treatment methods for vulvovaginal candidiasis in pregnancy. *Journal de mycologie medicale*, 31(3), 101138.
- Bérard, A., Sheehy, O., Zhao, J. P., Gorgui, J., Bernatsky, S., de Moura, C. S., & Abrahamowicz, M. (2019). Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, 191(7), E179–E187.
- Biggs, W. S., & Williams, R. M. (2009). Common gynecologic infections. *Primary care*, 36(1), 33–viii.
- Bristow, C. C., Mathelier, P., Ocheretina, O., Benoit, D., Pape, J. W., Wynn, A., & Klausner, J. D. (2017). Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis screening and treatment of pregnant women in Port-au-Prince, Haiti. *International journal of STD & AIDS*, 28(11), 1130–1134.
- Brocklehurst P. (2002). Antibiotics for gonorrhoea in pregnancy. *The Cochrane database of systematic reviews*, CD000098.
- Brunham, R. C., & Paavonen, J. (2020). Reproductive system infections in women: lower genital tract syndromes. *Pathogens and disease*, 78(5), ftaa022.
- Chapman, D. K., Bartlett, J., Powell, J., & Carter, N. (2016). Bacterial Vaginosis Screening and Treatment in Pregnant Women. *Journal of midwifery & women's health*, 61(5), 628–631.
- Chiaffarino, F., Parazzini, F., De Besi, P., & Lavezzari, M. (2004). Risk factors for bacterial vaginosis. *European journal of obstetrics, gynecology, and reproductive biology*, 117(2), 222–226.
- Cluver, C., Novikova, N., Eriksson, D. O., Bengtsson, K., & Lingman, G. K. (2017). Interventions for treating genital Chlamydia trachomatis infection in pregnancy. *The Cochrane database of systematic reviews*, 9(9), CD010485.
- Cotch, M. F., Hillier, S. L., Gibbs, R. S., & Eschenbach, D. A. (1998). Epidemiology and outcomes associated with moderate to heavy Candida colonization during pregnancy. *Vaginal Infections and Prematurity Study Group. American journal of obstetrics and gynecology*, 178(2), 374–380.
- Danby, C. S., Cosentino, L. A., Rabe, L. K., Priest, C. L., Damare, K. C., Macio, I. S., Meyn, L. A., Wiesenfeld, H. C., & Hillier, S. L. (2016). Patterns of Extragenital Chlamydia and Gonorrhea in Women and Men Who Have Sex

- With Men Reporting a History of Receptive Anal Intercourse. Sexually transmitted diseases, 43(2), 105–109.
- de Oliveira, J. M., Cruz, A. S., Fonseca, A. F., Vaz, C. P., Rodrigues, A., Aurea, F., Maia, J., & Sousa, J. A. (1993). Prevalence of *Candida albicans* in vaginal fluid of asymptomatic Portuguese women. *The Journal of reproductive medicine*, 38(1), 41–42.
- Dize, L., Barnes, P., Jr, Barnes, M., Hsieh, Y. H., Marsiglia, V., Duncan, D., Hardick, J., & Gaydos, C. A. (2016). Performance of self-collected penile-meatal swabs compared to clinician-collected urethral swabs for the detection of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and *Mycoplasma genitalium* by nucleic acid amplification assays. *Diagnostic microbiology and infectious disease*, 86(2), 131–135.
- Dobbler, P., Mai, V., Procianoy, R. S., Silveira, R. C., Corso, A. L., & Roesch, L. (2019). The vaginal microbial communities of healthy expectant Brazilian mothers and its correlation with the newborn's gut colonization. *World journal of microbiology & biotechnology*, 35(10), 159.
- Donati, L., Di Vico, A., Nucci, M., Quagliozzi, L., Spagnuolo, T., Labianca, A., Bracaglia, M., Ianniello, F., Caruso, A., & Paradisi, G. (2010). Vaginal microbial flora and outcome of pregnancy. *Archives of gynecology and obstetrics*, 281(4), 589–600.
- Duerr, A., Heilig, C. M., Meikle, S. F., Cu-Uvin, S., Klein, R. S., Rompalo, A., Sobel, J. D., & HER Study Group (2003). Incident and persistent vulvovaginal candidiasis among human immunodeficiency virus-infected women: Risk factors and severity. *Obstetrics and gynecology*, 101(3), 548–556.
- Farr, A., Effendy, I., Frey Tirri, B., Hof, H., Mayser, P., Petricevic, L., Ruhnke, M., Schaller, M., Schaefer, A., Sustr, V., Willinger, B., & Mendling, W. (2021). Guideline: Vulvovaginal candidosis (AWMF 015/072, level S2k). *Mycoses*, 64(6), 583–602.
- Forbes, G. L., Drayton, R., & Forbes, G. D. (2016). A case of metronidazole-resistant *Trichomonas vaginalis* in pregnancy. *International journal of STD & AIDS*, 27(10), 906–908.
- Foxman B. (1990). The epidemiology of vulvovaginal candidiasis: risk factors. *American journal of public health*, 329–331.
- Gaydos, C. A., Klausner, J. D., Pai, N. P., Kelly, H., Coltart, C., & Peeling, R. W. (2017). Rapid and point-of-care tests for the diagnosis of *Trichomonas vaginalis* in women and men. *Sexually transmitted infections*, 93(S4), S31–S35.
- Geiger, A. M., Foxman, B., & Sobel, J. D. (1995). Chronic vulvovaginal candidiasis: characteristics of women with *Candida albicans*, *C glabrata* and no candida. *Genitourinary medicine*, 71(5), 304–307.
- Genc M. R. (2002). Treatment of genital *Chlamydia trachomatis* infection in pregnancy. *Best practice & research. Clinical obstetrics & gynaecology*, 913–922.
- Gonçalves, B., Ferreira, C., Alves, C. T., Henriques, M., Azeredo, J., & Silva, S. (2016). Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. *Critical reviews in microbiology*, 42(6), 905–927.

- Goplerud, C. P., Ohm, M. J., & Galask, R. P. (1976). Aerobic and anaerobic flora of the cervix during pregnancy and the puerperium. *American journal of obstetrics and gynecology*, 126(7), 858–868.
- Grant, J. S., Chico, R. M., Lee, A. C., Low, N., Medina-Marino, A., Molina, R. L., Morroni, C., Ramogola-Masire, D., Stafylis, C., Tang, W., Vallely, A. J., Wynn, A., Yeganeh, N., & Klausner, J. D. (2020). Sexually Transmitted Infections in Pregnancy: A Narrative Review of the Global Research Gaps, Challenges, and Opportunities. *Sexually transmitted diseases*, 47(12), 779–789.
- Groves M. J. (2016). Genital Herpes: A Review. *American family physician*, 93(11), 928–934.
- Gupta, R., Warren, T., & Wald, A. (2007). Genital herpes. *Lancet (London, England)*, 370(9605), 2127–2137.
- Gupta, P., Singh, M. P., & Goyal, K. (2020). Diversity of Vaginal Microbiome in Pregnancy: Deciphering the Obscurity. *Frontiers in public health*, 8, 326.
- Hainer, B. L., & Gibson, M. V. (2011). Vaginitis. *American family physician*, 83(7), 807–815.
- He, W., Jin, Y., Zhu, H., Zheng, Y., & Qian, J. (2020). Effect of Chlamydia trachomatis on adverse pregnancy outcomes: a meta-analysis. *Archives of gynecology and obstetrics*, 302(3), 553–567.
- Holmes KK, S. W. L. g. t. i. s. i. w. I. H. K., Sparling F, Mardh P-A, et al, editors. Sexually transmitted diseases. 3rd edition. New York: McGraw-Hill; 1999. p. 761–81.
- Hook, E. W., 3rd, Reichart, C. A., Upchurch, D. M., Ray, P., Celentano, D., & Quinn, T. C. (1992). Comparative behavioral epidemiology of gonococcal and chlamydial infections among patients attending a Baltimore, Maryland, sexually transmitted disease clinic. *American journal of epidemiology*, 136(6), 662–672.
- Horowitz, B. J., Giaquinta, D., & Ito, S. (1992). Evolving pathogens in vulvovaginal candidiasis: implications for patient care. *Journal of clinical pharmacology*, 32(3), 248–255.
- Iqbal, U., & Wills, C. (2022). Cervicitis. In StatPearls. StatPearls Publishing.
- Jayaram PM, M. M., Konje J. Bacterial vaginosis in pregnancy - a storm in the cup of tea. *Eur J Obstet Gynecol Reprod Biol*. 2020 Oct;253:220-224.
- Jayaram, P. M., Mohan, M. K., & Konje, J. (2020). Bacterial vaginosis in pregnancy - a storm in the cup of tea. *European journal of obstetrics, gynecology, and reproductive biology*, 253, 220–224.
- Kampan, N. C., Suffian, S. S., Ithnin, N. S., Muhammad, M., Zakaria, S. Z., & Jamil, M. A. (2011). Evaluation of BV(®) Blue Test Kit for the diagnosis of bacterial vaginosis. *Sexual & reproductive healthcare : official journal of the Swedish Association of Midwives*, 2(1), 1–5.
- Kissinger P. (2015). *Trichomonas vaginalis: a review of epidemiologic, c. a. t. i. B. i. d.*, 15, 307.
- Larsson, P. G., Carlsson, B., Fåhraeus, L., Jakobsson, T., & Forsum, U. (2004). Diagnosis of bacterial vaginosis: need for validation of microscopic image area used for scoring bacterial morphotypes. *Sexually transmitted infections*, 80(1), 63–67.
- Leeper, C., & Lutzkanin, A., 3rd (2018). *Infections During Pregnancy. Primary care*, 45(3), 567–586.

- MacDonald, N., & Wong, T. (2007). Canadian guidelines on sexually transmitted infections, 2006. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, 176(2), 175–176.
- Major, C. A., Towers, C. V., Lewis, D. F., & Garite, T. J. (2003). Expectant management of preterm premature rupture of membranes complicated by active recurrent genital herpes. *American journal of obstetrics and gynecology*, 188(6), 1551–1555.
- Marai W. (2001). Lower genital tract infections among pregnant women: a review. *East African medical journal*, 581–585.
- Marrazzo, J. M., & Martin, D. H. (2007). Management of women with cervicitis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 44 Suppl 3, S102–S110.
- Martin Lopez J. E. (2015). Candidiasis (vulvovaginal). *BMJ clinical evidence*, 0815.
- McGregor, J. A., & French, J. I. (2000). Bacterial vaginosis in pregnancy. *Obstetrical & gynecological survey*, 55(5 Suppl 1), S1–S19.
- Mei, C., Yang, W., Wei, X., Wu, K., & Huang, D. (2019). The Unique Microbiome and Innate Immunity During Pregnancy. *Frontiers in immunology*, 10, 2886.
- Mielczarek, E., & Blaszowska, J. (2016). *Trichomonas vaginalis*: pathogenicity and potential role in human reproductive failure. *Infection*, 44(4), 447–458.
- Mølgaard-Nielsen, D., Pasternak, B., & Hviid, A. (2013). Use of oral fluconazole during pregnancy and the risk of birth defects. *The New England journal of medicine*, 369(9), 830–839.
- Mtibaa, L., Fakhfakh, N., Kallel, A., Belhadj, S., Belhaj Salah, N., Bada, N., & Kallel, K. (2017). Vulvovaginal candidiasis: Etiology, symptomatology and risk factors. *Journal de mycologie medicale*, 27(2), 153–158.
- Nugent, R. P., Krohn, M. A., & Hillier, S. L. (1991). Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *Journal of clinical microbiology*, 29(2), 297–301.
- O'Brien R. F. (2005). Bacterial vaginosis: many questions--any answers?. *Current opinion in pediatrics*, 473–479.
- Paladine, H. L., & Desai, U. A. (2018). Vaginitis: Diagnosis and Treatment. *American family physician*, 97(5), 321–329.
- Ramus, R. M., Sheffield, J. S., Mayfield, J. A., & Wendel, G. D., Jr (2001). A randomized trial that compared oral cefixime and intramuscular ceftriaxone for the treatment of gonorrhoea in pregnancy. *American journal of obstetrics and gynecology*, 185(3), 629–632.
- Romanik, M., & Martirosian, G. (2004). Częstość występowania, kryteria diagnostyczne i następstwa bakteryjnego zakażenia pochwy u kobiet ciężarnych [Frequency, diagnostic criteria and consequences of bacterial vaginosis in pregnant women]. *Przegląd epidemiologiczny*, 58(3), 547–553.
- Rowley, J., Vander Hoorn, S., Korenromp, E., Low, N., Unemo, M., Abu-Raddad, L. J., Chico, R. M., Smolak, A., Newman, L., Gottlieb, S., Thwin, S. S., Broutet, N., & Taylor, M. M. (2019). Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bulletin of the World Health Organization*, 97(8), 548–562P.
- Schumann, J. A., & Plasner, S. (2021). Trichomoniasis. In StatPearls. StatPearls Publishing.
- Schumann, J. A., & Plasner, S. (2021). Trichomoniasis. In StatPearls. StatPearls Publishing.

- Smith, J. R., & Taylor-Robinson, D. (1993). Infection due to *Chlamydia trachomatis* in pregnancy and the newborn. *Bailliere's clinical obstetrics and gynaecology*, 7(1), 237–255.
- Silver, B. J., Guy, R. J., Kaldor, J. M., Jamil, M. S., & Rumbold, A. R. (2014). *Trichomonas vaginalis* as a cause of perinatal morbidity: a systematic review and meta-analysis. *Sexually transmitted diseases*, 41(6), 369–376.
- Sobel J. D. (1997). Vaginitis. *The New England journal of medicine*, 1896–1903.
- Sindhuja, T., Gupta, V., Bhari, N., & Gupta, S. (2021). Asian guidelines for genital herpes. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*, 27(10), 1389–1399.
- Sobel J. D. (2007). Vulvovaginal candidosis. *Lancet (London, E.)*, 369(9577), 1961–1971.
- Sobel, J. D., & Chaim, W. (1997). Treatment of *Torulopsis glabrata* vaginitis: retrospective review of boric acid therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 24(4), 649–652.
- Sullivan, C., & Smith, L. G., Jr (1993). Management of vulvovaginitis in pregnancy. *Clinical obstetrics and gynecology*, 36(1), 195–205.
- Suzuki, S., Hoshi, S. I., Sekizawa, A., Sagara, Y., Tanaka, M., Kinoshita, K., & Kitamura, T. (2019). Current status of *Neisseria gonorrhoeae* cervicitis in pregnant women in Japan. *PloS one*, 14(2), e0211595.
- Teisala K. (1987). Endometrial microbial flora of hysterectomy specimens. *European journal of obstetrics, g., and reproductive biology*, 26(2), 151–155.
- Tosh, A. K., Van Der Pol, B., Fortenberry, J. D., Williams, J. A., Katz, B. P., Batteiger, B. E., & Orr, D. P. (2007). *Mycoplasma genitalium* among adolescent women and their partners. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*, 40(5), 412–417.
- Unemo, M., Seifert, H. S., Hook, E. W., 3rd, Hawkes, S., Ndowa, F., & Dillon, J. R. (2019). Gonorrhoea. *Nature reviews. Disease primers*, 5(1), 79.
- Van Der Pol B. (2016). Clinical and Laboratory Testing for *Trichomonas vaginalis* Infection. *Journal of clinical microbiology*, 54(1), 7–12.
- Wilson J. F. (2009). In the clinic. Vaginitis and cervicitis. *Annals of internal medicine*, ITC3–ITC16.
- Workowski, K. A., Bolan, G. A., & Centers for Disease Control and Prevention (2015). Sexually transmitted diseases treatment guidelines, 2015. *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports*, 64(RR-03), 1–137.
- Young C, Argáez C. Management and Treatment of Cervicitis: A Review of Clinical Effectiveness and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Sep 21. PMID: 30234930.
- Yudin M. H. (2005). Bacterial vaginosis in pregnancy: diagnosis, s., and management. *Clinics in perinatology*, 32(3), 617–627.
- Zeger, W., & Holt, K. (2003). Gynecologic infections. *Emergency medicine clinics of North America*, 21(3), 631–648.

CHAPTER 10

BLEEDING DUE TO MYOMS DURING PREGNANCY

Dr. Başak ERGİN¹

¹ Department of obstetrics and gynecology, Reşadiye State Hospital, Tokat Turkey, Orcid No: 0000-0002-6411-2541, E-mail: drbasakergin@hotmail.com

INTRODUCTION

Vaginal bleeding during pregnancy can be scary. Most bleeding appear as light spotting and short-living. However, in some patients it may be more intense and long lasting. Usually, active bleeding is in fresh red color, while old blood appears darker brown. Some patients may have accompanying cramps. Bleeding pregnant women should first monitor the amount of bleeding by using a pad but vaginal tampons or douches are not recommended. Even if pain, cramp or water leakage does not accompanying the bleeding, a doctor examination is definitely recommended.

Some of these bleedings which occur during the early period of pregnancy are implantation bleeding. In early pregnancy, the amount of bleeding and pain existance are required to be investigated. Vaginal examination may also be required. In some cases, beta HCG measurement may be done in the blood. In addition, if your blood type is Rh negative and you have an Rh incompatibility with your partner, an anti D injection may be required. Ultrasonography can be applied. Polyps and fibroids in the cervix should be considered especially in pregnant women with postcoital bleeding. However, the reason of the bleeding may not always be able to determined. In pregnant women with second and third trimester bleeding, serious conditions such as premature birth and detachment should be appeared, and fetal well-being should be evaluated.

Uterine leiomyomas are benign smooth muscle tumors of the uterus. The potential effects of fibroids on pregnancy and the potential effects of pregnancy on fibroids are a common clinical concern in pregnant women with fibroids. (1) The incidence of uterine fibroids during pregnancy is estimated between 1-10%. The reason for this difference is the time to report myoma (trimester), and the different sizes of the threshold (non-reporting of cases below 1 to 3 cm). Although many women with uterine fibroids do not experience adverse events during pregnancy, data in the literature suggest that uterine fibromyomas are associated with a variety of complications. The prevalence of fibroids increases with maternal age and is higher in black than in White race. (2) The most important clinical question is the effect of myoma on pregnancy and the possibility of surgical treatment in special cases that guarantees pregnancy course and fertility preservation. (3) Pain is the most common symptom, and there may be an increased risk of obstetric complications such as bleeding, early pregnancy loss, preterm labor and

delivery, fetal malpresentation and placental abruption, especially in patients with multiple fibroids, retroplacental fibroids, and larger sizes.

Since fibroid growth is stimulated by estrogen and progesterone, and both of these hormones are elevated during pregnancy, it is reasonable to expect these masses to grow during pregnancy. Existing data show that more than half of fibroids remain stable without growing during pregnancy, while the remaining twenty-five percent enlarge and shrink between eight and ten percent.(4,5) Growth or degeneration of a fibroid is not linear throughout pregnancy and considerable growth occurs during early in pregnancy, especially in the first trimester. One of the factors in the growth of fibroids is their size. In a study, it was shown that fibroids larger than 5 cm are more likely to grow.(6)



Figure 1: A pregnant uterus with fibroids

The observation that fibroids grow by about 30-35% in diameter during early pregnancy is worrisome, as an asymptomatic or apparently "innocent" fibroid near the endometrium is likely to grow and cause unexpected problems during pregnancy. However, it is important to note that there is no evidence that "prophylactic surgical treatment" is beneficial.

All risks should be considered in bleeding during pregnancy. Information about the onset of bleeding, amount, gestational week, size and location of the previously known fibroid (if any) should be evaluated and the action should be selected accordingly. As we mentioned above, although there are no complications in most pregnant women with fibroids, the following conditions should be considered in pregnant women with fibroids presenting with bleeding:

Degeneration and torsion: The problem encountered in pregnant women who apply to the clinic with pain and bleeding, are known to have fibroids, or are diagnosed later, is generally the rapid growth of myomas and their degeneration by necrosis.

Rapid growth causes ischemia and then necrosis (red degeneration). This leads to the release of prostaglandins, resulting in a decrease in perfusion. Although it is rare in pedunculated fibroids, a risk of torsion exists. (7)



Picture 1: Ultrasound picture of a pregnant woman with a myoma pressing on the cavity

Degeneration in fibroids is most common between 20-22 weeks and may cause the onset of labor.

Miscarriage: Although there are studies showing that the presence of fibroids is not related to miscarriage when the location of fibroids is not taken into account (8), submucosal fibroids may affect implantation, placentation and current pregnancy negatively in some patients. The location of fibroids gains importance in these cases, for example, pedunculated or subserosal fibroids are more innocent in such cases, while submucosal and intramural fibroids cause negative results more frequently. In this case, two hypotheses have been put forward in the pathogenesis of myoma-related miscarriage. First, a large fibroid protruding into the endometrial cavity may disrupt the vascularization of the decidualized endometrium and cause atrophy. The second hypothesis is that fast growing fibroids with or without degeneration cause contraction and catalytic enzyme production in the uterus. In both cases, placentation is disrupted. Especially in patients presenting with bleeding in the first trimester, the relationship between myoma and pregnancy should be evaluated by ultrasonography, and if the sac is not visible, bhcg should be followed.

Premature birth and delivery: Premature birth may be triggered in cases such as the presence of multiple fibroids and fibroid sizes larger than 5 cm in pregnant women. (10) In pregnant women in the last trimester, for bleeding with or without pain, cervical dilation should be checked after the necessary ultrasound control, the presence of contraction should be checked with nst, these pregnant women should be followed closely. Due to the frequency of routine pain or bleeding due to the presence of fibroids, the threat of premature birth should not be ignored and every bleeding and pain should be taken seriously.

Antepartum hemorrhages and placental abruption: Many studies have shown that antepartum hemorrhage is more common in pregnant women with fibroids.(11) The position of myoma relative to

the placenta is an important determining factor. Although the available data show that the risk of detachment increases 3 times in women with fibroids, the prevalence of detachment itself is 2 in 1000, resulting in low rates in the absolute risk calculation. (12) Submucosal and retroplacental fibroids with a volume greater than 200 ml (7-8 cm in diameter) have the highest associated with the risk of detachment.

Although fibroids cause various other complications such as malpresentation, fetal growth restriction, deformities and urinary retention in obstetric terms, these patients do not come to the clinic with bleeding complaints.

TREATMENT OPTIONS

The first treatment choice for painful fibroids in pregnant women is normally acetaminophen, but the priority in the treatment of bleeding pregnant women is to determine the source and severity of the bleeding. After evaluation of fetal well-being, progesterone support and steroid administration for lung maturation may be considered if the risk of preterm delivery is high. Opioid and non-steroidal anti-inflammatory drugs are recommended to be used in patients in whom acetaminophen therapy is inadequate. (13) Since there are studies in some publications showing that opioid use in the first trimester may cause congenital anomalies, opioid use in the first trimester is not considered.

NSAID drug options include standard doses of ibuprofen (14) or indomethacin 25 mg orally every 6 hours for up to 48 hours (15). On the other hand, these drugs have risks of inducing premature closure of the ductus arteriosus, neonatal pulmonary hypertension, oligohydramnios, and fetal/neonatal platelet dysfunction. Therefore, NSAID therapy should be limited to pregnancies less than 32 weeks.

Decisions about myomectomy in pregnancy are made on a patient basis and depend on a variety of factors, including the patient's age, gestational week, past reproductive history, severity of symptoms, and size and location of fibroids. If myomectomy during pregnancy cannot be safely delayed, there is consensus to avoid myomectomy during pregnancy, especially if an intramyometrial incision is required. The reason for this is that uncontrollable bleeding during myomectomy is an important possibility

and hysterectomy may be performed. (16) In pregnant women with vaginal fibroid prolapse, clinically significant bleeding, excessive pain, and urinary retention may be indications for fibroid resection.

In a systematic review including 97 patients who underwent myomectomy during pregnancy, the following findings were recorded.(17): Abdominal pain was the most common symptom in pregnant women with myoma, and this symptom was the most common reason for the indication for surgery. The second most common symptom was fever. The median gestational age at myomectomy was 16 weeks (6 to 26 weeks). A single fibroid was removed in three-quarters of the patients; in the remainder more than one fibroid was removed. Most myomectomies (48 out of 66 [73 percent]) were for pedunculated fibroids, but 26 of 66 cases (39 percent) were intramural. The average blood loss during surgery was 350 mL (range of 30 to 4500 mL). Five patients received transfusion. Pregnancy loss was observed in 5 patients after surgery, and ninety-two ongoing pregnancies were observed. The mean gestational ages at birth of patients who had a single and multiple myomectomy were 37.2 and 36.8 weeks, respectively, and the cesarean delivery rates were 51 percent and 83 percent, respectively. Most of the ongoing pregnancies were uneventful. However, one patient developed abscess formation and full-thickness myometrial necrosis in which a 7 x 2 cm portion of the amniotic sac was exposed after resection of a degenerated peduncle leiomyoma with monopolar diathermy at 17 weeks. Antibiotic treatment, abscess drainage, and repair of the defect were successful, and the patient was allowed to deliver at 37 weeks by planned cesarean section.

Most patients with fibroids during pregnancy give birth naturally. Cesarean delivery is performed for standard obstetric indications (eg, malpresentation, failure to progress), including obstruction of the birth canal by a fibroid. Elective cesarean section is recommended for patients who have had myomectomy before and who have had their uterine cavity entered or more than one myoma removed during this operation. (18)

Removal of myoma during cesarean section is also a controversial issue. Some argue that there should be no intervention due to the highly

increased risk of bleeding when the fibroids are removed due to the increased blood supply to the uterus during pregnancy.



Picture 2: A patient whose fibroids were removed during cesarean section, From the archive of Dr. Başak Ergin

Some authors argue that the number and location of myoma is important here as well. If the location of myomas is not very deep, if the fibroids can be removed from the same incision line with cesarean section, if there are subserous myomas that have grown outward, myomectomy can be performed during cesarean section. However, there are also studies showing that there is a greater decrease in hemoglobin value, need for blood transfusion and increase in hospital stay in patients whose fibroids were removed during cesarean section.(19) If myoma is located in the implantation site of the placenta, infection may occur after delivery.

HIGHLIGHTS

- The incidence of fibroids during pregnancy varies between 2 and 10 percent, the growth of myoma occurs mostly in the

first trimester. The most common symptoms in pregnant women with fibroids are pain, fever and bleeding.

- While most pregnant women with fibroids do not have a complication during pregnancy, risk factors for complications are fibroid size, location, number and placental relationship.
- Surgical removal of fibroids should be avoided as far as possible during pregnancy because of the significant risk of morbidity and mortality.
- Fetal well-being should always be evaluated first in pregnant women with pain and bleeding.
- Clinically significant bleeding, excessive pain, urinary retention in pregnant women with vaginal fibroid prolapse may be indications for fibroid resection.
- Cesarean section should be preferred in the presence of myoma obstructing the birth canal, malpresentations, and failure to progress in labor.
- Cesarean section is recommended if the patient has a previous myomectomy or if the patient has a history of multiple myoma removal during surgery.
- If the fibroids are not located very deep during cesarean section, if the fibroids can be removed from the same incision line with cesarean section, if there are subserous myomas grown outward, myomectomy can be performed during cesarean section. However, increased bleeding and the possibility of hysterectomy should be considered.

Literatures

- 1) Coutinho LM, Assis WA, Spagnuolo-Souza A, Reis FM. Uterine Fibroids and Pregnancy: How Do They Affect Each Other? *Reprod Sci* 2021.
- 2) Strobelt N, Ghidini A, Cavallone M, et al. Natural history of uterine leiomyomas in pregnancy. *J Ultrasound Med* 1994; 13:399.
- 3) Qidwai GI, Caughey AB, Jacoby AF. Obstetric outcomes in women with sonographically identified uterine leiomyomata. *Obstet Gynecol* 2006; 107:376.
- 4) Aharoni A, Reiter A, Golan D, et al. Patterns of growth of uterine leiomyomas during pregnancy. A prospective longitudinal study. *Br J Obstet Gynaecol* 1988; 95:510.
- 5) Terry KL, De Vivo I, Hankinson SE, Missmer SA. Reproductive characteristics and risk of uterine leiomyomata. *Fertil Steril* 2010; 94:2703.
- 6) Exacoustòs C, Rosati P. Ultrasound diagnosis of uterine myomas and complications in pregnancy. *Obstet Gynecol* 1993; 82:97.
- 7) Segars JH, Parrott EC, Nagel JD, et al. Proceedings from the Third National Institutes of Health International Congress on Advances in Uterine Leiomyoma Research: comprehensive review, conference summary and future recommendations. *Hum Reprod Update* 2014; 20:309.
- 8) Blum M. Comparative study of serum CAP activity during pregnancy in malformed and normal uterus. *J Perinat Med* 1978; 6:165.
- 9) Winer-Muram HT, Muram D, Gillieson MS, et al. Uterine myomas in pregnancy. *Can Med Assoc J* 1983; 128:949.
- 10) Wallach EE, Vu KK. Myomata uteri and infertility. *Obstet Gynecol Clin North Am* 1995; 22:791.
- 11) Vergani P, Ghidini A, Strobelt N, et al. Do uterine leiomyomas influence pregnancy outcome? *Am J Perinatol* 1994; 11:356.

- 12) Jenabi E, Ebrahimzadeh Zagami S. The association between uterine leiomyoma and placenta abruption: A meta-analysis. *J Matern Fetal Neonatal Med* 2017; 30:2742.
- 13) Hasan F, Arumugam K, Sivanesaratnam V. Uterine leiomyomata in pregnancy. *Int J Gynaecol Obstet* 1991; 34:45.
- 14) Katz VL, Dotters DJ, Droegemeuller W. Complications of uterine leiomyomas in pregnancy. *Obstet Gynecol* 1989; 73:593.
- 15) Dildy GA 3rd, Moise KJ Jr, Smith LG Jr, et al. Indomethacin for the treatment of symptomatic leiomyoma uteri during pregnancy. *Am J Perinatol* 1992; 9:185.
- 16) Febo G, Tessarolo M, Leo L, et al. Surgical management of leiomyomata in pregnancy. *Clin Exp Obstet Gynecol* 1997; 24:76.
- 17) Spyropoulou K, Kosmas I, Tsakiridis I, et al. Myomectomy during pregnancy: A systematic review. *Eur J Obstet Gynecol Reprod Biol* 2020; 254:15.
- 18) Spong CY, Mercer BM, D'alton M, et al. Timing of indicated late-preterm and early-term birth. *Obstet Gynecol* 2011; 118:323.
- 19) Goyal M, Dawood AS, Elbohoty SB, et al. Cesarean myomectomy in the last ten years; A true shift from contraindication to indication: A systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2021; 256:145.

CHAPTER 11

BLEEDING DUE TO OBSTETRIC INTERVENTIONAL METHODS: A REVIEW

Dr. Gizem Ceren EKİCİ¹

¹ Department of Obstetrics and Gynecology, Hayat Hospital, Siirt, Turkey Orcid ID: 0000-0003-0021-4626 Corresponding author: c.gizem.ekici@gmail.com

1. Introduction

The most prevalent cause of major obstetric bleeding is postpartum haemorrhage, which is usually caused by uterine atony. In recent years, pharmacological treatment has remained mostly unchanged, with oxytocin and ergometrine maintaining first-line treatments. Despite the debate regarding its benefits over alternative uterotonics, misoprostol use is on the rise, particularly in resource-poor nations. As the prevalence of caesarean sections rises, placenta accreta is becoming more common. In some circumstances, interventional radiology may help to minimize blood loss. In the recent decade, uterine compression sutures, intrauterine tamponade balloons, and cell salvage have all made their debuts. Maternal morbidity and death can be reduced if obstetric bleeding is correctly diagnosed and managed (Wise & Clark, 2008).

The haemostatic management of large obstetric bleeding is still a difficult task. Interest in the implications of relative hypofibrinogenaemia, point-of-care monitoring of coagulation abnormalities, and the prospect of providing goal-directed therapy to correct coagulopathies has generated the possibility of considerably challenging and modifying recommendations in recent years. There is evidence that haemostatic impairment in pregnant women differs from trauma-induced bleeding, and that the kind and rate of coagulopathy development differs depending on the underlying etiology (Collis & Collins, 2015).

Postpartum haemorrhage is the most prevalent type of obstetric haemorrhage, with a woman dying from major postpartum haemorrhage every 4 minutes around the world. In addition, many suffer from major morbidity such as multi-organ failure, complications from repeated blood transfusions, peripartum hysterectomy and unintentional pelvic organ damage, loss of fertility, and psychological effects such as posttraumatic stress disorder. Anticipation of massive postpartum haemorrhage, prompt recognition of the cause, and implementation of timely and appropriate measures to control bleeding and replace lost blood volume, restore oxygen carrying capacity (i.e. haemoglobin), and correct the 'washout phenomenon' leading to coagulopathy will all help save lives. The use of tranexamic acid, oxytocics, and prompt peripartum hysterectomy, if suitable, can assist save lives by preventing underestimate of blood loss. The Triple P treatment, which has recently been established as a conservative surgical option for

women with aberrant placental invasion, has been found to drastically reduce blood loss and inpatient stay (Sebghati & Chandraharan, 2017).

There are a variety of interventional approaches that can help an obstetrician or gynecologist care for their patients in an emergency situation. In the instance of postpartum bleeding, embolization can save a woman's life. Cervical cancer bleeding or the potential of bleeding from a cervical ectopic pregnancy can be embolized, as can hemorrhage from uterine arteriovenous malformations. Deep vein thrombosis and pulmonary emboli are particularly common in postpartum women, and they may benefit from evaluation and treatment by an interventional radiologist. The purpose of this article is to discuss how important interventional radiologists are in the treatment of certain obstetric and gynecologic disorders (Josephs, 2008).

2. Role of interventional methods in haemorrhage

In total, 8172 US-guided intraabdominal interventions were examined in 30 institutions (liver n = 5903; pancreas n = 501; kidney n = 434; lymph node = 272, biliary system n = 153; other abdominal organs and extra-organic targets n = 999). The vast majority of the biopsies were diagnostic, with 1780 liver parenchyma, 3400 localized liver lesions, and 404 pancreatic lesions among them. In hospitalized patients, 7525 interventions (92.1%) were conducted (mean age 62.6 years). The majority of operators had extensive expertise with US-guided procedures (n = 5729; 70.1 percent) previous to the trial. In 1131 patients (13.8 percent), sedation was used. In 7162 punctures (87.9%), the needle diameter was less than 1 mm, with the focus on core needle biopsies (18 G, n = 4185). Clinically important bleeding problems such as transfusion (0.4%), surgical bleeding management (0.1%), and radiological coiling (0.05%) were quite infrequent. Four patients (0.05 percent) had bleeding issues that resulted in death. Patients with an INR > 1.5 (p 0.001) and those using a drug that could interfere with platelet function or plasmatic coagulation had a considerably greater risk of serious bleeding problems. The vast range of percutaneous US-guided intraabdominal procedures is confirmed in this prospective multicenter investigation. However, diagnostic liver biopsies are the most common, with core needle biopsies being the most common (18 G). The risk of bleeding is reduced with percutaneous US-guided procedures performed by competent sonographers. Significant bleeding problems are quite

uncommon. A pre-interventional INR of 1.5 is advised, as well as an individual medication risk assessment (Strobel et al., 2015).

The risk of obstetric anal sphincter injury is a major worry for women giving delivery (Rasmussen et al., 2016). Obstetric hemorrhage is still a leading cause of maternal mortality and morbidity around the world. Obstetricians have traditionally resorted to major surgery in cases of obstetric bleeding recalcitrant to conservative treatment, with the hazards of general anesthesia, laparotomy, and, in the event of hysterectomy, loss of fertility. Pelvic artery embolization has progressed from a novel therapy option to a critical component in the management of obstetric hemorrhage over the last two decades. Interventional radiology is now the only minimally invasive, fertility-preserving therapy option available (Gonsalves & Belli, 2010).

Interventional radiology is reshaping current practice in a variety of clinical areas. It is a relatively new and revolutionary area of medicine in which physicians use small catheters guided to the target by fluoroscopic and other imaging modalities to treat diseases non-operatively (Ganeshan et al., 2010).

3. Causes

Excessive bleeding is linked to surgery and invasive procedures, and is impacted by both patient-related factors (e.g., constitutional hemostatic abnormalities, antithrombotic medication, diseases that affect hemostasis) and the type of intervention. Laboratory screening tests (typically PT, aPTT, and platelet count) are still routinely performed to estimate the risk of perioperative bleeding prior to surgery or other invasive operations, while coagulation screening in unselected patients is not recommended. The need of an accurate bleeding history, which includes details of personal and family history, previous post-traumatic or post-surgical hemorrhage, and anti-thrombotic drug use, is highlighted in preoperative assessment guidelines. Many anesthesiologists and other clinicians still give non-specific coagulation tests (PT, aPTT, platelet count) for reassurance because no questionnaire on bleeding diathesis has been validated during the preoperative period. Given the low prevalence of bleeding problems, conducting routine coagulation tests resulted in a significant number of false positives, resulting in additional unneeded investigations, and a large number of false negatives, resulting in false reassurance. Similarly, traditional

hemostatic tests fail to predict the risk of bleeding associated with regional anaesthetic procedures, such as neuraxial anesthesia. Regardless of anesthesia type, it is suggested that hemostasis tests not be ordered in patients whose history and clinical examination indicate no bleeding issues (general, neuraxial, peripheral, or combined). In the event of neuraxial anesthesia, the use of medications that may interfere with hemostasis should be carefully examined, as medication-induced acquired hemostatic problem is one of the leading causes of spinal/epidural hematoma (Bonhomme et al., 2016).

The French Society of Anaesthesia and Intensive Care (Société Française d'Anesthésie et de Réanimation [SFAR]) recently announced recommendations for routine preoperative testing prior to any surgical or non-surgical operation that requires anaesthesia. Thirty clinical experts conducted a systematic review of the literature before developing recommendations utilizing the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. Haemostatic evaluation is included in one section of these recommendations. Pre-anaesthetic screening for inherited or acquired haemostatic disorders aims to prevent perioperative haemorrhagic problems by implementing appropriate medical and surgical therapy. A careful patient interview is required to discover any personal or family history of haemorrhagic diathesis, and a physical examination is required to detect symptoms of coagulopathy prior to surgery. Laboratory testing for haemostasis should be ordered on a case-by-case basis, based on clinical examination and patient history. In the general population, standard tests (prothrombin time, activated partial thromboplastin time, platelet count) have a low positive predictive value for bleeding risk. Pre-interventional haemostasis testing should be avoided in patients with no history of haemorrhagic diathesis or diseases that could interfere with haemostasis. A positive history or an illness that could interfere with haemostasis, on the other hand, should prompt clinically appropriate testing (Bonhomme et al., 2013).

Epidural hematoma is a rare but potentially fatal complication of treatments involving the central neuraxis, such as interlaminar, caudal, and transforaminal epidural injections. While it has long been assumed that the vast majority of these occurrences occur in people using anticoagulant drugs, we have now realized that some people can acquire an epidural hematoma despite having no obvious risk factors. 90 percent of claims for neuraxial

hematoma in the Anesthesia Closed Claims Project were for patients who were treated with anticoagulation drugs; all of these cases resulted in long-term, severe, and permanent injuries, owing to a significant delay in diagnosis and treatment after the first appearance of clinical signs and symptoms (Kent et al., 2017).

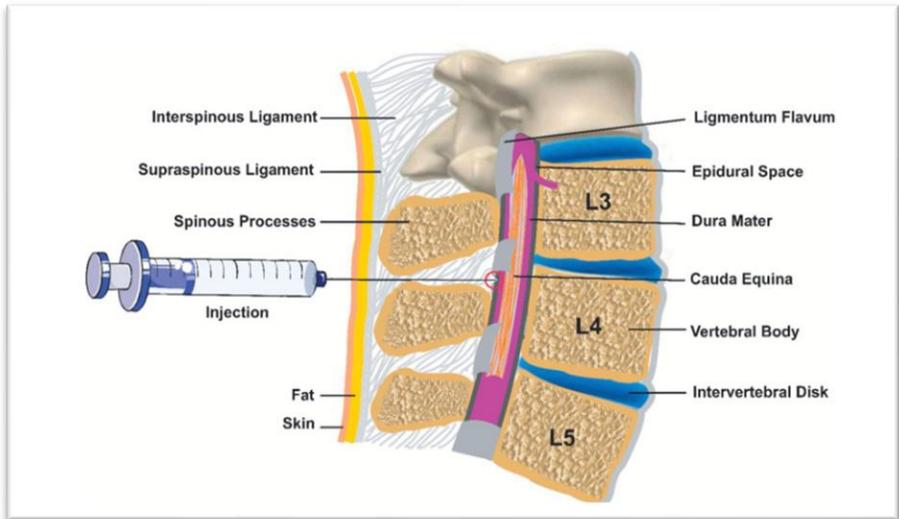


Fig 1. Epidural anesthesia (Kafshdooz et al., 2019)

The danger of major and minor bleeding is inherent in all interventional pain procedures. Percutaneous procedures are becoming more widely accepted for the diagnosis and treatment of chronic pain disorders. There is a growing body of data that these techniques are effective. The prevalence of illnesses requiring anticoagulant therapy and interventional pain therapies will rise as the population ages. The dangers of bleeding must be considered against the procedure's advantages. Anticoagulation may be stopped prior to a procedure if the risk of bleeding outweighs the risk of thrombosis. The patient, the proceduralist, and the anticoagulation physician should all work together in the best case scenario. Finally, a decision must be taken about whether to continue with or abandon a procedure. Significant bleeding after an interventional pain procedure is a very uncommon occurrence. Practitioners would benefit from tools that could assist them foresee these events. Unfortunately, data is scant, and the number of people required in a clinical trial to address concerns regarding which factors

increase the risk of bleeding would be enormous. Nonetheless, several assumptions can be made to tackle this problem, such as the likelihood of substantial bleeding is based on the underlying hemostatic disorders and the procedure used. In stratifying the risk of bleeding with interventional pain procedures, independent risk variables for perioperative bleeding, such as advanced age or sex, have not been incorporated. They should not, however, be overlooked. Based on a stratification of technique-specific and patient-specific parameters, an overall bleeding risk score can be derived. To lower the total bleeding risk score, strategies can be implemented to eliminate technique- and patient-specific risk factors. Such tactics may aid in making judgments on whether to avoid, abort, or continue with a surgery (Raj et al., 2004).

Blood accumulating in the epidural space causes a spontaneous spinal epidural hematoma, squeezing the spinal cord and causing severe neurological impairments. Decompressive laminectomy is the standard treatment, though spontaneous recovery has been documented. The 5.7 percent mortality rate of spontaneous spinal epidural hematoma is due to sub-optimal treatment principles; however, it is uncertain whether patients would benefit from surgery (Raasck et al., 2017).

Patients who are in a state of prolonged recumbency and limited mobility following major operational spinal interventions may be at a higher risk of developing thromboembolic illness. When selecting whether or not to start chemoprophylaxis, spine surgeons must consider the danger of a symptomatic postoperative epidural hematoma against the benefit of DVT/PE prevention, among other things. A symptomatic postoperative epidural hematoma's catastrophic morbidity remains a significant deterrent to starting chemoprophylaxis following spine surgery. Because of the rarity of this condition, determining its risk factors is difficult. Despite the fact that many surgeons believe the risk is higher, the recorded occurrences of clinically meaningful postoperative epidural hematoma are modest, ranging from 0% to 1%. Despite this discovery, there is a lack of published data to define the safety of postoperative chemoprophylaxis accurately. Though not related to prophylaxis, the existing evidence suggests that therapeutic doses of heparin may increase the risk of bleeding problems in postoperative spinal patients who develop a PE (Glitzbecker et al., 2010).

Alcohol consumption of more than 10 units per week, prior spinal surgery, and multilevel treatments have all been identified as risk factors.

After a median of 2.7 hours, the first signs of SEH appeared. The presence of a spinal epidural hematoma early in the postoperative phase emphasizes the significance of vigilant patient monitoring during the first four hours after surgery. An earlier surgical intervention could lead to a better neurological outcome (Amiri et al., 2013).

Literatures

- Amiri, A. R., Fouyas, I. P., Cro, S., & Casey, A. T. (2013). Postoperative spinal epidural hematoma (SEH): incidence, risk factors, onset, and management. *The Spine Journal*, 13(2), 134-140.
- Bonhomme, F., Ajzenberg, N., Schved, J. F., Molliex, S., & Samama, C. M. (2013). Pre-interventional haemostatic assessment: Guidelines from the French Society of Anaesthesia and Intensive Care. *European Journal of Anaesthesiology (EJA)*, 30(4), 142-162.
- Bonhomme, F., Boehlen, F., Clergue, F., & De Moerloose, P. (2016). Preoperative hemostatic assessment: a new and simple bleeding questionnaire. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie*, 63(9), 1007-1015.
- Collis, R. E., & Collins, P. W. (2015). Haemostatic management of obstetric haemorrhage. *Anaesthesia*, 70, 78-e28.
- Ganeshan, A., Nazir, S. A., Hon, L. Q., Upponi, S. S., Foley, P., Warakaulle, D. R., & Uberoi, R. (2010). The role of interventional radiology in obstetric and gynaecology practice. *European journal of radiology*, 73(2), 404-411.
- Glantzbeck, M. P., Bono, C. M., Wood, K. B., & Harris, M. B. (2010). Postoperative spinal epidural hematoma: a systematic review. *Spine*, 35(10), E413-E420.
- Gonsalves, M., & Belli, A. (2010). The role of interventional radiology in obstetric hemorrhage. *Cardiovascular and interventional radiology*, 33(5), 887-895.
- Josephs, S. C. (2008). Obstetric and gynecologic emergencies: a review of indications and interventional techniques. In *Seminars in interventional radiology* (Vol. 25, No. 04, pp. 337-346). © Thieme Medical Publishers.
- Kafshdooz, L., Kahroba, H., Kafshdooz, T., Sheervalilou, R., & Pourfathi, H. (2019). Labour analgesia; Molecular pathway and the role of nanocarriers: a systematic review. *Artificial Cells, Nanomedicine, and Biotechnology*, 47(1), 927-932.
- Kent, C. D., Stephens, L. S., Posner, K. L., & Domino, K. B. (2017). What adverse events and injuries are cited in anesthesia malpractice claims for nonspine

- orthopaedic surgery?. *Clinical Orthopaedics and Related Research*®, 475(12), 2941-2951.
- Raasck, K., Habis, A. A., Aoude, A., Simões, L., Barros, F., Reindl, R., & Jarzem, P. (2017). Spontaneous spinal epidural hematoma management: a case series and literature review. *Spinal cord series and cases*, 3(1), 1-6.
- Raj, P. P., Shah, R. V., Kaye, A. D., Denaro, S., & Hoover, J. M. (2004). Bleeding risk in interventional pain practice: assessment, management, and review of the literature. *Pain Physician*, 7(1), 3-51.
- Rasmussen, O. B., Yding, A., Anhøj, J., Andersen, C. S., & Boris, J. (2016). Reducing the incidence of Obstetric Sphincter Injuries using a hands-on technique: an interventional quality improvement project. *BMJ Open Quality*, 5(1), u217936-w7106.
- Sebghati, M., & Chandrabaran, E. (2017). An update on the risk factors for and management of obstetric haemorrhage. *Women's Health*, 13(2), 34-40.
- Strobel, D., Bernatik, T., Blank, W., Will, U., Reichel, A., Wüstner, M., ... & Müller, T. (2015). Incidence of bleeding in 8172 percutaneous ultrasound-guided intraabdominal diagnostic and therapeutic interventions—results of the prospective multicenter DEGUM interventional ultrasound study (PIUS study). *Ultraschall in der Medizin-European Journal of Ultrasound*, 36(02), 122-131.
- Wise, A., & Clark, V. (2008). Strategies to manage major obstetric haemorrhage. *Current Opinion in Anesthesiology*, 21(3), 281-287.

CHAPTER 12

VULVOVAGINAL BLEEDING IN PREGNANCY

Dr. Betül DİK¹

¹ Selcuk University Faculty of Medicine, Department of Gynecological Oncology, Konya, Turkey orcid no: 0000 0001 9460 4793 dr.betuldik@hotmail.com

INTRODUCTION

Vulvovaginal bleeding can be observed during all periods of pregnancy. Bleeding is almost never of fetal origin. Bleeding is usually of decidua origin. The diagnosis is made according to the week of pregnancy and the type of the bleeding (eg, painful or painless, intermittent or continuous), as well as by laboratory and imaging methods.

Bleeding in the first trimester

Bleeding can occur in approximately 20-40% of pregnancies in the first trimester. Bleeding may be painful or painless. Early pregnancy loss is the most common cause of bleeding. It occurs in 15 to 20 percent of average pregnancies. Almost all patients remain hemodynamically stable, although bleeding is heavy. 1 percent of patients need a blood transfusion.(Nanda K, Lopez LM, 2012). Although ectopic pregnancy occurs in approximately 2%, it is the most serious condition of first trimester bleeding. Ectopic pregnancy rupture can be fatal, therefore, this diagnosis should be excluded first.

Causes of bleeding in early pregnancy :

- Ectopic pregnancy
- Early pregnancy loss
- Abortus imminens
- Bleeding from implantation
- Cervical, vaginal or uterine pathologies

Evaluation : The goal here is to be able to diagnose patients and exclude the presence of serious conditions. It is not easy to determine the etiology of bleeding in the first trimester. It is especially important to exclude this diagnosis, since an ectopic pregnancy is a vital condition. At first, it is necessary to evaluate the patient by ultrasound. Although the previous examination showed that the pregnancy was normal intrauterine, the diagnosis of heterotopic pregnancy or cornual pregnancy should also be kept in mind and the ultrasound examination should be repeated.

Medical examination

The patient should undergo an abdominal examination before the ultrasound examination. After an abdominal examination, the patient is assigned a pelvic examination. The patient is assigned a speculum examination to determine the amount and source of bleeding. It is checked

whether there are pregnancy products in the blood clots and, if necessary, the material is sent to the pathology (Jindal P, Regan L 2007). With a vaginal examination, the presence of bleeding that has nothing to do with pregnancy can be detected. For example; in some cases, it is possible to view the internal cervical os, and the appearance of the sac of pregnancy in the cervical os often indicates that you will have a miscarriage. On examination, a closed cervical os is more often associated with abortus imminens, and if there are no obvious bleeding lesions on a vaginal examination, the speculum is removed, the patient is evaluated by ultrasound.

Transvaginal ultrasonography

It should be determined whether pregnancy with ultrasound is intrauterine or ectopic in these patients, and if it is intrauterine, the diagnosis of heterotopic pregnancy should be considered in the differential diagnosis. If more than 5.5 to 6 weeks have passed since the patient's last menstrual period, failure to monitor the intrauterine pregnancy sac supports the diagnosis of ectopic pregnancy. However, an intrauterine pregnancy at an earlier gestational age, may not yet be visible with ultrasound. In these patients, the signs of ultrasound and blood hCG levels are correlated. It can also detect conditions such as gestational trophoblastic disease or fetal loss due to multiple pregnancy.

Other imaging methods:

Magnetic resonance imaging (MRI) is rarely used in the diagnosis. The second-line imaging method can be used for further evaluation of atypical ectopic pregnancy, trophoblastic disease and severe pelvic pain, as well as adnexal lesions.

Tomography (CT) is not a preferred method due to its radiation content, but it should be used in cases where other imaging methods do not provide sufficient diagnostic information.

Differential diagnosis and management

The described examinations are used to make a diagnostic and management plan. Patients should be looked at their blood type. Anti-D immunoglobulin is administered to Rh D-negative patients to protect against RHD alloimmunization. Some guidelines 12. anti-D immune globulin is not

administered to patients who have had a miscarriage or curettage before the week of pregnancy .(Sperling Jd,Dahlke JD 2018).

Ectopic pregnancy - The diagnosis of ectopic pregnancy in patients with bleeding at an early gestational age should be strictly excluded.The risk is highest in patients with a previous history of ectopic pregnancy.

In the diagnosis, it is important to show the gestational sac by transvaginal ultrasound. Intrauterine pregnancy should be monitored when the transabdominal usg is also hcg 6500 mIU/ml, and the transvaginal usgde is 2000-2500 mIU/ml (although it varies depending on the laboratory), otherwise an ectopic pregnancy is diagnosed.

Treatment of ectopic pregnancy is usually medical or surgical.

Even if the diagnosis of intrauterine pregnancy is made, although rare (1 in 30,000 pregnancies), the diagnosis of heterotopic pregnancy is also possible. This condition is especially common during treatment pregnancies

Other anormally localized pregnancies

In cervical pregnancy , pregnancy is located in the endocervical canal, it is rare.It is often accompanied by vaginal bleeding. Scar pregnancy consists in implantation of the pregnancy into the hysterotomy scar of a patient who has cesarean section. As the pregnancy grows, here may be painful or painless vaginal bleeding.

Early pregnancy loss

Abortus imminens

Clinically, bleeding is mild, may be accompanied by pain, the cervix is closed on examination. Rest is recommended for these patients. Between 90 and 96 percent of pregnancies with vaginal bleeding in the early weeks of pregnancy do not result in abortion. Percentage of ongoing pregnancies is associated with bleeding in later weeks (Tonsong T, Srisombon J 1995; Tannirandom Y, Sangsawang S 2003).Current studies do not show the benefit of progesterone support in these patients.(Speerth H-Guttmacher AF 1954).

Abortus incipiens

In these patients, vaginal bleeding is abundant, pain is increased, and cervical opening is present; abortion is inevitable, pregnancy should be terminated.

Complete abortion

It usually causes complete pregnancy loss in pregnancies younger than 12 weeks. It is distinguished from ectopic pregnancy by a decrease in hCG levels and a decrease in pain and bleeding in the patient. However, if the villi have not been identified or samples are not available for pathological examination, they should be monitored serially until serum hCG levels are negative.

Incomplete abortion

The internal cervical os expands, vaginal bleeding increases. The pregnancy material can be seen in the cervical canal. The patient complains of painful vaginal bleeding and the patient is immediately subjected to revision curettage and the patient's bleeding is stopped.

Missed abortion

It means the death of the embryo or fetus in utero before 20 weeks. There may be vaginal bleeding. The internal cervical os is usually closed. Ultrasound does not monitor embryonic/fetal cardiac activity. In these patients, curettage should be performed urgently.

The vanishing twin

"Vanishing twin " is a very early loss of one of the multiple pregnancies, it usually occurs in patients who are conceived with assisted reproductive methods may be associated with bleeding. (De Sutter P, Bontinck J 2006).

Vaginit, trauma, tumor, warts, polyps, fibroids

These conditions are diagnosed by visual inspection. Even if the source of bleeding on a pelvic examination seems to be a lesion, in patients with first trimester bleeding, the diagnosis of ectopic pregnancy should

always be considered. Depending on the condition of the lesion, treatment is given.

Ectropion

Cervical ectropion (eversion of the cervix) is a common and non-abnormal condition in pregnancy. Cervix is prone to bleeding during sexual intercourse when vaginal examination.

Bleeding from implantation

Normally, a fairly small amount of spotting or bleeding occurs about 10 -14 days after implantation. It is thought to be related to the adhesion of the embryo to the decidua. No intervention is required. (Harville EW, Wilcox AJ 1991).

Prognosis

Studies show that there is a relationship between first trimester bleeding and negative consequences later in pregnancy (for example, early pregnancy loss, premature birth, premature prenatal membrane rupture, fetal development retardation) (Williams MA, Mitendorf R 1991; Hasan R, Baird DD 2009; Lykke JA, Dideriksen KL 2010;Velez Edwards DR, Bird DD 2012; McPherson JA, Odibo AO; Bever AM, Pugh SJ 2018;Everett C 1997). The prognosis for first trimester bleeding is good, if the bleeding continues in the second trimester, the prognosis is poor. (Weiss JL , Malone FD 2004; Yang J, Hartmann KE 2004; Chung TK, Sahato 1999; Gracia CR, Sammel MD 2005; Harger JH, Hsing AW 1990). There are no effective interventions. In particular, rest does not improve the result.

Bleeding in the second and third trimester

Overview - Vaginal bleeding is less in the second trimester (from 14+0 to 27+6 weeks) and in the third trimester (from birth to 28+0 weeks).

Causes of bleeding this week of pregnancy:

- * Loss of pregnancy (14 -20. between weeks of gestation))
- * Cervical incompetency
- * Placenta previa

- * Placental abruption
- * Uterine rupture
- * Vasa previa
- *Cervical, vaginal or uterine pathology and non-tubal ectopic pregnancy are of other etiology.

Bleeding before 20 gestation of week

Evaluation- The evaluation of these patients is the same as in the first trimester . It is necessary to determine the amount of bleeding and whether the bleeding is accompanied by pain. Only mild, intermittent, painless bleeding may occur due to cervical incompetency, a small marginal placental abruption, or due to a cervical or vaginal lesion (eg., polyps,infection, cancer).

The loss of a previously observed fetal heartbeat indicates fetal death, it should always be confirmed by an ultrasound examination.

An abdominal exam is done to evaluate for pain or other abnormalities. After the abdominal examination, the patient is given a vaginal examination. The external genitalia are examined, followed by a vaginal examination. A physical examination can reveal a source of non-pregnancy bleeding, such as cervical ectropion, rupture, or bloody-purulent discharge.

To diagnose cervical incompetency, an enlarged internal os or a direct view of the fetal membranes may be sufficient.

Transvaginal ultrasonography is important in the evaluation of bleeding.

Cervical incompetency - Cervical incompetency is diagnosed clinically; in the absence of pain, it is cervical dilatation and erasure in the second trimester, when fetal membranes can be seen on the external os or beyond. Premature dilatation of the cervix is the main cause of fetal loss or births. Cervical dilatation and shortening should be evaluated by transvaginal ultrasonography. Cervical insufficiency usually leads to bleeding in the second trimester, but it can also cause preterm births.

Vaginal bleeding and spotting may occur. In asymptomatic patients, monitoring of the short cervix on ultrasound (≥ 25 mm before 24 weeks) in a patient who has previously given birth prematurely supports the diagnosis. Prophylactic cervical sutures can be placed during 12-15 gestational weeks

(cerclage). There is insufficient evidence that cerclage prevents preterm birth or prevents fetal loss (Harger JH 2002).

Vaginitis of the cervix or uterine pathologies

Ectopic pregnancy - Ectopic pregnancy in advanced gestational week is rare. It is diagnosed after the first trimester of non-tubal (abdominal, cervical, cesarean scar or corneal or heterotopic (combination of intrauterine and extrauterine pregnancies) pregnancies).

Placental abruption -Placental abruption is the detachment of the placenta before delivery. It occurs once every 1/75-1/226 births (Clark SL 2004). Placenta detachment can be clinically manifested by vaginal bleeding, abdominal pain, uterine hypertonicity, an unreliable fetal heart rate pattern, fetal death, and a DIC table. The diagnosis is primarily clinical, it can also be supported by ultrasound, laboratory. Placental abruption usually cannot be displayed on an ultrasound examination. When diagnosing an placental abruption, precautions should be taken against shock. If there is hypovolemic shock, blood transfusion and replacement with crystalloids should be started.

Treatment: The timing of childbirth is decided based on the maternal and fetal condition, gestational age and severity of symptoms. The choice of emergency delivery depends on the severity of the detachment and whether the fetus is alive or dead. If the fetus is dead, vaginal delivery can be performed, the mother should be followed up for coagulopathy. If the fetus is preterm, birth can be delayed by closely monitoring fetal condition, but in general, tocolytic therapy is not recommended.

Bleeding after 20 gestation of week

20th of pregnancy vaginal bleeding that occurs after the week is called antepartum bleeding. Bleeding may be associated with childbirth, it may not be due to childbirth. Antepartum bleeding is severe in 4-5 percent of pregnancies.

The exact etiology of antepartum hemorrhage cannot be determined. It is attached to the marginal detachment of the placenta.

The main reasons are the following:

- * Placenta previa
- * Placental abruption
- * Uterine rupture
- * Vasa previa

Evaluation - In patients admitted with bleeding in the second trimester, vaginal examination should be avoided until the diagnosis of placenta previa is excluded. Vaginal examination may cause sudden and severe bleeding.

Differential diagnosis

Bloody show - " Bloody show " is the term used to describe a small amount of blood with a mucous discharge, which can be up to 72 hours before the onset of labor.

Placenta previa — Placenta previa is the condition when the placenta is on or near the cervical os; if the placental tissue closes the cervical os, it is called placenta previa. If the placenta extends into the 2-3 cm of the cervical os, but does not surround the cervix. , the placenta is called the marginalis. The incidence of placenta previa is 4/1000 births (Speert H, Guttmacher AF 1954). Clinically painless vaginal bleeding is observed bleeding can sometimes also be accompanied by uterine contractions.

Especially in every patient admitted with vaginal bleeding, the diagnosis can usually be made with an accuracy of 98-100% using ultrasound. Vaginal examination for placenta previa should not be done.

Placental abruption - Placental abruption is the detachment of the placenta before birth. A history of detachment , trauma, smoking, cocaine use, hypertension, and early rupture of membranes are the most common risk factors. The most common symptoms are vaginal bleeding (80 percent), uterine tenderness (70 percent) and uterine contractions (35 percent). There may be uterine tenderness due to extravasation of blood to the myometrium (Couvelaire uterus) .In severe cases, the blood can go all the way to the peritoneal cavity. Ultrasound may show placental abruption, but this is not common (only 2 percent of separations can be viewed on ultrasound). The diagnosis of previa is excluded by ultrasound examination.

Cervical, vaginal or uterine pathology

Uterine rupture - Uterine rupture is a rare condition. The possibility of uterine rupture should always be considered in patients with vaginal bleeding and who have previously undergone cesarean delivery or transmyometrial surgery. Usually seen during childbirth or as a result of abdominal trauma. Deterioration of fetal heart rate and deterioration of hemodynamics due to intra-abdominal bleeding are monitored and are an obstetric emergency.

Vasa previa - Vasa previa is a condition in which the fetal vessels remain between the presenting part and the cervix. The incidence is 1/6000 (Lee W, Lee VL 2000). Veins can connect the lobes of a two-lobed placenta. Vasa previa rupture, which can cause fetal death, is an obstetric emergency. Risk factors include multiple pregnancy and IVF treatment.

Prognosis - Bleeding in the second and third trimesters is associated with such negative consequences of as premature birth. The amount and degree of bleeding determine the prognosis (poor outcome in bleeding that is not due to previa) (Towers CV, Burkhart AE 2008). Antepartum bleeding, the cause of which is unknown, increases the risk of premature birth in the second half of pregnancy by two to three times. (Magann EF, Cummings JE 2005; Bhandari S, Raja EA).

Management - The week of pregnancy, the etiology of bleeding, the amount of bleeding is determined depending on many factors, such as fetal condition.

Uncommon causes of antepartum hemorrhage

Choriocarcinoma -The most important risk factor for choriocarcinoma is that the patient has a previous history of mole pregnancy., but it can also occur after a normal pregnancy. (spontaneous abortion or optional termination, early or timely postpartum). The most common symptom is vaginal bleed and can occur at any week of pregnancy. It can be caused by vaginal metastases or an intrauterine tumor.

Choriocarcinoma should be considered in the diagnosis after excluding other causes of bleeding, especially in patients with respiratory or neurological symptoms. (Steigrad SJ, Cheung AP 1999; Jorgensen K, Roychowdhury M 2019).

References

- Ananth CV, Savitz DA. Vaginal bleeding and adverse reproductive outcomes: a meta-analysis. *Paediatr Perinat Epidemiol* 1994; 8:62.
- Berkowitz, G. S., Harlap, S., Beck, G. J., Freeman, D. H., & Baras, M. (1983). Early gestational bleeding and pregnancy outcome: a multivariable analysis. *International journal of epidemiology*, 12(2), 165–173.
- Bever AM, Pugh SJ, Kim S, et al. Fetal Growth Patterns in Pregnancies With First-Trimester Bleeding. *Obstet Gynecol* 2018; 131:1021.
- Bhandari, S., Raja, E. A., Shetty, A., & Bhattacharya, S. (2014). Maternal and perinatal consequences of antepartum haemorrhage of unknown origin. *BJOG : an international journal of obstetrics and gynaecology*, 121(1), 44–52.
- Chung, T. K., Sahota, D. S., Lau, T. K., Mongelli, J. M., Spencer, J. A., & Haines, C. J. (1999). Threatened abortion: prediction of viability based on signs and symptoms. *The Australian & New Zealand journal of obstetrics & gynaecology*, 39(4), 443–447.
- Clark SL. Placenta previa and abruptio placentae. In Creasy RK, Resnik R (eds): *Maternal-fetal Medicine: Principles and Practice*, 5th ed, Philadelphia, WB Saunders Company 2004; ss: 713.
- Coomarasamy, A., Devall, A. J., Brosens, J. J., Quenby, S., Stephenson, M. D., Sierra, S., Christiansen, O. B., Small, R., Brewin, J., Roberts, T. E., Dhillon-Smith, R., Harb, H., Noordali, H., Papadopoulou, A., Eapen, A., Prior, M., Di Renzo, G. C., Hinshaw, K., Mol, B. W., Lumsden, M. A., ... Gallos, I. D. (2020). Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. *American journal of obstetrics and gynecology*, 223(2), 167–176.
- De Sutter, P., Bontinck, J., Schutysers, V., Van der Elst, J., Gerris, J., & Dhont, M. (2006). First-trimester bleeding and pregnancy outcome in singletons after assisted reproduction. *Human reproduction (Oxford, England)*, 21(7), 1907–1911.
- Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. *BMJ* 1997; 315:32.
- Gracia, C. R., Sammel, M. D., Chittams, J., Hummel, A. C., Shaunik, A., & Barnhart, K. T. (2005). Risk factors for spontaneous abortion in early symptomatic first-trimester pregnancies. *Obstetrics and gynecology*, 106(5 Pt 1), 993–999.
- Harger J. H. (2002). Cerclage and cervical insufficiency: an evidence-based analysis. *Obstetrics and gynecology*, 100(6), 1313–1327.
- Harger, J. H., Hsing, A. W., Tuomala, R. E., Gibbs, R. S., Mead, P. B., Eschenbach, D. A., Knox, G. E., & Polk, B. F. (1990). Risk factors for preterm premature rupture of fetal membranes: a multicenter case-control study. *American journal of obstetrics and gynecology*, 163(1 Pt 1), 130–137.

- Harville, E. W., Wilcox, A. J., Baird, D. D., & Weinberg, C. R. (2003). Vaginal bleeding in very early pregnancy. *Human reproduction* (Oxford, England), 18(9), 1944–1947.
- Hasan, R., Baird, D. D., Herring, A. H., Olshan, A. F., Jonsson Funk, M. L., & Hartmann, K. E. (2009). Association between first-trimester vaginal bleeding and miscarriage. *Obstetrics and gynecology*, 114(4), 860–867.
- Jindal, P., Regan, L., Fourkala, E. O., Rai, R., Moore, G., Goldin, R. D., & Sebire, N. J. (2007). Placental pathology of recurrent spontaneous abortion: the role of histopathological examination of products of conception in routine clinical practice: a mini review. *Human reproduction* (Oxford, England), 22(2), 313–316.
- Jorgensen, K., Roychowdhury, M., da Cunha, G., Kim, Y. B., & Schorge, J. O. (2019). Stage IV Gestational Choriocarcinoma Diagnosed in the Third Trimester. *Obstetrics and gynecology*, 133(1), 163–166.
- Lee, W., Lee, V. L., Kirk, J. S., Sloan, C. T., Smith, R. S., & Comstock, C. H. (2000). Vasa previa: prenatal diagnosis, natural evolution, and clinical outcome. *Obstetrics and gynecology*, 95(4), 572–576.
- Lykke, J. A., Dideriksen, K. L., Lidegaard, Ø., & Langhoff-Roos, J. (2010). First-trimester vaginal bleeding and complications later in pregnancy. *Obstetrics and gynecology*, 115(5), 935–944.
- Magann, E. F., Cummings, J. E., Niederhauser, A., Rodriguez-Thompson, D., McCormack, R., & Chauhan, S. P. (2005). Antepartum bleeding of unknown origin in the second half of pregnancy: a review. *Obstetrical & gynecological survey*, 60(11), 741–745.
- McPherson JA, Odibo AO, Shanks AL, et al. Adverse outcomes in twin pregnancies complicated by early vaginal bleeding. *Am J Obstet Gynecol* 2013; 208:56.e1.
- Nanda, K., Lopez, L. M., Grimes, D. A., Peloggia, A., & Nanda, G. (2012). Expectant care versus surgical treatment for miscarriage. *The Cochrane database of systematic reviews*, 2012(3), CD003518.
- Sperling, J. D., Dahlke, J. D., Sutton, D., Gonzalez, J. M., & Chauhan, S. P. (2018). Prevention of RhD Alloimmunization: A Comparison of Four National Guidelines. *American journal of perinatology*, 35(2), 110–119.
- Steigrad, S. J., Cheung, A. P., & Osborn, R. A. (1999). Choriocarcinoma co-existent with an intact pregnancy: case report and review of the literature. *The journal of obstetrics and gynaecology research*, 25(3), 197–203.
- Tannirandorn, Y., Sangsawang, S., Manotaya, S., Uerpairojkit, B., Samritpradit, P., & Charoenvithya, D. (2003). Fetal loss in threatened abortion after embryonic/fetal heart activity. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, 81(3), 263–266.
- Tongsong, T., Srisomboon, J., Wanapirak, C., Sirichotiyakul, S., Pongsatha, S., & Polsrisuthikul, T. (1995). Pregnancy outcome of threatened abortion with demonstrable fetal cardiac activity: a cohort study. *Journal of obstetrics and gynaecology* (Tokyo, Japan), 21(4), 331–335.

- Towers, C. V., & Burkhart, A. E. (2008). Pregnancy outcome after a primary antenatal hemorrhage between 16 and 24 weeks' gestation. *American journal of obstetrics and gynecology*, 198(6), 684.e1–684.e5.
- Velez Edwards, D. R., Baird, D. D., Hasan, R., Savitz, D. A., & Hartmann, K. E. (2012). First-trimester bleeding characteristics associate with increased risk of preterm birth: data from a prospective pregnancy cohort. *Human reproduction (Oxford, England)*, 27(1), 54–60.
- Weiss, J. L., Malone, F. D., Vidaver, J., Ball, R. H., Nyberg, D. A., Comstock, C. H., Hankins, G. D., Berkowitz, R. L., Gross, S. J., Dugoff, L., Timor-Tritsch, I. E., D'Alton, M. E., & FASTER Consortium (2004). Threatened abortion: A risk factor for poor pregnancy outcome, a population-based screening study. *American journal of obstetrics and gynecology*, 190(3), 745–750.
- Williams MA, Mittendorf R, Lieberman E, Monson RR. Adverse infant outcomes associated with first-trimester vaginal bleeding. *Obstet Gynecol* 1991; 78:14.
- Yang, J., Hartmann, K. E., Savitz, D. A., Herring, A. H., Dole, N., Olshan, A. F., & Thorp, J. M., Jr (2004). Vaginal bleeding during pregnancy and preterm birth. *American journal of epidemiology*, 160(2), 118–125.

CHAPTER 13

HEMORRHAGE DUE TO OPERATIVE VAGINAL DELIVERY

Dr. Arife Ebru TAŞCI¹

¹ Necmettin Erbakan University, Meram Faculty of Medicine, Department of Gynecological Oncology, Konya, Turkey ebrukuzu_dr@hotmail.com orcid no: 0000-0003-0610-7098

Introduction

Operative Vaginal Delivery

Operative vaginal delivery refers to a delivery in which the operator uses forceps or a vacuum device to extract the fetus from the vagina during the second stage of labor. The decision to use a device to deliver the fetus balances the maternal, fetal, and neonatal impact of the procedure against the alternative option as cesarean delivery.

Prevalence

Prevalence rates vary worldwide depending on local practice patterns and availability of trained clinicians and other necessary resources (Ameh & Weeks, 2009). 3.1 percent of all births in 2017 were accomplished via an operative vaginal approach (Martin, 2018). Forceps births accounted for 0.5 percent of vaginal births, and vacuum births accounted for 2.6 percent of vaginal births. It is noteworthy that the rate of operative vaginal deliveries decreased with the increase in cesarean section rates (Cunningham, Leveno, Bloom, Spong, & Dashe, 2014).

Indications

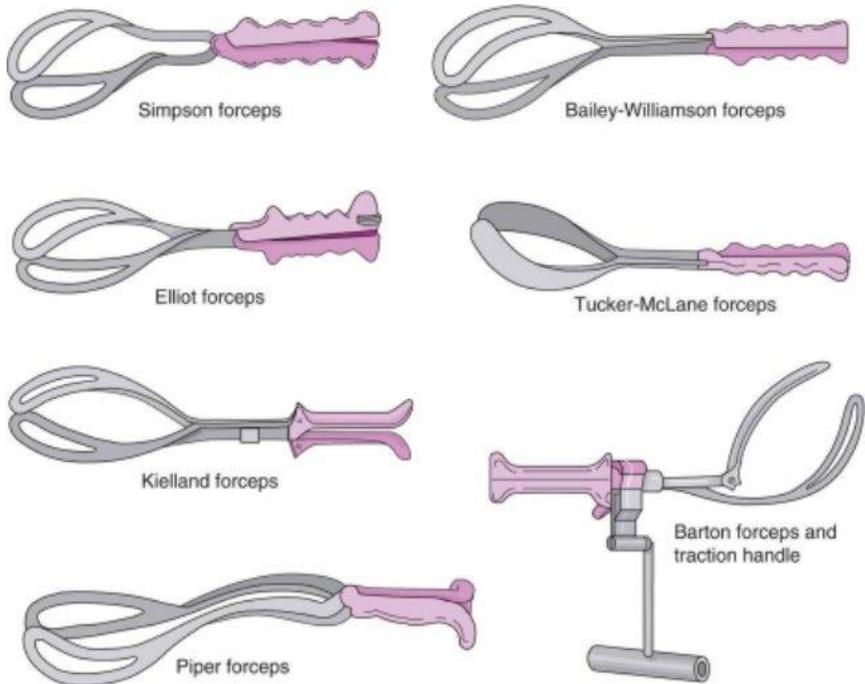
Termination of second stage labor by operative vaginal delivery is indicated in any condition threatening the mother or fetus that is likely to be relieved by delivery. Maternal exhaustion and an inability to push effectively; maternal medical indications, such as maternal cardiac disease and a need to avoid pushing in the second stage of labor; prolonged second stage of labor and suspicion of immediate or potential fetal compromise are the most common indications for operative vaginal deliveries (Peaceman, 2020). Cesarean delivery is also an option in these clinical situations.

Contraindications

Operative vaginal birth is contraindicated if the risk to mother or fetus is unacceptable. Extreme fetal prematurity; fetal demineralizing disease (eg, osteogenesis imperfecta); fetal bleeding diathesis (eg, fetal hemophilia, neonatal alloimmune thrombocytopenia (Richards et al., 2012)); unengaged head; unknown fetal position; brow or face presentation; suspected fetal-pelvic disproportion are the main contraindications. (Peaceman, 2020), (Gei & Belfort, 1999). Also <34 weeks of gestation and prior fetal scalp sampling are relative contraindication for vacuum extraction.

Forceps Delivery

Forceps device consist of two crossing branches. Each branch has four components: blade, shank, lock and handle. Each blade has two curves: the outward cephalic curve conforms to the round fetal head, and the upward pelvic curve corresponds more or less to the axis of the birth canal (Cunningham et al., 2014). There are various forceps types according to the shapes of the blades (Picture 1). The type of forceps selected for a particular procedure depends on the size and shape of the fetal head and maternal pelvis, which should match the size, cephalic curve, and pelvic curve of the forceps. Also fetal head position, station and whether rotation is planned should be considered. Operator experience and preference also effects the choice.

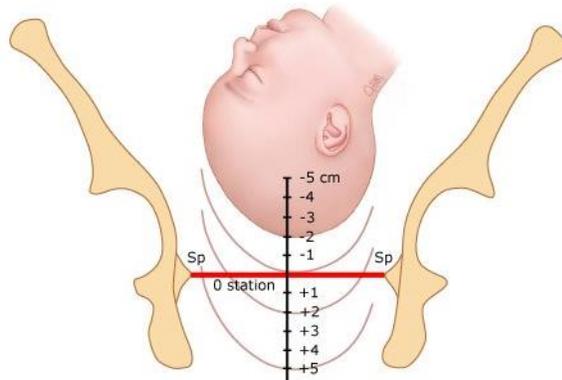


Picture 1: Commonly Used Forceps

Simpson type forceps, which have long tapered blades, tend to be the best fit for a molded head because of the less concave cephalic curve. Elliott type forceps or Tucker-McLane type forceps are better suited to a round, unmolded head as the cephalic curve of the forceps is more concave.

Fenestrated blades allow for a better grip and therefore are less likely to slip, but the fenestrations increase the risk for tissue laceration when greater forces are applied. Solid blades are less likely to lacerate the fetal head but may be more likely to slip with increased traction. Pseudo fenestrated blades have a shallow indentation rather than a true fenestrated, which may reduce slippage while also reducing risks of laceration. Kielland forceps are useful for rotations because of their minimal pelvic curve and sliding lock. A sliding lock is helpful when there is asynclitism. Piper forceps are used to assist the birth of the aftercoming head in vaginal breech births (Gabbe et al., 2016).

Classification system for forceps deliveries is based on station and extent of rotation (Peaceman, 2020). Fetal station is measured using the -5 to +5 centimeter classification system. Deliveries are categorized as outlet, low and midpelvic procedures (Cunningham et al., 2014).



Picture 2: Fetal Station Classification (Sp: ischial spine)

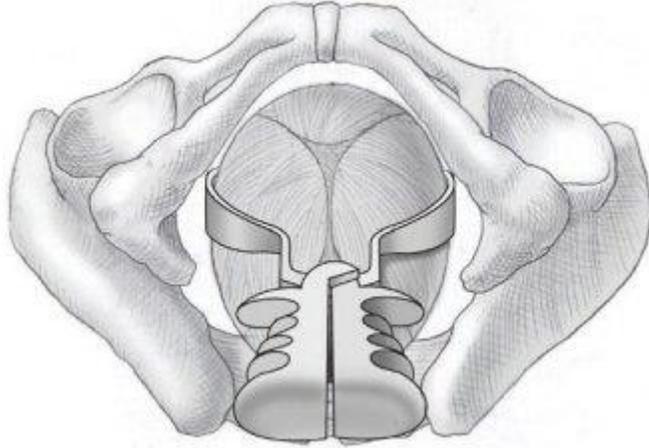
Table 1: Classification Of Assisted Vaginal Deliveries According To Station And Rotation (Hankins & Rowe, 1996)

Type Of Procedure	Classification
Outlet	1) Scalp is visible at the introitus without separating the labia
	2) Fetal skull has reached the pelvic floor
	3) Sagittal suture is in anteroposterior diameter or right or left occiput anterior posterior position
	4) Fetal head is at or on perineum
	5) Rotation does not exceed 45 degrees
Low	1) Leading point of fetal skull is at station $\geq +2$ cm, and not on the pelvic floor
	2) Rotation ≤ 45 degrees (left or right occiput anterior to occiput anterior, or left or right occiput posterior to occiput posterior)
	3) Rotation > 45 degrees
Mid	1) Station above +2 cm but head engaged

Prerequisites for forceps delivery include the following:

- The head must be engaged.
- The cervix must be fully dilated and retracted.
- The position of the head must be known.
- Clinical assessment of pelvic capacity should be performed.
- The membranes must be ruptured.
- The patient must have adequate analgesia.

While applying forceps sagittal suture should be equidistant with the forcep's shanks and the posterior fontanel should be one finger above the handle and the lambdoid suture should be equidistant from the blades.



Picture 3: Forceps Are Symmetrically Placed And Articulated

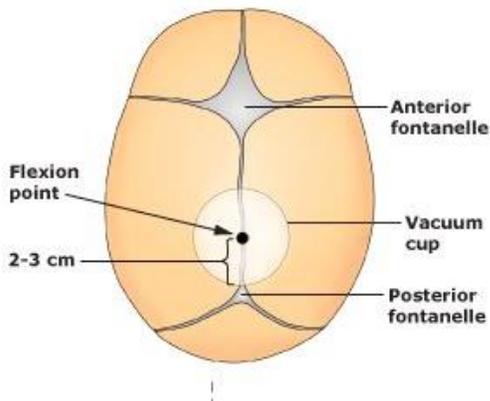
Vacuum Extraction

With vacuum delivery technique, suction is created within a cup placed on the fetal scalp. Instrumentation consists of a vacuum pump, a cup to attach to the fetal scalp, and some type of handle attached to the cup, which is pulled to generate traction. Suction can be generated manually or with an electrical suction device. Vacuum cups may be soft (pliable) or rigid and the shape may be bell or "M" shaped. When rigid cups and soft cups compared the rate of maternal injury was similar for both cups.



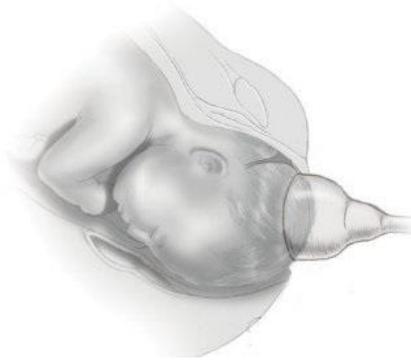
Picture 4: Vacuum delivery equipment

Good placement of a vacuum cup requires proper assessment of the fetal position and station. The flexion point is a critical landmark for the safe and effective use of a vacuum. The flexion point is in the midline, over the sagittal suture, approximately 6 cm from the anterior fontanelle and 3 cm from the posterior fontanelle (Picture 4). The center of the vacuum cup should be directly over the flexion point.



Picture 5: Flexion Point In Relation To Fetal Skull Landmarks

After correct placement of the cup is confirmed, vacuum pressure should be raised to 100 to 150 mmHg to maintain the cup's position. The edges of the cup should again be swept with a finger to insure that no maternal tissues are entrapped. Rapid application to the maximum suction pressure of 600 mmHg is acceptable, although pressures in excess of 450 mmHg are rarely necessary. Slow, stepwise application of suction does not improve safety or efficacy. Between contractions, suction pressure can be fully maintained or reduced to <200 mmHg. Gentle traction should be applied along the axis of the pelvic curve.



Picture 6: Cup Placed Before Application Of Traction

Complications

Maternal complications associated with operative vaginal birth include lower genital tract laceration, vulvar and vaginal hematomas, urinary tract injury, and anal sphincter injury (Dell, Sightler, & Plauché, 1985) (Liu et al., 2005). Forceps or vacuum assisted vaginal birth increases the risk of postpartum hemorrhage (Sheiner, Sarid, Levy, Seidman, & Hallak, 2005).

Lower Genital Tract Laceration

Lower genital tract laceration after operative vaginal delivery could cause serious hemorrhage.

Randomized trials generally report less maternal genital trauma with vacuum versus forceps extraction, which is not unexpected given that a correctly applied vacuum cup does not take up additional space between the fetal head and the birth canal and does not make contact with maternal soft tissue (Verma et al., 2021). Also vacuum assisted births have been

associated with lower rates of maternal morbidity and mortality than cesarean births in the second stage.

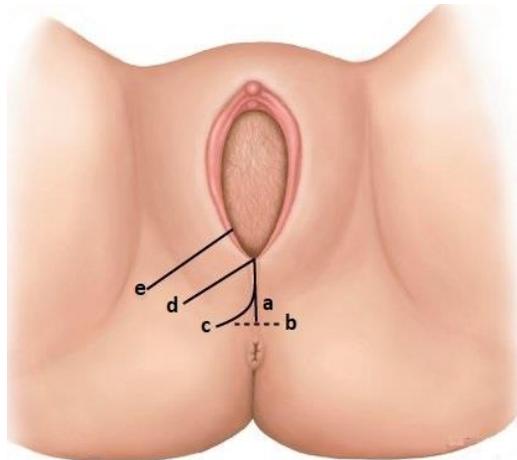
There is a higher risk of maternal genital trauma with forceps versus vacuum extraction (any perineal, vulval, or vaginal trauma) (Verma et al., 2021). Rotational and midforceps procedures have been considered major risk factors for serious maternal trauma during operative vaginal birth.

Occiput posterior position is a risk factor for maternal trauma during operative vaginal birth (Damron & Capeless, 2004) (Benavides, Wu, Hundley, Ivester, & Visco, 2005), particularly third-fourth degree perineal lacerations (spontaneous delivery 2 percent, vacuum extraction 10 to 11 percent, forceps-assisted birth 17 to 20 percent (Landy et al., 2011) (Angioli, Gómez-Marín, Cantuaria, & O'Sullivan, 2000)).

When operative midpelvic procedures compared with cesarean birth the overall risk of severe maternal morbidity and mortality was similar for midpelvic procedures and cesarean birth, but midpelvic procedures were associated with a high rate of maternal obstetric trauma (eg, third and fourth degree perineal lacerations, cervical laceration, high vaginal laceration) (Muraca et al., 2017).

Episiotomy

Episiotomy is the surgical enlargement of the posterior aspect of the vagina by an incision to the perineum during the last part of the second stage of labor (Carroli & Belizan, 1999).



Picture 7: Types Of Episiotomy Incisions

In median episiotomy the incision commences from the center of the fourchette and extends posteriorly along the midline (a). In mediolateral episiotomy the incision is made downwards and outwards from the midpoint of the fourchette either to the right or to the left (d). If the incision starts from 1 cm away from the center of the fourchette and extends laterally it is called as lateral episiotomy (e). In 'J' shaped episiotomy the incision begins in the center of the fourchette and is directed posteriorly along the midline and then directed to downwards and outwards along 5 or 7 o'clock position to avoid the anal sphincter (c). Also there are various modifications of the above techniques that may be preferred by individual practitioners as shown on the Picture 7. The T shape episiotomy is a modification of the median episiotomy in which bilateral transverse incisions are made at the inferior apex to create an inverted T shaped incision (b) (May, 1994).

Routine use of episiotomy has fallen out of favor based on evidence of increased complications with use and it is not recommended performing an episiotomy routinely at operative vaginal deliveries. Episiotomy is considered when the clinical circumstances place the patient at high risk of a third or fourth degree laceration or when the fetal heart tracing is showing fetal distress signs and hastening vaginal delivery is required. Mediolateral episiotomy is associated with a lower risk of third fourth degree laceration than a median episiotomy. Common complications of episiotomy include extension of the incision deeper into the perineum or the anal sphincter complex, infection, breakdown, postpartum pain, and dyspareunia. Although vulvovaginal hematomas can occur after episiotomies, this complication is rare.

Puerperal Hematomas Incurred As A Result Of Operative Vaginal Delivery

In pregnancy, vulva and vagina have rich vascular supplies that are at risk of trauma during the delivery process, and trauma may result in formation of a hematoma. Puerperal hematomas occur in 1:300 to 1:1500 deliveries and, rarely, are a potentially life-threatening complication of childbirth (Zahn & Yeomans, 1990) (Villella et al., 2001).

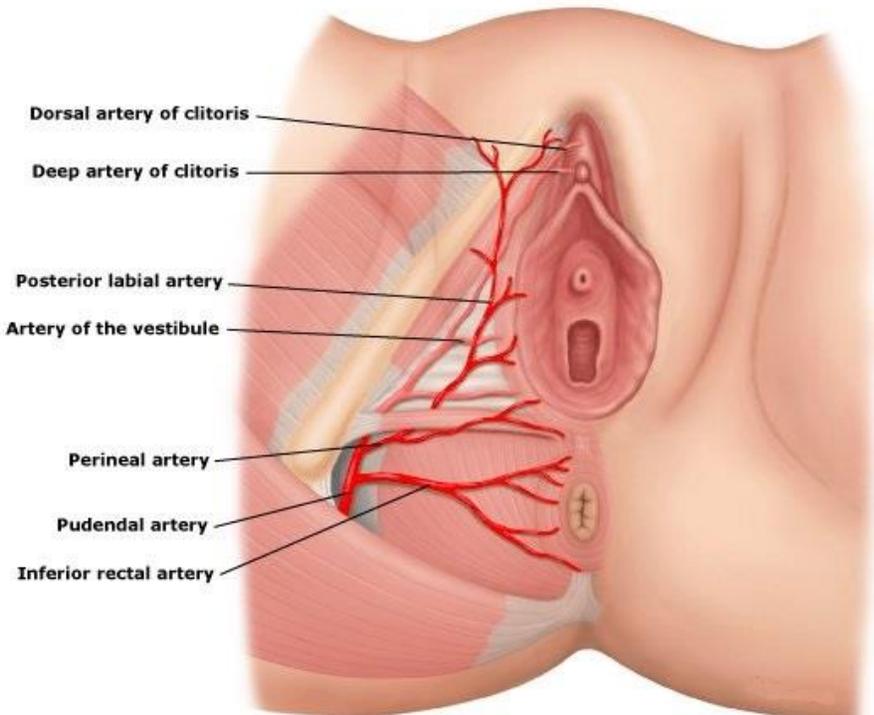
Most puerperal hematomas arise from bleeding lacerations related to operative deliveries or episiotomy; however, a hematoma may also result from injury to a blood vessel in the absence of laceration/incision of the

surrounding tissue (eg, pseudoaneurysm, traumatic arteriovenous fistula) (Zahn & Yeomans, 1990) (Guerriero et al., 2004) (Nagayama et al., 2011).

Those who gave birth by operative vaginal delivery have an increased risk for puerperal hematoma development (Saleem & Rydhström, 2004).

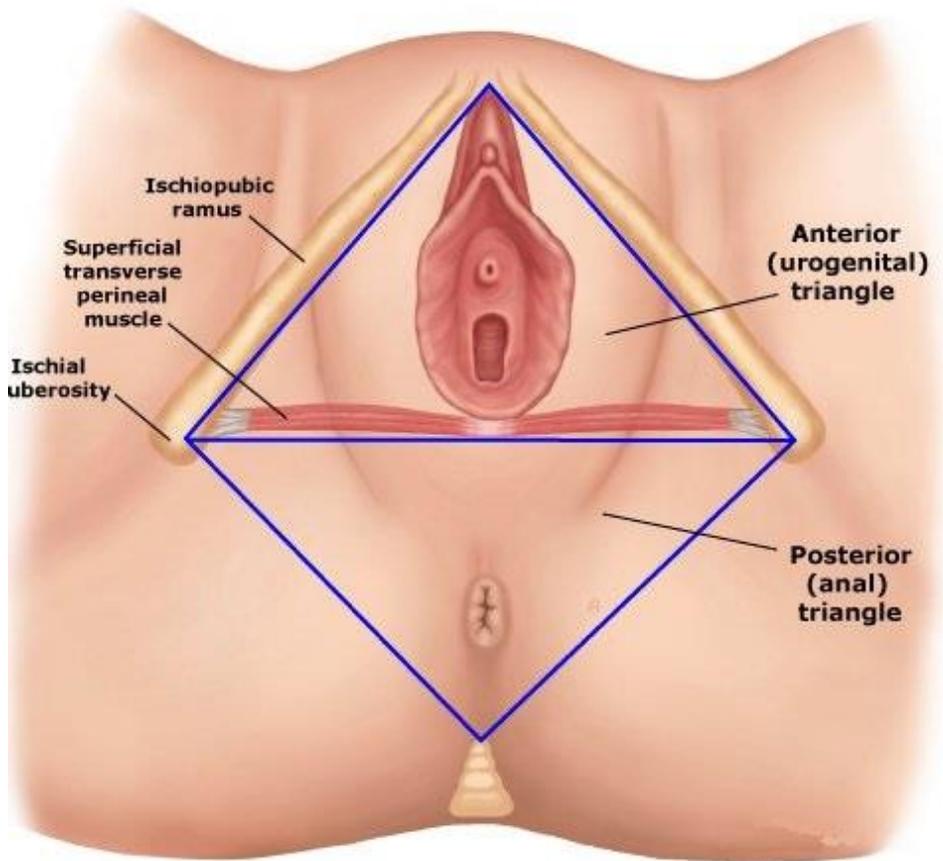
The most common locations for puerperal hematomas are the vulva, vaginal and paravaginal area, and retroperitoneum. While extremely rare, bowel hematoma is also a reported complication of delivery (Bacalbaşa, Bohilţea, Dumitru, Turcan, & Cîrstoiu, 2017).

Most vulvar hematomas result from injuries to branches of the pudendal artery (inferior rectal, perineal, posterior labial, and urethral arteries; the artery of the vestibule; and the deep and dorsal arteries of the clitoris) that occur during episiotomy or from perineal lacerations (Zahn & Yeomans, 1990) (Guerriero et al., 2004).



Picture 8: Arteries Of The Female Perineum

These vessels are typically located in the superficial fascia of the anterior (urogenital) or posterior pelvic triangle.

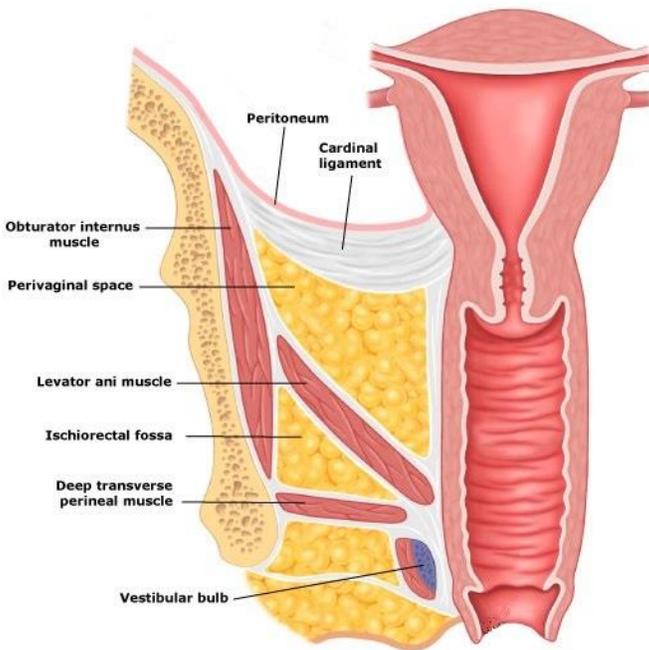


Picture 9: Triangles Of The Female Perineum

The superficial compartment of the anterior triangle communicates with the subfascial space of the lower abdomen below the inguinal ligament. Extension of bleeding in the anterior triangle is limited by Colles' fascia and the urogenital diaphragm, while the anal fascia limits extension of hemorrhage in the posterior triangle. As a result, hemorrhage is directed toward the skin where the loose subcutaneous tissues afford little resistance to hematoma formation. Superficial hematomas can extend from the posterior margin of the anterior triangle (at the level of the transverse perineal muscle) anteriorly over the mons to the fusion of fascia at the

inguinal ligament. Necrosis caused by pressure and rupture of the tissue surrounding the hematoma may lead to external hemorrhage (Ridgway, 1995).

Vaginal and paravaginal hematomas result from injuries to branches of the uterine artery, mainly the descending branch. These hematomas are commonly associated with forceps delivery, but may also occur during spontaneous delivery. (Zahn & Yeomans, 1990) (Ridgway, 1995). Vessels in the vagina are surrounded by soft tissue and do not lie in the superficial fascia; therefore, trauma to these vessels can lead to a large accumulation of blood in the paravaginal space or ischioanal fossa. Most vaginal and paravaginal hematomas also extend into the upper portion of the vaginal canal, and may occlude its lumen. Extension and dissection into the retroperitoneum may occur and form a palpable tumor above inguinal ligament. Dissection may also extend cephalad, potentially reaching the lower margin of the diaphragm.



Picture 10: Pelvic Extraperitoneal Space

Compared with vulvar and vaginal and paravaginal hematomas, retroperitoneal hematomas are a rare complication of operative vaginal delivery. In peripartum women, retroperitoneal hematomas are typically caused by injury to branches of the internal iliac (ie, hypogastric) artery. The most common delivery related causes are laceration of a uterine artery during hysterotomy or from uterine rupture and extension of a paravaginal hematoma. The resulting hemorrhage can be quite severe and lead to immediate hemodynamic instability.

The diagnosis of most puerperal hematomas is based upon the presence of characteristic symptoms and findings on physical examination. Symptoms usually develop in the first twenty four hours after delivery. The clinical manifestations of puerperal hematomas vary depending upon the location of the hematoma. Although small hematomas may be asymptomatic, most hematomas are associated with pain and mass effects. A large mass may displace the vagina or rectum or both and hemodynamic instability may result from continued significant hemorrhage.

Vulvar hematomas usually present with rapid development of a tense, severely painful, compressible mass covered by skin with purplish discoloration. A vulvar hematoma may be an extension of a vaginal hematoma that has dissected through loose subcutaneous tissue into the vulva.

Vaginal hematomas often present with rectal pressure; however, hemodynamic instability due to bleeding into the ischiorectal fossa and paravaginal space may be the first indication of a vaginal hematoma, and can result in hypovolemic shock. On physical examination, a large mass protruding into the vagina is usually palpable (Guerriero et al., 2004).

Retroperitoneal hematomas extending between the folds of the ligamentum latum uteri may be asymptomatic at first. Due to the significant amount of blood that can accumulate in the retroperitoneal space, these patients often present with symptoms of hemodynamic instability, including hypotension, tachycardia, or in the severe cases, shock. Patients with a retroperitoneal hematoma usually do not present with pain unless the hematoma is associated with trauma. Palpation of an abdominal mass or fever can also be signs of a retroperitoneal hematoma.

The management of puerperal hematomas is based on practice patterns established over the years, rather than clinical trials with clearly defined outcomes. The three primary approaches for managing puerperal

hematomas are conservative management with observation and supportive care, surgical intervention, and selective arterial embolization. The literature is inconclusive regarding the benefits of conservative treatment versus surgical intervention (Benrubi, Neuman, Nuss, & Thompson, 1987).

Nonexpanding, small vulvar hematomas will often resolve with conservative management, such as application of cold packs and analgesia. There are no proven criteria that can be used to select vulvar hematomas likely to have a better outcome with surgical intervention rather than supportive care (SHEIKH, 1971).(Zahn, Hankins, & Yeomans, 1996).

The approach to vaginal hematomas is similar to that for vulvar hematomas. As with vulvar hematomas, vaginal hematomas larger than approximately 4 cm may need to be evacuated.

There are no large or randomized trials comparing surgical versus angiographic approaches to management of retroperitoneal hematomas. Because the retroperitoneal space is large, many patients with a retroperitoneal hematoma require either surgical or angiographic intervention. However, since it is a confined space, conservative management may suffice because the hematoma tamponades slowly bleeding vessels. Laparotomy is required in virtually all cases of puerperal retroperitoneal hemorrhage. It is suggested that selective arterial embolization as an alternative to surgical intervention in the hemodynamically stable patient or when surgical intervention fails to control the bleeding from a puerperal hematoma. Retroperitoneal bleeding is rarely a consequence of operative vaginal delivery.

References

- Ameh, C., & Weeks, A. (2009). The role of instrumental vaginal delivery in low resource settings. *BJOG: An International Journal of Obstetrics & Gynaecology*, *116*, 22-25.
- Angioli, R., Gómez-Marín, O., Cantuaria, G., & O'Sullivan, M. J. (2000). Severe perineal lacerations during vaginal delivery: the University of Miami experience. *American journal of obstetrics and gynecology*, *182*(5), 1083-1085.
- Bacalbaşa, N., Bohilţea, R., Dumitru, M., Turcan, N., & Cîrstoiu, M. (2017). Subserosal hematoma of the sigmoid colon after vaginal delivery. *Journal of Medicine and Life*, *10*(1), 76.
- Benavides, L., Wu, J. M., Hundley, A. F., Ivester, T. S., & Visco, A. G. (2005). The impact of occiput posterior fetal head position on the risk of anal sphincter injury in forceps-assisted vaginal deliveries. *American journal of obstetrics and gynecology*, *192*(5), 1702-1706.
- Benrubi, G., Neuman, C., Nuss, R., & Thompson, R. (1987). Vulvar and vaginal hematomas: a retrospective study of conservative versus operative management. *Southern medical journal*, *80*(8), 991-994.
- Carroli, G., & Belizan, J. (1999). Episiotomy for vaginal birth. *Cochrane Database of Systematic Reviews*(3).
- Cunningham, F. G., Leveno, K. J., Bloom, S. L., Spong, C. Y., & Dashe, J. S. (2014). *Williams obstetrics, 24e*: Mcgraw-hill New York, NY, USA.
- Damron, D. P., & Capeless, E. L. (2004). Operative vaginal delivery: a comparison of forceps and vacuum for success rate and risk of rectal sphincter injury. *American journal of obstetrics and gynecology*, *191*(3), 907-910.
- Dell, D. L., Sightler, S. E., & Plauché, W. C. (1985). Soft cup vacuum extraction: a comparison of outlet delivery. *OBSTETRICS AND GYNECOLOGY*, *66*(5), 624-628.
- Gabbe, S. G., Niebyl, J. R., Simpson, J. L., Landon, M. B., Galan, H. L., Jauniaux, E. R.,... Grobman, W. A. (2016). *Obstetrics: normal and problem pregnancies e-book*: Elsevier Health Sciences.
- Gei, A. F., & Belfort, M. A. (1999). Forceps-assisted vaginal delivery. *Obstetrics and gynecology clinics of North America*, *26*(2), 345-370.
- Guerriero, S., Ajossa, S., Bargellini, R., Amucano, G., Marongiu, D., & Melis, G. B. (2004). Puerperal vulvovaginal hematoma: sonographic findings with MRI correlation. *Journal of Clinical Ultrasound*, *32*(8), 415-418.
- Hankins, G. D., & Rowe, T. F. (1996). Operative vaginal delivery-year 2000. *American journal of obstetrics and gynecology*, *175*(2), 275-282.
- Landy, H. J., Laughon, S. K., Bailit, J., Kominiarek, M. A., Gonzalez-Quintero, V. H., Ramirez, M.,... Branch, D. W. (2011). Characteristics associated with severe perineal and cervical lacerations during vaginal delivery. *OBSTETRICS AND GYNECOLOGY*, *117*(3), 627.
- Liu, S., Heaman, M., Joseph, K. S., Liston, R. M., Huang, L., Sauve, R., & Kramer, M. S. (2005). Risk of maternal postpartum readmission associated with mode of delivery. *Obstetrics & Gynecology*, *105*(4), 836-842.

- Martin, J. A. (2018). MPH, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: final data for 2017 [internet]. *National Vital Statistics Reports*. CDC.
- May, J. L. (1994). Modified median episiotomy minimizes the risk of third-degree tears. *OBSTETRICS AND GYNECOLOGY*, 83(1), 156-157.
- Muraca, G. M., Sabr, Y., Lisonkova, S., Skoll, A., Brant, R., Cundiff, G. W., & Joseph, K. (2017). Perinatal and maternal morbidity and mortality after attempted operative vaginal delivery at midpelvic station. *Cmaj*, 189(22), E764-E772.
- Nagayama, C., Gibo, M., Nitta, H., Uezato, T., Hirakawa, M., Masamoto, H.,... Aoki, Y. (2011). Rupture of pseudoaneurysm after vaginal delivery successfully treated by selective arterial embolization. *Archives of gynecology and obstetrics*, 283(1), 37-40.
- Peaceman, A. M. (2020). Operative Vaginal Birth ACOG Practice Bulletin, Number 219. *OBSTETRICS AND GYNECOLOGY*, 135(4), E149-E159.
- Richards, M., Lavigne Lissalde, G., Combescure, C., Batorova, A., Dolan, G., Fischer, K.,... Pérez, R. (2012). Neonatal bleeding in haemophilia: a European cohort study. *British journal of haematology*, 156(3), 374-382.
- Ridgway, L. E. (1995). Puerperal emergency: vaginal and vulvar hematomas. *Obstetrics and gynecology clinics of North America*, 22(2), 275-282.
- Saleem, Z., & Rydhström, H. (2004). Vaginal hematoma during parturition: a population-based study. *Acta obstetrica et gynecologica Scandinavica*, 83(6), 560-562.
- SHEIKH, G. N. (1971). Perinatal genital hematomas. *Obstetrics & Gynecology*, 38(4), 571-575.
- Sheiner, E., Sarid, L., Levy, A., Seidman, D. S., & Hallak, M. (2005). Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study. *The Journal of Maternal-Fetal & Neonatal Medicine*, 18(3), 149-154.
- Verma, G. L., Spalding, J. J., Wilkinson, M. D., Hofmeyr, G. J., Vannevel, V., & O'Mahony, F. (2021). Instruments for assisted vaginal birth. *Cochrane Database of Systematic Reviews*(9).
- Villella, J., Garry, D., Levine, G., Glanz, S., Figueroa, R., & Maulik, D. (2001). Postpartum angiographic embolization for vulvovaginal hematoma. A report of two cases. *The Journal of reproductive medicine*, 46(1), 65-67.
- Zahn, C. M., Hankins, G., & Yeomans, E. R. (1996). Vulvovaginal hematomas complicating delivery. Rationale for drainage of the hematoma cavity. *The Journal of reproductive medicine*, 41(8), 569-574.
- Zahn, C. M., & Yeomans, E. R. (1990). Postpartum hemorrhage: placenta accreta, uterine inversion, and puerperal hematomas. *Clinical obstetrics and gynecology*, 33(3), 422-431.

CHAPTER 14

PERIOPERATIVE MANAGEMENT OF BLEEDING PREGNANT: AN OVERVIEW

Dr. Gizem Ceren EKİCİ¹

¹ Department of Obstetrics and Gynecology, Hayat Hospital, Siirt, Turkey Orcid ID: 0000-0003-0021-4626 Corresponding author: c.gizem.ekici@gmail.com

1. Introduction

Placental dysfunction is indicated by bleeding, which is more likely to occur around the time of the luteal-placental shift (Hasan et al., 2010). During the first trimester, 20% to 40% of pregnant women will suffer bleeding. The general practitioner is usually the first person to whom the patient is introduced. The most prevalent diagnosis are miscarriage complications, such as impending miscarriage and ectopic pregnancy. Ectopic pregnancy is a major health problem (Yılmaz, 2022). A woman's life could be jeopardized if she is not diagnosed with an ectopic pregnancy. Early pregnancy bleeding is a painful sign for which a woman seeks confirmation that her pregnancy is still going on. It's not always possible to make a diagnosis immediately when a patient presents. Follow-up investigations or referral to a gynecologist may be necessary in some circumstances. We should continue to evaluate and update our knowledge in the management of this prevalent presentation as healthcare practitioners in order to deliver the best possible treatment to these patients (Breeze, 2016).

Recognition of potentially serious disorders such as placenta previa, placental abruption, and vasa previa is necessary for effective management of vaginal bleeding in late pregnancy. Placenta previa is typically detected on routine ultrasonography before 20 weeks of pregnancy, however it resolves in approximately 90% of cases. Women with asymptomatic previa can resume normal activities after a 28-week ultrasonographic assessment. Persistent previa in the third trimester necessitates pelvic rest and, if substantial bleeding occurs, hospitalization. Placental abruption, which affects one percent of pregnancies, is the most prevalent cause of significant vaginal bleeding. To avoid infant morbidity and mortality, abruption may necessitate a quick surgical delivery. Vasa previa is an uncommon condition that can cause fetal exsanguination and membrane rupture. Significant vaginal bleeding, regardless of the origin, is treated with a prompt assessment of mother and fetal condition, fluid resuscitation, blood product replacement if needed, and a timely delivery (Sakornbut et al., 2007).

Deficiencies of fibrinogen, prothrombin, factor V, factor VII, factor X, factor XI, and factor XIII, as well as combination deficiency syndromes, factor V+VIII insufficiency, and deficiency of vitamin K-dependent components, are all rare bleeding disorders (factor II, VII, IX and X). They are responsible for 3–5% of all hereditary coagulation abnormalities. Because of their rarity, information on pregnancy problems and their care is

scarce, and it is primarily based on case reports. Both fibrinogen and FXIII deficiency have been linked to an increased risk of recurrent miscarriage and placental abruption. To mitigate these dangers, factor replacement is performed. In women with other bleeding problems, however, the likelihood of miscarriage and ante-partum complications is less obvious. In women with rare bleeding diseases, haemostatic abnormalities appear to last throughout pregnancy, especially if the impairment is severe. As a result, women who suffer from these diseases are at risk for postpartum hemorrhage. The fetus may also be harmed, putting him or her at risk of bleeding issues. To reduce the risk of maternal and newborn problems and assure the best possible outcome, specialized multidisciplinary management is required (Kadir et al., 2009).

Women who suffer first-trimester bleeding in their first pregnancy are more likely to have difficulties later in the pregnancy, as well as a recurrence of first-trimester bleeding and other complications in their second pregnancy (Lykke et al., 2010). Vaginal bleeding occurs in 15% to 25% of first-trimester pregnancies. While 50% of women who experience vaginal bleeding in the first trimester of pregnancy will have a viable pregnancy, the occurrence causes significant concern for the woman and can be treated in a variety of ways. Spontaneous abortion, ectopic pregnancy, and gestational trophoblastic illness are the three most common differential diagnosis for vaginal hemorrhage (Snell, 2009).

2. Evaluation

Based on the patient's gestational age and the nature of her bleeding, the clinician usually forms a tentative clinical diagnosis of the reason of vaginal bleeding (light or heavy, associated with pain or painless, intermittent or constant). The original diagnosis is then confirmed or revised using laboratory and imaging studies. The four major sources of nontraumatic bleeding in early pregnancy are: 1) Ectopic pregnancy, 2) Miscarriage (threatened, inevitable, incomplete, complete), 3) Implantation of the pregnancy, 4) Cervical, vaginal, or uterine pathology (eg, polyps, inflammation/infection, trophoblastic disease). One of the most critical goals in evaluating women with early-pregnancy bleeding is to rule out the possibility of an ectopic pregnancy, as a ruptured ectopic pregnancy can cause serious hemorrhage and mortality. Bloody show associated with labor (by definition, labor occurs after 20 weeks) or cervical insufficiency;

miscarriage (by definition, miscarriage occurs before 20 weeks); placenta previa; abruptio placenta; and, rarely, uterine rupture or vasa previa are the most common causes of bleeding in the second and third trimesters. Other etiologies include cervical, vaginal, or uterine pathology (e.g., polyps, inflammation/infection, trophoblastic disease) and non-tubal ectopic pregnancy. Because digital examination of a placenta previa can induce immediate, severe hemorrhage, digital examination of the cervix should be avoided in women presenting with bleeding in the second half of pregnancy until placenta previa has been ruled out. Anti-D immune globulin may be indicated for Rh(D)-negative women with uterine bleeding to guard against Rh(D) alloimmunization (Norwitz & Park, 2012).

3. Perioperative management

In about 2% of all pregnancies, abdominal procedures are performed. They are a unique circumstance for not just the patient, but also the surgeons and anesthesiologists involved. The two most common types of operations performed during pregnancy are appendectomy and cholecystectomy. Even while laparoscopy is safe even during pregnancy and has the benefits of minimally invasive surgery, it has a greater miscarriage rate than laparotomy and a similar preterm birth rate. Patients should be fully educated about the procedure they are going to have, as well as the benefits and drawbacks of the various surgical options (Juhasz-Böss et al., 2014).

Takeda et al. (2006) investigated the feasibility and safety of ectopic pregnancy with extensive hemoperitoneum treated with laparoscopic laparoscopy and intraoperative autologous blood transfusion. One hundred and twelve women with ectopic pregnancy (interstitial/cornual: 4; isthmic: 18; ampullary: 86; and ovarian: 4) were treated with laparoscopic surgery from January 2000 to June 2005. Seventeen patients with more than 501 g of intraabdominal bleeding were diagnosed with extensive hemoperitoneum and were studied retrospectively. Site of pregnancy in these 17 patients was interstitial/cornual: 3; isthmic: 5; ampullary: 7; and ovarian: 2. All of the patients had rupture at the pregnancy site, with the exception of two women who suffered tubal abortion of an ampullary pregnancy. Blood accumulated in the abdominal cavity during laparoscopic surgery was collected using an irrigation and aspiration process and delivered to an autologous blood-salvage device to generate concentrated red blood cell solution. Through a leukocyte reduction filter, processed blood was instantly transfused back to

the patient. The difference between the volumes of aspirated and irrigated fluids was utilized to compute the mean amount of estimated intraabdominal bleeding, which was 1362.1 491.4 g, and the mean volume of reinfused processed blood was 680.6 209.5 g. At no time did any patient receive blood from a bank. The shock index, computed by dividing the heart rate by the systolic blood pressure at triage ($r = 0.72$; 95 percent CI 0.37–0.89; $p = .001$), was well linked with the degree of hemoperitoneum ($r = 0.72$; 95 percent CI 0.37–0.89; $p = .001$). There was no need for laparotomic conversion in any of the patients of major hemoperitoneum, and homologous blood transfusion was avoided. Researchers determined that laparoscopic surgery with intraoperative autologous blood transfusion can be safely performed by skilled laparoscopists in women with ectopic pregnancy and massive hemoperitoneum if hemodynamic stability is obtained with perioperative care.

Laparoscopic surgery is a minimally invasive method that has a number of benefits. A 15-year-old girl presented with acute abdomen and hemoperitoneum, according to Takeda et al., (2007). After a urine pregnancy test revealed a gestational sac in the uterine cavity and an ultrasound revealed a gestational sac, the preoperative differential diagnosis was restricted to either intrauterine pregnancy with ruptured corpus luteum cyst or heterotopic pregnancy. To determine the etiology of the hemoperitoneum, an emergency laparoscopic surgery was conducted, and a burst corpus luteum cyst of pregnancy was diagnosed. The rupture site with active bleeding was laparoscopically sutured and hemostasis was accomplished after extracting pooled blood in the abdominal cavity for intraoperative autologous blood transfusion. At the same time, the patient and her family requested that an intrauterine pregnancy be terminated. The recovery period was unremarkable. Researchers determined that a ruptured corpus luteum cyst during pregnancy resulting in extensive hemoperitoneum is a rare but life-threatening condition that can affect even young girls. Laparoscopic ovarian conservative therapy with intraoperative autologous blood transfusion is possible.

The process of saving and then reinfusing blood spilled into the surgical field is known as intraoperative autologous blood transfusion. Yamada et al. (2003) looked at the effectiveness and safety of intraoperative autologous blood transfusion during laparoscopic surgery for hemoperitoneum in benign gynecologic illness. The Cell Saver, Haemo Lite

2, an intraoperative autologous blood salvage device, was used in laparoscopic surgery on 18 patients with ectopic pregnancies or ovarian bleeding who had a large hemoperitoneum with/without severe anemia and hypovolemic shock who had a large hemoperitoneum with/without severe anemia and hypovolemic shock. In ectopic pregnancy instances, the blood loss was 1186 789 mL, while the volume of reinfused processed blood was 661 405 mL. In ovarian hemorrhage, the blood loss was 716 219 mL, while the volume of reinfused processed blood was 496 138 mL. There was no need for homologous blood transfusion in any of the patients who underwent laparoscopic surgery. There were no adverse responses or procedural issues with the autologous blood infusions. Researchers found that performing laparoscopic surgery for extensive hemoperitoneum caused by ectopic pregnancies or ovarian hemorrhage without a homologous blood transfusion was possible using intraoperative autologous blood transfusion.

The use of intraoperative cell salvage (ICS) in patients with ectopic pregnancy raises several theoretical difficulties. The goal of Huang et al., (2017) was to see how intraoperative cell salvage affected coagulation function and clinical outcomes in patients with ruptured ectopic pregnancy and substantial blood loss. Patients with ICS had a shorter hospital stay, a reduced need for allogenic blood products, and greater hemoglobin levels at discharge than controls. There were no difficulties or negative effects. Hemoglobin at discharge and thrombin time were lower in the ICS group 24 hours after surgery, whereas APTT was higher. Hemoglobin at discharge was lower in the control group after surgery, whereas the activated partial thromboplastin time was longer. Hemoglobin levels in the ICS group were greater upon discharge. In individuals with a ruptured ectopic pregnancy and severe blood loss, ICS was linked to positive clinical outcomes.

De Braud et al. (2021) investigated the link between demographic and ultrasonography factors and large intra-operative blood loss after surgical transcervical evacuation of live caesarean scar pregnancies. All women diagnosed with a live caesarean scar ectopic pregnancy who decided to seek surgical care in the study center were included in the study. Each patient had an ultrasound before to surgery. Under ultrasound guidance, all of the women had transcervical suction curettage. The rate of postoperative blood transfusion was their primary outcome. Estimated intra-operative blood loss (mL), rate of retained products of conception, need for repeat surgery, requirement for uterine artery embolization, and hysterectomy rate were the

secondary outcomes. 80 women were identified with a live caesarean scar pregnancy during the research period, with 62 (78%) opting for surgical care at our center. The median length of the crown-rump was 9.3 mm (range 1.4–85.7). The average amount of blood lost during surgery was 100 mL (range: 10–2300), and six women (10%) required blood transfusions. At univariate analysis, crown-rump length and the existence of placental lacunae were significant predictors of the need for blood transfusion and blood loss > 500 ml; however, only crown-rump length was a significant predictor of the need for blood transfusion at multivariate analysis. Blood transfusion was necessary in 6/18 (33%) of instances with a crown-rump length of less than 23 mm (9+0 weeks of pregnancy), but none of 44 women with a crown-rump length of less than 23 mm (p.01). The risk of significant intraoperative bleeding and the requirement for blood transfusion during or after surgical evacuation of live caesarean scar pregnancies increases with gestational age and is higher when placental lacunae are present, according to the researchers. A third of women who presented at 9 weeks of pregnancy required blood transfusions, and their care should be coordinated in specialized tertiary hospitals.

Takeda et al., (2014) described their experience with pregnancy outcomes following urgent laparoscopic surgery for acute adnexal diseases at fewer than 10 weeks of pregnancy, when surgical intervention might be more intrusive to the intrauterine fetus. The abdominal wall-lift approach was used to secure the surgical view during gasless multiport laparoscopic surgery or transumbilical laparoendoscopic single-site surgery. In cases of severe hemoperitoneum, autologous blood salvage and donation were conducted intraoperatively. After salpingectomy, six cases of ovarian hemorrhage with ruptured corpus luteal cyst, three cases of adnexal torsion with corpus luteal cyst, and one case each of ruptured heterotopic ampullary pregnancy and heterotopic tubal stump isthmic pregnancy were treated. Hemostasis was achieved for a ruptured corpus luteal cyst by removing the hematoma and suturing the wound. Detorsion with cyst aspiration was performed in two cases and detorsion alone was performed in one case for adnexal torsion. Unilateral salpingectomy was used to treat a ruptured heterotopic ampullary pregnancy. After salpingectomy, the ejected villous tissue was removed and hemostatic coagulation was used to treat a ruptured heterotopic tubal stump isthmic pregnancy. To avoid homologous blood transfusion, intraoperative autologous blood salvage and donation were

conducted in five patients associated with extensive hemoperitoneum. Seven live births were recorded after surgery, with two cases of biochemical pregnancy loss and one case of total miscarriage. Despite the risk of miscarriage during the perioperative phase, the researchers found that gasless laparoscopic surgery for acute adnexal diseases at less than 10 weeks of pregnancy proved to be feasible.

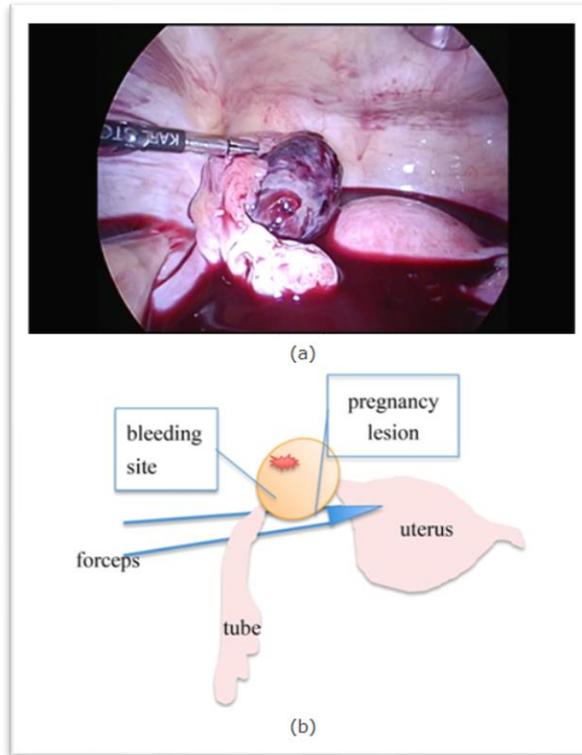


Fig. 1. Bleeding may be immediately stopped by lifting the pregnancy lesion with a pair of forceps. (a) Approach to confirm a pregnancy lesion. Operative findings of case 1. Isthmus pregnancy of the left tube: scooping before vacuuming the blood; (b) Illustration of (a) (Oishi et al., 2019).

Maternal problems such as hemorrhage and infection have been linked to cesarean birth at a premature gestational age. Previous accounts, on the other hand, are contradictory, and there is no consensus on the subject. Kino et al. (2019) wanted to know more about the negative effects of preterm cesarean delivery, specifically maternal bleeding. They compared the frequency of maternal unfavorable outcomes between preterm emergency

cesarean delivery and term emergency cesarean delivery in a retrospective research. A total of 947 preterm cases and 1056 full-term cases were included in the research. They looked at the frequency of abnormal bleeding defined as 1500 mL or more as the major event, as well as the incidence of blood transfusion and antibiotic therapy after surgery as secondary outcomes. Age at delivery, primiparity, obesity, prior history of uterine surgery, irregular placental position, abnormal glucose tolerance, hypertension during pregnancy, early rupture of membranes, and general anesthetic use during operation were all considered complicating variables. Researchers evaluated poor outcomes among classical cesarean delivery, inverted T incision, and upper segment incision within preterm emergency cesarean delivery as a secondary analysis to study the impact of manner of incision. Compared to term cesarean delivery, preterm cesarean delivery had considerably greater incidence of abnormal bleeding, transfusion, and antibiotic use. Classic incision was linked to a higher likelihood of blood transfusion and the requirement for antibacterial treatment in premature deliveries. Researchers concluded that preterm cesarean delivery increases the risk of maternal bleeding. This should be considered especially in the setting of early preterm birth.

The safety and effectiveness of transvaginal surgical management of cesarean scar pregnancy were explored by Li et al., (2014). The 49 cesarean scar pregnancy patients were separated into two groups in a retrospective analysis. Patients in Group A (30 patients) had never received any treatment prior to transvaginal surgical management. Patients in Group B (19 patients) had previously undergone any treatment. Both groups' preoperative, intraoperative, and postoperative data were gathered and examined retrospectively. Preoperative serum β -hCG level, preoperative hemoglobin level and average serum β -hCG resolution time of group A and group B were 53,458.50 (36,382.00–94,100.50) versus 9779.00 (932.50–29623.00) U/l, 123.87 ± 10.95 versus 109.94 ± 16.05 g/l and 3.55 ± 1.81 versus 1.83 ± 1.15 weeks. Vaginal bleeding and gestational age in group A were significantly lower than in group B, 2.5 (0.50–11.00) versus 15.00 (3.50–31.50) days and 52.50 (46.50–56.70) versus 60.00 (48.00–90.00) days, respectively. The operative time, estimated blood loss, postoperative hospital stay, hospitalization expenses and menstruation recovery time of group A and group B were 56.61 ± 24.40 versus 67.56 ± 43.52 min, 45.65 ± 27.83 versus 76.67 ± 50.87 ml, 5.10 ± 2.89 versus 5.33 ± 3.99 days, $9001.94 \pm$

1848.37 versus 11,032.33 \pm 5534.14 RMB and 1.16 \pm 0.47 versus 1.26 \pm 0.63 month respectively, which were similar between the two groups. Group A had a much lower intraoperative complication rate than group B, with 0 (0/30) against 21.05 percent (4/19). Group A had a postoperative complication rate of 10.00 percent (3/30) versus 21.05 percent (4/19) and group B had a total complication rate of 10.00 percent (3/30) compared 31.58 percent (6/19), respectively. Transvaginal surgery is an excellent and reasonably safe therapeutic option for cesarean scar pregnancy patients, according to the researchers.

Shukla et al. (2014) investigated assessed the efficacy and safety of intraoperative autologous blood transfusion during laparotomy for hemoperitoneum in ectopic pregnancy, as well as the safety of homologous blood transfusion in combination with autologous blood transfusion. Fresh blood was drawn from the peritoneal cavity, filtered through eight layers of sterile gauze, and collected in a sterile bowl for autotransfusion. The collected blood was put into a blood infusion bag containing a citrate phosphate dextrose adenine solution in a five-to-one ratio of blood to citrate solution. In individuals who did not get homologous transfusion, the average volume of autologous blood transfused was 573 328 mL. Preoperative hemoglobin levels were 4.95 1.5, while postoperative hemoglobin levels were 6.85 1.3. As a result, hemoglobin increased by 1.9 percent. The total volume of autologous blood transfused in 29 individuals (who required homologous blood transfusion) was 488 216 mL. Hemoglobin was 4.35 1.94 before surgery. The findings were compared to those of previous studies. In hemodynamically unstable ectopic pregnancy patients who did not have access to homologous blood transfusion, intraoperative autologous blood transfusion allowed laparotomy to be performed. Autologous blood transfusion and homologous blood transfusion are both safe.

Literatures

- Breeze, C. (2016). Early pregnancy bleeding. *Australian family physician*, 45(5), 283-286.
- De Braud, L. V., Knez, J., Mavrellos, D., Thanatsis, N., Jauniaux, E., & Jurkovic, D. (2021). Risk prediction of major haemorrhage with surgical treatment of live cesarean scar pregnancies. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 264, 224-231.
- Hasan, R., Baird, D. D., Herring, A. H., Olshan, A. F., Funk, M. L. J., & Hartmann, K. E. (2010). Patterns and predictors of vaginal bleeding in the first trimester of pregnancy. *Annals of epidemiology*, 20(7), 524-531.
- Huang, J., Qin, D., Gu, C., Huang, Y., Ma, H., Huang, H., ... & Ling, M. (2017). Autologous and nonautologous blood transfusion in patients with ruptured ectopic pregnancy and severe blood loss. *BioMed Research International*, 2017.
- Juhasz-Böss, I., Solomayer, E., Strik, M., & Raspé, C. (2014). Abdominal surgery in pregnancy—an interdisciplinary challenge. *Deutsches Ärzteblatt International*, 111(27-28), 465.
- Kadir, R., Chi, C., & Bolton-Maggs, P. (2009). Pregnancy and rare bleeding disorders. *Haemophilia*, 15(5), 990-1005.
- Kino, T., Yamamoto, Y., Saigusa, Y., Aoki, S., & Miyagi, E. (2019). Adverse pregnancy outcomes related to preterm cesarean delivery. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 234, 89-91.
- Li, J. B., Kong, L. Z., Fan, L., Fu, J., Chen, S. Q., & Yao, S. Z. (2014). Transvaginal surgical management of cesarean scar pregnancy: analysis of 49 cases from one tertiary care center. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 182, 102-106.
- Lykke, J. A., Dideriksen, K. L., Lidegaard, Ø., & Langhoff-Roos, J. (2010). First-trimester vaginal bleeding and complications later in pregnancy. *Obstetrics & Gynecology*, 115(5), 935-944.
- Norwitz, E. R., & Park, J. S. (2012). Overview of the etiology and evaluation of vaginal bleeding in pregnant women. UpToDate. Waltham, MA: UpToDate.

- Oishi, S., Mekaru, K., Miyagi, M., Akamine, K., Heshiki, C., & Aoki, Y. (2019). Tubal Pregnancy with Acute Bleeding Treated by Laparoscopic Surgery: Tips and Case Presentation. *Open Journal of Obstetrics and Gynecology*, 10(1), 100-107.
- Sakornbut, E., Leeman, L., & Fontaine, P. (2007). Late pregnancy bleeding. *American family physician*, 75(8), 1199-1206.
- Shukla, P., Dwivedi, S., Bhargava, M., Singh, R., & Singh, S. (2014). Intraoperative autologous blood transfusion of peritoneal blood during laparotomy for ectopic pregnancy: Prospective study. *The Journal of Obstetrics and Gynecology of India*, 64(5), 358-361.
- Snell, B. J. (2009). Assessment and management of bleeding in the first trimester of pregnancy. *Journal of midwifery & women's health*, 54(6), 483-491.
- Takeda, A., Hayashi, S., Imoto, S., Sugiyama, C., & Nakamura, H. (2014). Pregnancy outcomes after emergent laparoscopic surgery for acute adnexal disorders at less than 10 weeks of gestation. *Journal of Obstetrics and Gynaecology Research*, 40(5), 1281-1287.
- Takeda, A., Manabe, S., Mitsui, T., & Nakamura, H. (2006). Management of patients with ectopic pregnancy with massive hemoperitoneum by laparoscopic surgery with intraoperative autologous blood transfusion. *Journal of minimally invasive gynecology*, 13(1), 43-48.
- Takeda, A., Sakai, K., Mitsui, T., & Nakamura, H. (2007). Management of ruptured corpus luteum cyst of pregnancy occurring in a 15-year-old girl by laparoscopic surgery with intraoperative autologous blood transfusion. *Journal of pediatric and Adolescent Gynecology*, 20(2), 97-100.
- Yamada, T., Okamoto, Y., Kasamatsu, H., & Mori, H. (2003). Intraoperative autologous blood transfusion for hemoperitoneum resulting from ectopic pregnancy or ovarian bleeding during laparoscopic surgery. *JSLs: Journal of the Society of Laparoendoscopic Surgeons*, 7(2), 97.
- Yilmaz, M. (2022). Ectopic Pregnancy: A Review of Systematic Reviews and Meta-Analysis. *Current Approaches in Gynecology and Gyneco-Oncology*, pp:3-20.

CHAPTER 15

MEDICAL TREATMENT OF OBSTETRIC BLEEDINGS

Dr. Cemile ÖZCAN UÇAR¹

¹ Sultanbeyli State Hospital, İstanbul-TURKEY
ORCHID: <http://orchid.org/000-0003-1407-2577> E-mail:
cemileozcan7@hotmail.com

Overview:

Vaginal bleeding can happen at any stage of pregnancy. In most developed countries, the main reason for admission of pregnant women to intensive care units is bleeding (Gilbert et al, 2003).

An obstetric hemorrhage may occur before or after delivery, however it has been stated that more than 80% of cases occur postpartum (McLintock, 2011).

A- First Trimester Bleeding:

By definition, bleeding before 20 weeks of gestation constitutes threatened abortion. However, the majority of such pregnancies progress normally. About one fourth of all pregnant women experience spotting or bleeding in the first several weeks of pregnancy, and one half of those who bleed miscarry (Paspulati et al, 2004).

Possible causes of bleeding include subchorionic hemorrhage, embryonic demise, anembryonic pregnancy, incomplete abortion, ectopic pregnancy, and gestational trophoblastic disease. A speculum examination can help to identify nonobstetric causes of bleeding, such as vaginitis, cervicitis, or a cervical polyp.

Checking whether the patient is hemodynamically stable or not should be the first thing to do while evaluating a patient having bleeding. The hemodynamically unstable patient should be resuscitated immediately and surgical intervention should be performed if it is necessary. The cause of bleedings which are not due to obstetric causes should be determined and treatment should be performed accordingly.

A baseline hemoglobin level should be documented for all women with bleeding during pregnancy. Rh factor testing should be performed if Rh status is not known at the time of presentation. Women who are Rh negative and miscarry during the first trimester should receive 50 mcg of anti D immune globulin (ACOG, 1999).

The basis of medical treatment to be applied to the patient is the diagnosis of the patient.

Misoprostol

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a stable, synthetic form of prostaglandin E1 analogue. The optimal dose varies widely from 20 to 600 mcg depending on the indication and gestation. Use of the

correct dose is important, since too low a dose will be ineffective and overdosage can be dangerous for mother and baby (Elati and Weeks, 2009). The original pricing of the Cytotec (Pfizer Inc, New York, NY, USA) brand of misoprostol was based on a 6- week course of 600 mcg daily for gastric ulcer treatment.

-First trimester termination of pregnancy (induced abortion):

Recently, the mifepristone/misoprostol regimen has become more widely available and is now considered to be the gold standard for early pregnancy termination (Kulier et al, 2004).

The regimen is also very successful when used without the mifepristone, achieving complete termination rates of 80–90%. A recent study compared a single dose of 800 mcg vaginal misoprostol to suction evacuation under local anesthetic and found the success rate to be similar (94 and 95%, respectively), but with fewer side effects in those taking misoprostol (Prasad et al, 2009).

The way misoprostol is used changes its effectiveness. While the vaginal route is the most effective route, the sublingual route is more effective than the oral route (Blanchard et al, 2005; Faundes et al, 2007). It is recommended that 800 mcg of misoprostol should be administered vaginally a maximum of 3 times with an interval of 12 hours (Faundes et al, 2007).

-Early fetal demise (missed abortion):

Various studies have shown that misoprostol is as effective as curettage (Trinder et al, 2006). In addition the net effect of adding mifepristone has not been demonstrated (Neilson et al, 2006). Recommended dose is stated to be 800 mcg vaginal misoprostol every 3 hours (maximum of two doses) or 600 mcg sublingual misoprostol every 3 hours (max. two doses) in (Gemzell-Danielsson et al, 2007).

-Incomplete miscarriage (abortion):

A single dose of 600 mcg oral misoprostol is as effective as vacuum aspiration (Weeks et al, 2005). A single dose can be given at intervals of 1 or 2 weeks when necessary.

Methotrexate

Another medical treatment used in first trimester bleeding is methotrexate. Methotrexate is also used in gestational trophoblastic diseases, especially in ectopic pregnancy.

-Ectopic pregnancy:

Ectopic pregnancy develops outside the uterus or in the scar tissue of the uterus and has high mortality and morbidity. Therefore, accurate diagnosis and treatment are important (Carusi, 2019). Ectopic pregnancy can be diagnosed with transvaginal ultrasound imaging, serial β hcg measurements, progesterone measurement and the patient's clinical picture. Randomized trials have shown medical management to be safer, more effective, and less expensive than conservative surgical treatment, and to result in equal or better subsequent fertility. (Cohen and Sauer, 1999; ACOG, 1998; Stovall and Ling, 1993; Lipscomb et al, 1999).

There are different treatment protocols, but the single-dose regimen is most common. This includes an intramuscular injection of 50 mg of methotrexate per m^2 , followed by close monitoring of symptoms and measurement of β -hCG levels four and seven days after injection. β -hCG levels should decrease by at least 15% from days 4 to 7; once this occurs, levels should be monitored weekly until undetectable, which may take five to seven weeks. β -hCG levels should be monitored after methotrexate administration until they are below pregnancy values (ACOG, 2018). Treatment failure is assumed if the β -hCG level plateaus or increases from days 4 to 7.

-Gestational trophoblastic diseases (GTD):

Gestational trophoblastic diseases include benign and malignant components. Methotrexate can also be administered to some selected low-level gestational trophoblastic patients.

Progesterone

Progesterone is an endogenous steroid hormone that is commonly produced by the adrenal cortex as well as the gonads, which consist of the ovaries and the testes. Progesterone is also secreted by the ovarian corpus luteum during the first ten weeks of pregnancy, followed by the placenta in

the later phase of pregnancy. The conversion of progesterone generation from the corpus luteum to the placenta generally occurs after week ten (Kumar et al, 2012). There is no evidence to suggest that giving progesterone supplements to otherwise healthy women in the first trimester of pregnancy reduces the risk of spontaneous miscarriage (Haas et al, 2013). However, for some women who experience bleeding in early pregnancy, the use of progesterone supplements may reduce the risk of miscarriage. For women who become pregnant with in-vitro fertilisation (IVF), the use of progesterone supplements is beneficial and improves pregnancy outcomes. The net effect of routine progesterone use in patients with recurrent spontaneous miscarriages has not been demonstrated (Coomarasamy et al, 2015; Saccone et al, 2017). It has been observed that the use of synthetic progesterone in IVF patients increases the live birth rate (Van der Linden et al, 2015).

The usage areas of progesterone forms should be chosen according to the gestational week. Based on data from recent systematic reviews and metaanalyses, dydrogesterone(oral progesterone) effectively prevents miscarriage in pregnant women experiencing threatened or idiopathic miscarriage (Carp H, 2012; Lee HJ, 2017; Wang et al, 2019). Recent studies have shown no benefit for all types of progesterone used vaginally (Yassae et al, 2014; Coomarasamy et al, 2019).

There is still uncertainty over the electiveness and safety of alternative progestogen treatments for threatened and recurrent miscarriage. There is no clear consensus on the use of progesterone due to differences in studies.

B- Second Trimester Bleeding

Antepartum bleeding complicates about 25% of all pregnancies and occurs in the second trimester in up to 2.5% (Axelsen, 1995). In the second trimester, cervical insufficiency and placental anomalies, placenta previa and placental abruption are seen. Genital infections, trauma or systemic diseases may also result in bleeding during pregnancy. While second trimester bleeding may originate from the vulva, vagina and vaginal part of the cervix, similar to third trimester bleeding, bleeding may also occur due to inferior placenta or placenta previa, or marginal and rarely total placental separation. However, the causative agent cannot be found in approximately 50% of the bleedings. Placental location anomalies are usually expected in second

trimester bleeding. Placental abruption is not a common condition in the second trimester, but the risk of fetal death is high when it occurs, however, placenta previa should be considered in the differential diagnosis of second trimester bleeding. While cervical or postcoital bleeding may be associated with vaginal or cervical infection, it should not be ignored that the presence of fragile ectropion or cervical polyp may lead to cervical insufficiency and, albeit rare, cancerous lesions. Approach in determining the cause of bleeding; Whether the bleeding is mild, painful or painless, or accompanied by uterine contraction, a thorough physical examination and ultrasound should be performed. Because bleeding in the second trimester can be a sign of cervical insufficiency, as well as cause early fetal losses. Preterm birth is a major contributor to perinatal mortality and morbidity and affects up to 12% of births in developed countries (ACOG, 2008). The risk of preterm birth is 30% or more when the bleeding occurs in the second trimester. (Sipila and Hartikainen-Sorri, 1992; Parant et al, 2000; Koifman et al, 2008). Women with singleton gestations at great risk for preterm birth are those with prior preterm birth, short cervical length and antepartum bleeding, particularly when these occurred in the second trimester. (Axelsen, 1995)

If the patient's hemodynamics is not stable at first, such as in first trimester bleeding, the patient is stabilized with support and replacement therapy. A dose of 625 IU (125 µg) Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D to ensure adequate protection against immunisation for the bleeding after 12 weeks gestation.

Misoprostol

Misoprostol has also become an important drug in obstetrical and gynecologic practice because of its uterotonic and cervical-ripening actions. Plasma concentrations of misoprostol acid peak in approximately 30 minutes and decline rapidly thereafter (Zieman et al, 1997).

-Induced Abortion (Termination of Pregnancy)

Medical management of miscarriage and induced abortion has become the gold standard in clinical practice in several northern European countries. In the second trimester of pregnancy, uterine evacuation may be performed due to maternal medical indications, severe fetal abnormalities or fetal death, or due to elective abortion. Early abortions in the second trimester are usually performed by aspiration curettage, while procedures performed in

the second trimester require cervical dilation and fetal removal or induction of labor. During the second trimester, misoprostol matures the cervix and may induce labor. One of the most effective uses for abortion is as follows: 200 mg oral mifepristone, then 600 µg vaginal misoprostol 36-48 hours later and followed by 400 µg oral or vaginal misoprostol every 3 hours (maximum of five doses). Other forms of use are as follows: 200-600 µg vaginal misoprostol every 12 hours and 400 µg vaginal misoprostol every 3 hours (maximum five doses) (Goldberg et al, 2001). When adjusting the dose of misoprostol, if the patient has a cesarean section, the dose can be reduced to avoid uterine rupture.

As the gestational week increases, the effectiveness of uterotonic drugs increases. Therefore, a dose of misoprostol given early in the second trimester may not be as effective as the same dose given late in the second trimester.

-Intrauterine fetal death

There are many issues where misoprostol is clinically very effective. One of them is intrauterine fetal deaths. Considering other areas of use, misoprostol was also found to be effective at low doses in intrauterine fetal deaths (Srisomboon et al, 1998). Between the vaginal, sublingual and oral routes, sublingual misoprostol has the shortest induction to expulsion interval. (Elhassan et al, 2008). Oral (400 mcg) use also acts faster than vaginal (200 mcg) use, but has more side effects. (Chittacharoen et al, 2003).

However, all completed within 48 hours. The vaginal route is therefore recommended for the treatment of IUFD. Doses vary according to the week of pregnancy. From 13 to 17 weeks, 200 mcg vaginal misoprostol is required 6 hourly (four doses maximum), 100 mcg of vaginal misoprostol 6 hourly (four doses maximum) is recommended for 18–26 weeks and 25–50 mcg every 4 hours (maximum six doses) is used for a gestational age of over 27 weeks. If the first dose does not produce effective contractions, the second dose can be doubled (Gómez Ponce de León R et al, 2007).

Mifepristone

Mifepristone is the only antiprogesterin. It uses in abortions. It is a 19-norsteroid, which binds with high affinity to the progesterone receptor, thus inhibiting the effect of progesterone. For second trimester abortion, medical

abortion with mifepristone followed by a PG analogue is an appropriate method and has been shown to be safe and effective, according to WHO and the RCOG.(Royal College of Obstetricians and Gynaecologists ,2004; Autry et al, 2002; 2004; Lalitkumar et al, 2007; WHO, 2004). Mifepristone use for abortion can be used alone or in combinations. After oral administration of Mifepristone 200 mg continues with the vaginal use of misoprostol.

Gemeprost

Gemeprost is another medical agent used for abortion. It is often included with drug combinations.

Progesteron

Progesterone is an effective drug as a primary preventive treatment in reducing the risk of preterm birth when given to women who had a second-trimester short cervix or a previous preterm birth. (Meis et al, 2003; Romero et al, 2016) The use of progesterone vaginally 200 mcg is recommended. Although the effect of progesterone is not clear, it has been shown to reduce cytokines in vitro studies (Cakmak et al, 2005).

Postpartum Hemorrhage

Postpartum hemorrhage is an obstetric emergency and has complications between 1 in 100 and 1 in 20 births. Obstetricians need to have a clear understanding of normal birth-related blood loss, as it is one of the main causes of maternal morbidity and mortality, so that postpartum hemorrhage can be effectively recognized and managed. The blood loss associated with normal delivery depends on the type of delivery. The mean blood loss for vaginal, cesarean delivery and cesarean hysterectomy is 500 , 1000 and 1500 ml, respectively.(Stafford et al, 2008) These values may not be clinically predictable due to the increase in blood volume accompanying a normal pregnancy.

Postpartum hemorrhage has been variably defined in the literature. Defines more subjective evaluation than standard norms; It includes a 10% reduction in hematocrit and the need for blood transfusion. A more practical definition is excessive blood loss associated with childbirth that causes the patient to be hemodynamically symptomatic and/or hypovolemic.

Rh D immunoglobulin can be recommended for routine postpartum prophylaxis in Rh D negative women with no preformed antibodies following birth of an Rh D positive infant.

Etiology of Postpartum Hemorrhage

Postpartum hemorrhage can be classified as primary (early) or secondary (late). Primary postpartum hemorrhage refers to excessive blood loss that occurs within 24 hours of birth, while secondary postpartum hemorrhage refers to bleeding from 24 hours to 12 weeks postpartum.

Causes of primary (early) postpartum hemorrhage: uterine atony, lower genital lacerations (perineal, vaginal, cervical, periclitral, periurethral, rectum), upper genital lacerations (broad lig.), lower urinary tract lacerations (urethra), retention products of pregnancy (placenta, membranes), invasive placentation (placenta accreta, placenta increta, placenta percreta), uterine rupture, uterine inversion, vasa previa and coagulopathy.

The causes of secondary (late) postpartum hemorrhage are: infection, retention products of pregnancy, placental subinvolution, and coagulation. The most important step is to improve the general condition of the patient and stabilize the situation immediately after the diagnosis of postpartum hemorrhage.

Prevention of Postpartum Hemorrhage

The best treatment for postpartum bleeding is to prevent it from happening in the first place. Active management of the third stage of labor to prevent postpartum hemorrhage is often discussed in guidelines. (BJOG, 2017; Sentilhes et al, 2016; WHO, 2021; Schlembach et al, 2018; Leduc et al, 2018; PAH, 2018)

The point that all guidelines agree is that the use of postpartum uterotonics reduces the rates of postpartum hemorrhage. Oxytocin is indicated in most guidelines as the drug of choice for the prevention of postpartum hemorrhage. However, dosages and route of administration vary greatly according to the mode of delivery (BJOG, 2017; Sentilhes et al, 2016; WHO, 2021; Schlembach et al, 2018).

WHO updated its recommendation for pharmacological PPH prevention and reinforced the use of oxytocin (10 IU intramuscularly or intravenously) as the drug of choice. WHO also recommends the use of carbetocin, ergot alkaloids or oral misoprostol in settings where oxytocin is

not available or its quality cannot be guaranteed (WHO, 2012). According to the Canadian Society of Obstetricians and Gynecologists (SOGC), carbetocin is the first line of treatment for postpartum hemorrhage prevention in cesarean or vaginal delivery (Leduc et al, 2018).

Treatment of Postpartum Hemorrhage

PPH guidelines generally recommend a multidisciplinary approach for effective early bleeding control. A set of initial measures also seems to be consensual in most guidelines and consist of maintenance of two large IV lines, supplementation of oxygen, strict monitoring of women, crystalloids infusion, and measures to avoid hypothermia and evaluate the PPH cause (BJOG, 2017; Sentilhes et al, 2016; WHO, 2021; Schlembach et al, 2018; Leduc et al, 2018; PAH, 2018, Fawcus, 2018, SLCOG, 2021).

1- Uterotonics

Ergometrine

John Stearns, the first scientist to highlight the use of ergots in postpartum hemorrhage (Stearns, 1822). The dose of methylergometrine is 0.2-0.5 mg orally, intramuscularly or intravenously. The duration of action varies with the route of administration (5-15 minutes after oral, 2-5 minutes after im, instantaneous after iv). The duration of action of methylergometrine is 2-4 hours. Side effects of methylergometrine are headache, nausea, vomiting, dizziness, hypertension, coronary artery spasm and intracerebral hemorrhage. Contraindications of methylergometrine are hypertension, heart disease, retained placenta, preeclampsia and eclampsia (Ramya et al, 2015).

Syntometrine

Syntometrine is a combined drug. It is (combination of 5 IU oxytocin plus 0.5 mg ergometrine. Syntometrine has same side effects and contraindications as oxytocin and ergometrine (Government of South Australia, 2016).

Oxytocin

Oxytocin is the most commonly used drug for induction of labor and prevention of postpartum hemorrhage. In 1953, Vincent Du Vigneud succeeded in synthesizing the structure and hormone of oxytocin. (Du Vigneud, 1953). In the 1980s, several randomized controlled trials and their meta-analyses confirmed the effectiveness of using oxytocin in the active

management of the third stage of labor in postpartum hemorrhage (Begley, 2011).

According to the 2012 FIGO guidelines, the use of oxytocin is as follows; loading dose 10 IU IM or 20-40 IU in 1 L of normal saline at 60 drops per minute, continue the oxytocin infusion (20 IU in 1 L IV fluid up to 40 drops/minute) until the bleeding stops. Oxytocin has side effects: Hypotension, myocardial ischemia, arrhythmias, nausea, vomiting, headache, flushing, and release of atrial and brain natriuretic. Oxytocin and ergometrine, as a well-known fact, have formed the basic components of first-line therapy in the management of primary PPH.

Carbetocin is a long-acting synthetic oxytocin. It may not usually be found in manuals. Carbetocin can be administered as a single dose (im/iv); produces a similar uterotonic effect as oxytocin. Carbetocin is administered iv and has a half-life of 40 minutes (four to 10 times longer than oxytocin). Uterine activity continues for 120 minutes and 60 minutes following intramuscular and intravenous injection, respectively (Hunter, 1992). Carbetocin is licensed in Europe only for atony developing after cesarean section. Carbetocin is as effective, but more expensive, than oxytocin (Su, 2007). The use of carbetocin is 100 µg IM or IV. It may have unpleasant side effects, including headaches, tremor, hypotension, flushing, nausea, abdominal pain, pruritus and a feeling of warmth (Rath 2009).

2- Prostaglandins

The prostaglandin F_{2α} series was discovered in the 1970s (Bergstrom 1962). A synthetic 15-methyl analogue of prostaglandin F_{2α}, as uterotonic agent the success rate alone is 88% and when used in combination, the success rate is 95%. The side effects of the drug are vomiting, diarrhea, hypertension and fever. (Oleen 1990).

Misoprostol, a methyl ester synthetic analogue of natural prostaglandin E₁, is a thermo-stable, cheap drug that can be used for prevention and treatment of PPH. It can be used orally, sublingually, buccally, vaginally or rectally. The use of misoprostol is mentioned in various guides as follows; 400–800 µg (oral, per rectum, per vagina or rectal route) and if injectable uterotonics are not available. The onset of action of misoprostol is 3-5 minutes. The duration of action of misoprostol is 75 minutes.

Carboprost tromethamine is also one of the synthetic 15-methyl analogue of Prostaglandin F_{2α}. The dose of carboprost is 250 µg intramuscularly (max: 2 mg). Another dose of use is 0.5 µg directly intramyometrial. The onset of action of carboprost is 20 minutes. The duration of action of misoprostol is 3 hours. It may have unpleasant side effects, including nausea, vomiting, diarrhea, headaches, hypertension and bronchial asthma. Contraindications for this drug are cardiac and pulmonary diseases. (Bai J et al, 2014)

3- Haemostatic drugs

Tranexamic Acid

Tranexamic acid (TXA) is a synthetic analogue of the amino acid lysine that inhibits fibrinolysis by reducing the binding of plasminogen and tissue plasminogen activator (tPA) to fibrin. (Ker K et al, 2012)

Administration of TXA is recommended as soon as the diagnosis of PPH is made if the diagnosis is made within 3 h of delivery. When more than 3 h has elapsed since delivery, there is no clear evidence of benefit from TXA administration. TXA for PPH treatment is given 1 g IV over 10 min within 3 h of vaginal or cesarean delivery. One gram (10 ml of a 100 mg/ml solution) is infused over 10–20 min because infusion >1 ml/min can cause hypotension. If bleeding continues after 30 min or stops and restarts within 24 h after the first dose, a second dose of 1 g may be given. The antifibrinolytic effect lasts up to 7–8 h in the serum. It has a short half-life of two hours. The use of tranexamic acid may be associated with side effects, including nausea, vomiting and diarrhoea. Other rare complications include hypotension, thrombosis, blurred vision, renal cortical necrosis and retinal artery obstruction (Novikova and Hofmeyr, 2010).

Recombinant Activated Factor VII

Recombinant activated factor VII (rFVIIa; Novo Nordisk A/S, Bagsvaerd, Denmark) has used for controlling life-threatening PPH. This drug is quite expensive. It reduces blood loss through enhancement of tissue factor-dependent coagulation. It should be given only when hematocrit is adequate, platelet count is >50x10⁹ /l, fibrinogen >1 gm/l, pH>7.2 and temperature >34°C. Dose is 90 µg/Kg IV over 3-5 minutes, repeated only if necessary.

REFERENCES

- Gilbert TT, Smulian JC, Martin AA, et al (2003). Obstetric admission to the intensive care unit: Outcomes and severity of illness. *Obstet Gynecol* 102:897.
- McLintock C. *J Thromb Haemost* (2011). Aug;9(8):1441-51.
- Paspulati RM, Bhatt S, Nour SG (2004). Sonographic evaluation of first trimester bleeding published correction appears in *Radiol Clin North Am*. 2008;46(2):437]. *Radiol Clin North Am*. 2004;42(2):297-314.
- ACOG practice bulletin. Prevention of Rh D alloimmunization. Number 4, May 1999 (replaces educational bulletin number 147, October 1990). Clinical management guidelines for obstetrician-gynecologists. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet*. 1999;66(1):63-70.
- A Elati , A D Weeks. The use of misoprostol in obstetrics and gynecology .*BJOG* 2009 Oct;116 Supply 1:61-9.
- Kulier R, Gulmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. *Cochrane Database Syst Rev* 2004;(2):CD002855.
- Prasad S, Kumar A, Divya A. (2009). Early termination of pregnancy by single-dose 800 mug misoprostol compared with surgical evacuation. *Fertil Steril*. 91:28–31.
- Blanchard K, Shochet T, Coyaji K, Thi Nhu Ngoc N, Winikoff B. (2005). Misoprostol alone for early abortion: an evaluation of seven potential regimens. *Contraception*; 72:91–7.
- Faundes A, Fiala C, Tang OS, Velasco A. (2007). Misoprostol for the termination of pregnancy up to 12 completed weeks of pregnancy. *Int J Gynaecol Obstet*;99 (Suppl 2):S172–7.
- Trinder J, Brocklehurst P, Porter R, Read M, Vyas S, Smith L. (2006). Management of miscarriage: expectant, medical, or surgical? Results of randomised controlled trial (miscarriage treatment (MIST) trial). *BMJ*. 332:1235–40.
- Neilson JP, Hickey M, Vazquez J. (2006). Medical treatment for early fetal death (less than 24 weeks). *Cochrane Database Syst Rev*. (3):CD002253.
- Gemzell-Danielsson K, Ho PC, Gomez Ponce de Leon R, Weeks A, Winikoff B.(2007). Misoprostol to treat missed abortion in the first trimester. *Int J Gynaecol Obstet*. 99 (Suppl 2):S182–5.
- Weeks A, Alia G, Blum J, Winikoff B, Ekwaru P, Durocher J, et al. (2005). A randomized trial of misoprostol compared with manual vacuum aspiration for incomplete abortion. *Obstet Gynecol*. 106:540–7.
- Carusi D. (2019). Pregnancy of unknown location: Evaluation and management. *Semin Perinatol*. Mar. 43(2):95-100.

- Cohen MA, Sauer MV. (1999) Expectant management of ectopic pregnancy. *Clin Obstet Gynecol.* 42(1):48-54.
- ACOG practice bulletin (1998). Medical management of tubal pregnancy. Number 3, December 1998. Clinical management guidelines for obstetrician-gynecologists. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet.* 65(1):97-103.
- Stovall TG, Ling FW. (1993) Single-dose methotrexate: an expanded clinical trial. *Am J Obstet Gynecol.* 168(6 pt 1):1759-1762.
- Lipscomb GH, McCord ML, Stovall TG, Huff G, Portera SG, Ling FW. (1999). Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *N Engl J Med.* 341(26):1974-1978.
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology (2018). ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy. *Obstet Gynecol.* Mar;131(3):e91-e103.
- Haas DM, Ramsey PS. (2013). Progesterone for preventing miscarriage. *Cochrane Database Syst Rev.* (10):CD003511.
- Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, et al (2015) A Randomized Trial of Progesterone in Women with Recurrent Miscarriages. *The New England journal of medicine.* 373(22):2141-8.
- Saccone G, Schoen C, Franasiak JM, Scott RT, Jr., Berghella V. (2017). Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials. *Fertil Steril.* 107(2):430-8 e3.
- Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. (2015) Luteal phase support for assisted reproduction cycles. *Cochrane Database Syst Rev.* (7):CD009154.
- Carp H. (2012). A systematic review of dydrogesterone for the treatment of threatened miscarriage. *Gynecol Endocrinol.* 28(12):983–990.
- Lee HJ, Park TC, Kim JH, Norwitz E, Lee B. (2017) The influence of oral dydrogesterone and vaginal progesterone on threatened abortion: a systematic review and meta-analysis. *Biomed Res Int.* 2017:3616875.
- Wang XX, Luo Q, Bai WP (2019). Efficacy of progesterone on threatened miscarriage: difference in drug types. *J Obstet Gynaecol Res.* 45(4):794–802.
- Yassae F, Shekarriz-Foumani R, Afsari S, Fallahian M. (2014). The effect of progesterone suppositories on threatened abortion: a randomized clinical trial. *J Reprod Infertil.* 15(3):147–151.
- Coomarasamy A, Devall AJ, Cheed V, et al. (2019). A randomized trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med.* 380(19):1815–1824.

- Axelsen SM, Henriksen TB, Hedegaard M, Secher NJ. (1995). Characteristics of vaginal bleeding during pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 63:131-1314.
- Society for Maternal Fetal Medicine Publications Committee. ACOG Committee Opinion number 419 October (2008) (replaces no. 291, November 2003). Use of progesterone to reduce preterm birth. *Obstet Gynecol.* 112:963-965.
- Sipila P, Hartikainen-Sorri A. (1992). Perinatal outcome of pregnancies complicated by vaginal bleeding. *Br J Obstet Gynecol.* 99:959-963.
- Parant O, Clouet-Delannoy M, Connan L, Duclusaud A, Chale J, Fournié A. (2000). Metrorrhagia during the second trimester of pregnancy: obstetrical and perinatal outcome. A retrospective study including 5 cases. *J Gynecol Obstet Biol Reprod (Paris).* 29:66-72.
- Koifman A, Levy A, Zaulan Y, et al. (2008). The clinical significance of bleeding during the second trimester of pregnancy. *Arch Gynecol Obstet.* 278:47-51.
- Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. (1997). Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol.* 90:88-92.
- Goldberg, A. B., Greenberg, M. B., & Darney, P. D. (2001). Misoprostol and Pregnancy. *New England Journal of Medicine.* 344(1), 38–47.
- Srisomboon J, Pongpisuttinun S (1998). Efficacy of intracervicovaginal misoprostol in second-trimester pregnancy termination: a comparison between live and dead fetuses. *J Obstet Gynaecol Res.* 24: 1–5.
- Elhassan EM, Abubaker MS, Adam I (2008). Sublingual compared with oral and vaginal misoprostol for termination of pregnancy with second-trimester fetal demise. *Int J Gynaecol Obstet.* 100:82–3.
- Chittacharoen A, Herabutya Y, Punyavachira P(2003) A randomized trial of oral and vaginal misoprostol to manage delivery in cases of fetal death. *Obstet Gynecol.* 101:70–3.
- Gómez Ponce de León R, Wing D, Fiala C. (2007). Misoprostol for intrauterine fetal death. *International Journal of Gynecology and Obstetrics* 99(Suppl 2):S190–3.
- Royal College of Obstetricians and Gynaecologists. *The Care of Women Requesting Induced Abortion. Guidelines No.7.* London, 2004.
- Autry AM, Hayes EC, Jacobson GF, et al. (2002) A comparison of medical induction and dilation and evacuation for second trimester abortion. *American Journal of Obstetrics & Gynecology.* 187(2):393–97.
- Lalitkumar S, Bygdeman M, Gemzell-Danielsson K. (2007). Mid-trimester induced abortion: a review. *Human Reproduction Update.* 13(1):37–52.

- World Health Organization (2004). *Unsafe Abortion: Global Estimates of the Incidence of Unsafe Abortion and Associated Mortality in 2000*. 4th ed. Geneva WHO.
- Meis PJ, Klebanoff M, Thom E, et al. (2003). Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med*. 348:2379-2385.
- Romero R, Nicolaides KH, Conde-Agudelo A, et al. (2016). Vaginal progesterone decreases preterm birth ≤ 34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study. *Ultrasound Obstet Gynecol*. 48:308-317.
- Cakmak H, Schatz F, Huang ST, et al. (2005). Progesterin suppresses thrombin and interleukin-1 β -induced interleukin-11 production in term decidual cells: implications for preterm delivery. *J Clin Endocrinol Metab*. 90:5279-5286.
- Stafford I, Dildy GA, Clark SL. (2008). Visually estimated and calculated blood loss in vaginal and cesarean delivery. *Am J Obstet Gynecol*. 199:519.
- Prevention and management of postpartum haemorrhage: greentop guideline no. 52. *BJOG*. 2017;124:e106–e149.
- Sentilhes L, Vayssière C, Deneux-Tharoux C, et al (2016). Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). *Eur J Obstet Gynecol Reprod Biol*. 198:12–21.
- World Health Organization (2021) WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage. Accessed August 11.
- Schlembach D, Helmer H, Henrich W, et al. (2018). Peripartum haemorrhage, diagnosis and therapy. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry No. 015/063, March 2016). *Geburtshilfe Frauenheilkd*. 78:382–399.
- Leduc D, Senikas V, Lalonde AB. (2018). No 235-active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. *J Obstet Gynaecol Can*. 40:e841–e855.
- Organization PAH (2018). Guidelines for the prevention, diagnosis and treatment of obstetric hemorrhage.
- World Health Organization (2021). WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage.
- Leduc D, Senikas V, Lalonde AB. (2018). No 235-active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. *J Obstet Gynaecol Can*. 40:e841–e855.
- Prevention and management of postpartum haemorrhage: greentop guideline no. 52. *BJOG*. 2017;124:e106–e149.

- Sentilhes L, Vayssière C, Deneux-Tharaux C, et al (2016). Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). *Eur J Obstet Gynecol Reprod Biol.* 198:12–21.
- World Health Organization. WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage. Accessed August 18, 2021.
- Fawcus S. (2018). Alerts for managing postpartum haemorrhage. *S Afr Med J.* 108:1013–1017.
- Sri Lanka College of Obstetrician and Gynecologists (2021). SLCOG Guideline on Management of Primary PostPartum Haemorrhage. Accessed August 25, 2021.
- Steans J. (1822). Observations on the secale cornutum or ergot, with directions for its use in parturition. *Medical Research.* 5:90.
- Ramya KS, Shivanna S, Gopal N. (2015). Intravenous methergin versus intramuscular oxytocin in active management of third stage labour. *Int J Recent Trends Sci Technol.* 14:260-4.
- Government of South Australia (2016). Ergot derivatives: prophylaxis for third stage management and postpartum haemorrhage. *South Aust Perinat Pract Guidelines.*
- Du Vigneaud V, Ressler C, Swan JM, Roberts CW, Katsoyannis PG, Gordon S. (1953). The synthesis of an octapeptide with the hormonal activity of oxytocin. *Journal of the American Chemical Society.* 75:4879–80.
- Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative metaanalysis. *BMJ.* 344:e3054.
- Hunter DJ, Schulz P, Wassenaar W (1992). Effect of carbetocin, a long acting oxytocin analogue in the postpartum uterus. *Clinical Pharmacology and Therapeutics.* 52:60–7.
- Begley CM, Gyte GML, Devane D, McGuire W, Weeks A (2011). Active versus expectant management for women in the third stage of labour. *Cochrane Database of Systematic Reviews* 2011, Issue 11.
- Su LL, Chong YS, Samuel M (2007). Oxytocin agonists for preventing postpartum haemorrhage. *Cochrane Database of Systematic Reviews* 2007, Issue 3.
- Rath W (2009). Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. *European Journal of Obstetrics & Gynecology, and Reproductive Biology.* 147(1):15–20.
- Bergstrom S, Ryhag ER, Samuelson B, Sjovall J. The structure of prostaglandin E, F1, F2 (1962). *Acta Chemica Scandinavica.* 16:501–2.

- Oleen MA, Mariano JP (1990). Controlling refractory atonic postpartum hemorrhage with hemabate sterile solution. *American Journal of Obstetrics and Gynecology*. 162(1): 205–8.
- Bai J, Sun Q, Zhai H(2014). A comparison of oxytocin and carboprost tromethamine in the prevention of postpartum hemorrhage in high-risk patients undergoing cesarean delivery. *Exp Ther Med*. 7(1):46-50.
- Novikova N, Hofmeyr GJ (2010). Tranexamic acid for preventing postpartum haemorrhage. *Cochrane Database of Systematic Reviews* 2010, Issue 7.

CHAPTER 16

SURGICAL TREATMENT METHODS IN OBSTETRIC HEMORRHAGES

Dr. Bayram CAN¹

¹ Selcuk University Faculty of Medicine ,Department of Gynecological
Oncology,Konya ,Turkey orcid no :0000-0002-3610-9089
bayramcan1986@hotmail.com

INTRODUCTION

Postpartum hemorrhages are life-threatening hemorrhages. In high-income countries, maternal deaths from postpartum hemorrhage are less due to good diagnosis and treatment opportunities. Still, it is among the leading causes of maternal death in both low-income and high-income countries. If postpartum hemorrhage occurs within the first 24 hours, it is early postpartum bleeding; If it occurs between 24 hours and 12 weeks postpartum, it is called late postpartum bleeding.

. In 2017, the American College of Obstetricians and Gynecologists defined the definition of postpartum hemorrhage as follows; It was defined as the clinical symptoms of hypovolemia with the amount of bleeding more than 1000 ml in 24 hours. The incidence of postpartum bleeding varies between 1-3%. (Obstetric committee Obstet Gynecol, 2017).

Causes of postpartum hemorrhage

Uterine atony: It is the most common cause of postpartum hemorrhage. It is defined as the absence of uterine contractions in the third stage of labor. Atonia may occur due to placental invasion anomalies, remaining placental rest in the uterus. Having a previous history of atony and prolonged labor increases the risk of atony.

Trauma: Postpartum bleeding due to vaginal and cervical lacerations may occur. Excessive intra-abdominal bleeding may occur due to uterine rupture. Vulvar hematomas may occur due to blunt traumas.

Coagulopathy or other bleeding diathesis

Due to coagulopathy, 1 delivery in 500 becomes complicated in the United States. It is responsible for 7% of postpartum hemorrhages. (Reale SC, 2020). von willebrand's disease; It is an important cause of postpartum hemorrhage due to coagulopathy and is a cause of life-threatening postpartum hemorrhage.

Obstetric bleeding risk factors

- Prolongation of labor -DIC
- Placental invasion anomalies - Abruptio placentae
- Lacerations -Placental localization anomalies

- Macrosomal birth -Intrauterine exitus fetus
- Hypertensive diseases
- Induction of labor

Management principles in postpartum bleeding

The amount of postpartum bleeding should be tried to be determined immediately. The cause of the bleeding should be revealed and the bleeding should be intervened in a systematic way.

To determine the amount of postpartum bleeding, the amount of drain and the amount of blood accumulated in the aspirator used should be calculated. The amount of pad and sponge used during the postpartum intervention should be calculated. Can be misleading and the amount of quantitative bleeding is more important.

Postpartum hemorrhage follow-up and intervention is a team effort. During hemorrhage follow-up, hemoglobin, coagulation tests, fibrinogen and calcium levels should be followed closely.

Postpartum bleeding team should be present. This team should include specialists such as gynecology team, surgical nurse, hematology specialist, interventional radiology specialist, urologist, anesthesiologist intensive care specialist.

Treatment goals should be to prevent organ hypoperfusion, correct coagulopathy, and provide tissue oxygenation. Detecting the bleeding focus should be the primary goal. The 4T rule should be evaluated.. 4T (TONUS: atonia, TRAUMA: hematoma, laceration, inversion, TISSUE (TEXT): invasive placenta, THROMBIN: coagulopathy should be evaluated.

The treatment protocol should be systematic and fast. Each step should be decided quickly and if each step is unsuccessful, the next treatment step should be started. The severity of bleeding is very important in determining the treatment decision. Minimally invasive methods and medical methods should be used primarily in the intervention of bleeding.

Medical treatment methods used: oxytocin, ergot alkaloids, tranexamic acid, carboprost, misoprostol, dinoprostone, recombinant human factor 7. These are the most commonly used medical treatment methods.

After determining the cause of obstetric bleeding, treatment for the cause should be applied. The team should gather quickly. If heavy bleeding

is detected, rapid intervention saves life. Two vascular accesses should be established for the patient, and arterial line should be opened if necessary. A urinary catheter should be inserted. The patient should be evaluated with ultrasound at the bedside and evaluated for intra-abdominal bleeding. If the uterus is atonic, bimanual massage should be started. Medical treatment options should be done quickly and systematically in uterine atony.

Surgical treatment methods in obstetric bleeding

Postpartum bleeding is an emergency that should be intervened with medical and surgical methods. In case of uterine atony after cesarean section, if no response is received after uterine massage and medical treatment, surgical methods are applied. Midline incision is preferred for better visibility in normal postpartum hemorrhages. After cesarean delivery, the abdomen is already open. Visibility is tried to be increased with various retractors (balfour). Abdomen should be evaluated systematically. Uterine rupture, atony and placental adhesion anomalies can be seen easily.

While preparing for surgical intervention, temporary maneuvers can be performed to save time in case of severe bleeding and to allow time for blood transfusion to the anesthesia team. These maneuvers are as follows.

- **Manuel aortic compression:** To find the source of bleeding and to save time, compression is done just above the iliac bifurcation by making a fist and palm of the hand. Or, by applying pressure to the renal artery level, blood flow from the anastomotic connections coming from the ovarian and inferior mesenteric arteries is reduced.

- **Insurance of balloon In the aorta:** Percutaneous insertion of a balloon in the middle may reduce uterine blood flow.

- **Installation of a resultative endovascular balloon into the aorta:** Aortic balloon can be inserted under ultrasound and fluoroscopy guidance by trained obstetricians in places where blood supply is insufficient. It is mostly used in trauma surgery. There is little information in the literature about its use in obstetrics. There is a risk of organ ischemia in this procedure.

- **Uterus tourniquie** A tourniquet can be applied to the uterus at the isthmic level by using a bladder catheter or penrose drain. The tourniquet is

applied tightly to surround the uterus at the isthmic level. It is applied to reduce the amount of blood loss and to save time for the anesthesia team.

Inutero balloon tamponade application: Balloon tamponade is used in case of bleeding after normal delivery and cesarean delivery. It can be applied through the cervix after normal delivery, or it can be passed through the cervix through the hysterotomy line and advanced to the vagina during cesarean section, and then used with compression sutures.

Balloon tamponade works with the principle of uterine tamponade, myometrial contraction, and accelerated coagulation of uterine vessels. Intrauterine balloon tamponade is a method used in postpartum hemorrhage in national guidelines.(Dahlke JD, 2015).

In a meta-analysis of more than 4700 patients with PPH (7 randomized or cluster randomized trials, 15 nonrandomized studies, 69 case series), the overall pooled uterine balloon tamponade success rate was 85.9 percent (95% CI 83.9–87.9). , highest success in uterine atony (87.1%) and placenta previa (86.8%) and placenta accreta spectrum (66.7%) and pregnancy products (76.8%) lowest success (Suarez S 2020) . When the balloon was placed after vaginal delivery (87.0 percent), bleeding stopped more frequently than after a cesarean delivery (81.7 percent).

There are 2 cannula systems in the mechanism of the balloon tamponade, one of which is the balloon system and the other cannula system is the blood drainage system. Although it varies from company to company, the balloon is inflated with 250-300 cc of sterile saline, but in heavy bleeding, it may be necessary to inflate the balloon up to 500 cc. Balloon tamponade can be inserted during cesarean section as well as in case of atony developing after normal delivery. The effectiveness of the balloon tamponade is determined by the tamponade test. If the uterine bleeding stops, the test is positive, and when the balloon tamponade is not effective, the test is called negative.

The balloon tamponade is inserted under ultrasound guidance while the patient is in the lithotomy position. Uterine compression sutures can be applied to make the tamponade more effective. Uterine compression sutures are applied before the balloon is inflated in order not to burst the balloon.

It is recommended that the balloon be removed within 24 hours of insertio.(Bakri® Postpartum Balloon with Rapid Installation Components.)

Antibiotic prophylaxis is recommended to reduce the risk of endometritis after balloon tamponade is inserted.(Wong MS, 2019)

It is recommended to use 2 g cefazolin every 6 hours or 1.5 mg/kg gentamicin every 8 hours plus 500 mg metronidazole every 8 hours or 300 mg clindamycin every 6 hours. After uterine tamponade administration, oxytocin infusion is continued for 6-12 hours. Uterine tamponade administration in the patient If signs of hypovolemia develop and bleeding continues, it is recommended to switch to surgical methods quickly.

During placement of balloon tamponade, uterine rupture and separation of the hysterectomy line may occur. Cervical trauma may occur after incorrect insertion of the tamponade.(Kaya B, 2014)

Uterine artery and uteroovarian artery ligation

In case of uterine atony, ligation of the uterine artery and the uteroovarian artery reduces the amount of bleeding.(O'Leary JL, 1966). After the ureters are located bilaterally, the suture material is passed close to the cervix, and the procedure is completed by tying the knot by passing through the ligament on the lateral uterine artery again.

If it does not stop with the ligation of the uterine vessels, it is ligated with ligamentum ovari propium suture material to take the myometrium from the cornu region. These methods are easier and more effective than internal iliac artery ligation. Bilateral ligation does not appear to affect future reproductive function (Doumouchtsis SK, 2014)

Uterine necrosis and placental insufficiency were not defined as complications in subsequent pregnancy. (AbdRabbo , 1994)

However, there is only one case report of ovarian failure and the development of intrauterine synechia after postpartum ligation of the uterine, utero-ovarian and ovarian arteries for PPC due to atony. (Roman H, 2005)

Pelvic bumper application

It is used temporarily to stop unrepaired retroperitoneal bleeding and for bleeding that does not stop after hysterectomy. Pelvic packing is used between 24-72 hours.

Hypogastric artery ligation

Hypogastric artery ligation may be attempted when procedures to stop hemostasis fail. Ligation of the hypogastric artery reduces pelvic pulse pressure by 85% and blood flow rate by 50%. Reduction in pressure increases clot formation and helps stop bleeding. (Burchell RC, 1968)

In a retrospective case series in which internal iliac artery ligation was performed, 8 out of 19 patients did not undergo postpartum hysterectomy. (Clark SL, 1985) Connecting the internal iliac artery can be difficult even for experienced pelvic surgeons, as it will be difficult to visualize in a bleeding patient.

To connect the internal iliac artery, firstly, the anterior leaf of the broad ligament is opened with metzenbaum scissors in a way that is parallel to the ligamentum suspensorium. The retroperitoneum is reached. The first structure seen in the retroperitoneum is the musculus psoa major muscle. Medial to the musculus psoa major muscle is the external iliac artery. The iliac bifurcatio, where the ureter also crosses, is reached. The iliac artery is ligated approximately 4 cm distal from the iliac bifurcatio. The aim here is to preserve the posterior branches of the iliac artery.

Two major complications may occur while the internal iliac artery is ligated. The first is the ligation of the external iliac artery. If the external iliac artery is ligated, the distal pulses go away and the leg may go to necrosis. If the external iliac artery is ligated, the tibialis posterior and dorsalis pedis pulses disappear. If such a complication occurs, the suture connecting the artery should be opened immediately. The second major complication is to damage the vein during ligation due to the proximity of the internal iliac artery and vein. The iliac vein is located at the posterior of the iliac artery and a very fine dissection must be performed to avoid damaging the vein during ligation. By connecting the internal iliac artery from the lateral to the medial, the possibility of damaging the iliac vein is reduced.

Uterus compression sutures

B-LYNCH: The B-lynch suture technique is named after Christopher Balogun-Lynch. With the sutures, the uterus is compressed similarly to manual compression. (B-Lynch 1997)

This technique is effective in case reports and uterine atony bleeding when other techniques do not work.(B-Lynch C, 1997), (Ferguson JE, 2000) Although the technique does not adversely affect future pregnancy outcomes, it has been observed that it increases the risk of placentation anomaly (Fuglsang J . ,2014)

B-lynch should only be discarded in case of atony. It is not effective in placental invasion anomalies.

The first suture is passed approximately 3 cm caudal to the lower uterine transverse incision and then crossed. The suture is bypassed at the uterine fundus level, the suture is passed from the posterior wall before the back, and the suture is passed from the front to the back at the same level. The suture material extending from the posterior is like the first suture in the lower uterine transverse segment line after passing through the fundus. It is tied under the transverse incision line by passing the lower and upper incision lips and manually compressing the uterus. B-lynch suture can be used together with balloon tamponade or alone. If used together, it is called the uterus sandwich method.

Hayman: It is a technique performed without hysterotomy. It is a vertical compression suture that starts from the lower uterine segment and is placed from the front of the uterus to the back of 2 or 4 sutures upwards.

It can be used in atony occurring after vaginal delivery (Hayman RG, 2002),(Ghezzi F, 2007),(Nanda S, 2011). If lower uterine bleeding occurs, transverse cervico isthmic suture is performed.

Pereira: By using absorbable sutures, the uterus is compressed by providing manual support to the uterus by suturing transverse and longitudinal sutures subserosally before reaching the uterine cavity.(Pereira A, 2005). Longitudinal sutures start from the cervix and are placed upwards. Try not to damage the ureters, fallopian tube and other structures while transverse sutures are being placed.

Cho sutura: Made using multiple square sutures.(Cho JH, 2000)

Ali acar compression suture It is a compression suture placed in the cavity. It is thrown into the uterine cavity during cesarean delivery. The location of the placenta in the uterine cavity is determined. The borders of the placenta are determined and the area covered by the placenta is

determined. Starting from the cavity, sutures are placed in a diagonal manner to the anterior posterior uterus. In the cavity, sutures are placed parallel to each other in the crossed uterus serosa. It was found to be 94% successful on (Acar A,2018)

It has been found to be effective in placental invasion anomalies and uterine atony.

Hysterectomy: Peripartum hysterectomy is considered to be performed in cases of ongoing bleeding despite medical treatment. Before the postpartum hysterectomy stage, an emergency team should be formed and the patient should be intervened systematically and quickly. A team consisting of high-risk anesthesiologist, gynecologist oncologist, interventional radiologist and urology specialists should be at hand if necessary. Immediate hysterectomy for patients who need hysterectomy reduces postpartum morbidity rates.(Knight M, 2007)

Supracervical hysterectomy may be surgically easier than total hysterectomy. Total hysterectomy is more difficult than supracervical hysterectomy due to the risk of ureteral injury due to the enlarged cervix. In case of placenta previa and invasion anomalies, the cervix should also be removed. Total hysterectomy; While it is mostly associated with gastrointestinal and bladder, ureter injuries, pulmonary and transfusion complications, it has been reported that reoperation and perioperative mortality rates are higher in supracervical hysterectomy.(Wright JD, 2010). Postpartum hysterectomy should be done quickly and in a controlled manner. During hysterectomy, the ureters should be visualized by opening the retroperitoneal area. The retroperitoneal area can be reached by cutting the uterus round ligaments and cutting the broad ligament. In this area, the ureter is visualized. Both sides of the ovaries are usually preserved. The bladder peritoneum is dissected if it can be dissected. If the bladder is very adherent, sharp dissection is performed with Metzenbaum scissors. If the bladder is highly adherent, a posterior approach is applied. The vagina can be entered from the Douglas and uterosacral ligament level and the bladder borders can be seen more easily. In case of placental adhesion anomalies, the paravesical areas can be opened and the uterine artery can be tied from the source point and blood supply can be reduced. The uterosacral ligaments are tied, the vagina is reached, and the vaginal cuff is closed. During postpartum

hysterectomy, if the patient's hemodynamics is close to death, preservation of the bowel, bladder and ureter may be ignored.

References

- AbdRabbo S. A. (1994). Stepwise uterine devascularization: a novel technique for management of uncontrolled postpartum hemorrhage with preservation of the uterus. *American journal of obstetrics and gynecology*, 171(3), 694–700.
- Acar, A., Ercan, F., Pekin, A., Elci Atilgan, A., Sayal, H. B., Balci, O., & Gorkemli, H. (2018). Conservative management of placental invasion anomalies with an intracavitary suture technique. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, 143(2), 184–190.
- Burchell R. C. (1968). Physiology of internal iliac artery ligation. *The Journal of obstetrics and gynaecology of the British Commonwealth*, 75(6), 642–651.
- B-Lynch, C., Coker, A., Lawal, A. H., Abu, J., & Cowen, M. J. (1997). The B-Lynch surgical technique for the control of massive postpartum haemorrhage: an alternative to hysterectomy? Five cases reported. *British journal of obstetrics and gynaecology*, 104(3), 372–375.
- Cho, J. H., Jun, H. S., & Lee, C. N. (2000). Hemostatic suturing technique for uterine bleeding during cesarean delivery. *Obstetrics and gynecology*, 96(1), 129–131.
- Clark, S. L., Phelan, J. P., Yeh, S. Y., Bruce, S. R., & Paul, R. H. (1985). Hypogastric artery ligation for obstetric hemorrhage. *Obstetrics and gynecology*, 66(3), 353–356.
- Dahlke, J. D., Mendez-Figueroa, H., Maggio, L., Hauspurg, A. K., Sperling, J. D., Chauhan, S. P., & Rouse, D. J. (2015). Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *American journal of obstetrics and gynecology*, 213(1), 76.e1–76.e10.
- Doumouchsis, S. K., Nikolopoulos, K., Talaulikar, V., Krishna, A., & Arulkumaran, S. (2014). Menstrual and fertility outcomes following the surgical management of postpartum haemorrhage: a systematic review. *BJOG : an international journal of obstetrics and gynaecology*, 121(4), 382–388.
- Fuglsang J. (2014). Later reproductive health after B-Lynch sutures: a follow-up study after 10 years' clinical use of the B-Lynch suture. *Fertility and sterility*, 101(4), 1194–1199.
- Ghezzi, F., Cromi, A., Uccella, S., Raio, L., Bolis, P., & Surbek, D. (2007). The Hayman technique: a simple method to treat postpartum haemorrhage. *BJOG : an international journal of obstetrics and gynaecology*, 114(3), 362–365.
- Kaya B, Tüten A, Dağlar K, Mısırlıoğlu M, Polat M, Yıldırım Y, Ünal O, Kılıç GS, Güralp O *J Perinat Med*. 2014;42(6):745.
- Knight, M., & UKOSS (2007). Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage. *BJOG : an international journal of obstetrics and gynaecology*, 114(11), 1380–1387.
- Nanda, S., & Singhal, S. R. (2011). Hayman uterine compression stitch for arresting atonic postpartum hemorrhage: 5 years experience. *Taiwanese journal of obstetrics & gynecology*, 50(2), 179–181.

- O'Leary, J. L., & O'Leary, J. A. (1966). Uterine artery ligation in the control of intractable postpartum hemorrhage. *American journal of obstetrics and gynecology*, 94(7), 920–924.
- Pereira, A., Nunes, F., Pedroso, S., Saraiva, J., Retto, H., & Meirinho, M. (2005). Compressive uterine sutures to treat postpartum bleeding secondary to uterine atony. *Obstetrics and gynecology*, 106(3), 569–572.
- Reale, S. C., Easter, S. R., Xu, X., Bateman, B. T., & Farber, M. K. (2020). Trends in Postpartum Hemorrhage in the United States From 2010 to 2014. *Anesthesia and analgesia*, 130(5), e119–e122.
- Roman, H., Sentilhes, L., Cingotti, M., Verspyck, E., & Marpeau, L. (2005). Uterine devascularization and subsequent major intrauterine synechiae and ovarian failure. *Fertility and sterility*, 83(3), 755–757.
- Suarez, S., Conde-Agudelo, A., Borovac-Pinheiro, A., Suarez-Rebling, D., Eckardt, M., Theron, G., & Burke, T. F. (2020). Uterine balloon tamponade for the treatment of postpartum hemorrhage: a systematic review and meta-analysis. *American journal of obstetrics and gynecology*, 222(4), 293.e1–293.e52.
- Uygulama Bültenleri-Obstetrik Komitesi *Obstet Gynecol.* 2017;130(4):e168.
- Wright, J. D., Devine, P., Shah, M., Gaddipati, S., Lewin, S. N., Simpson, L. L., Bonanno, C., Sun, X., D'Alton, M. E., & Herzog, T. J. (2010). Morbidity and mortality of peripartum hysterectomy. *Obstetrics and gynecology*, 115(6), 1187–1193.
- Wong, M. S., Dellapiana, G., Greene, N., & Gregory, K. D. (2019). Antibiotics during Intrauterine Balloon Tamponade Is Associated with a Reduction in Endometritis. *American journal of perinatology*, 36(12), 1211–1215.

CHAPTER 17

DISSEMINATED INTRAVASCULAR COAGULATION IN PREGNANCY: AN OVERVIEW

Dr. Asli ALTINORDU ATCI¹

Dr. Şükran DOĞRU²

¹ Necmettin Erbakan University Meram Faculty of Medicine Department of Obstetrics and Gynecology Perinatology Clinic
Corresponding author: drasliatci@hotmail.com ORCID: 0000-0002-2637-3150

² Necmettin Erbakan University Meram Faculty of Medicine Department of Obstetrics and Gynecology Perinatology Clinic ORCID: 0000-0002-3383-2837

1. Introduction

Obstetric hemorrhage is still the greatest cause of maternal death worldwide, and early detection of factors that cause haemorrhage, as well as early care of the underlying pathological condition, is the cornerstone of treatment. Disseminated intravascular coagulation is the most common pregnancy-related disorder that causes bleeding and has a high maternal death and morbidity rate (DIC). Early detection and active therapy of DIC, as well as recognition of the antecedent causes, may help to reduce morbidity (Kadikar et al., 2021). DIC is a condition marked by a systemic stimulation of coagulation that results in fibrin accumulation in the bloodstream without particular localization. Multiple organ failure is linked to fibrin accumulation in DIC, according to both experimental and pathological evidence. Massive and persistent coagulation activation can lead to platelet and coagulation factor depletion, which can lead to bleeding (consumption coagulopathy) (Levi, 2009).

Pregnancy is a very specific and complex period (Yılmaz & Aboalhasan, 2022). DIC is a life-threatening ectopic pregnancy complication. It happens when all of the key procoagulants are washed away. This is essentially a state of increased proclivity for clot formation triggered by a variety of stimuli related to a variety of disorders including sepsis, endothelial cell damage (heat stroke and shock), obstetrical complications (abruptio placenta, amniotic fluid embolism, severe preeclampsia, and retained intrauterine dead foetus), and obstetrical complications (abruptio (Sharma, 2022).

The outcome of uncontrolled systemic activation of the hemostatic system, DIC is a significant medical emergency. This results in extensive microvascular thrombosis, which reduces blood flow to multiple organs and can lead to organ failure and uncontrollable bleeding. Diffuse bleeding from various organs, hemorrhagic necrosis, microthrombi in small blood vessels, and thrombi in medium and large blood arteries are all common symptoms. Endothelial dysfunction, which causes platelet activation, and trophoblast breakdown, which releases tissue factor into the circulatory system, could be the underlying mechanisms of action (Erez et al., 2016).

DIC is a life-threatening condition that can occur for a variety of reasons, both obstetrical and nonobstetrical. Obstetrical DIC has been linked to a number of pregnancy-related problems, including: 1) uterine atony, cervical and vaginal lacerations, and uterine rupture); 2) placental abruption;

3) preeclampsia/eclampsia/hemolysis, elevated liver enzymes, and low platelet count syndrome; 4) retained stillbirth; 5) septic abortion and intrauterine infection; 6) amniotic fluid embolism; 7) acute fatty liver of pregnancy. A favorable outcome requires prompt diagnosis and knowledge of the underlying mechanisms of disease that lead to this consequence. Novel diagnostic scores and treatment techniques, as well as bedside point-of-care tests, have been developed in recent years, which may aid clinicians in the diagnosis and management of DIC. For the successful care of patients with DIC, collaboration and quick therapy are crucial (Erez et al., 2015).

Pregnancy is a time in a woman's life cycle when she is at risk for hemorrhagic episodes and obstetrical disorders that can lead to DIC. One of the most common causes of DIC in pregnancy is acute obstetrical bleeding, which is also one of the most preventable causes of maternal death. A novel pregnancy-specific DIC scoring system was established in order to develop a common vocabulary across physicians, and point-of-care testing is now being validated for use in pregnant women (Erez, 2017).

DIC is one of the primary causes of maternal death. It occurs as a result of obstetrical problems like placental abruption, amniotic fluid embolism, HELLP syndrome, retained stillbirth, and pregnancy-related acute fatty liver. DIC can be compensated (non-overt) or decompensated (overt) depending on whether the hemostatic system is activated abnormally. Overt and non-overt DIC can be diagnosed using specific scores that have been modified for physiological changes during pregnancy. For the diagnosis of DIC, the pregnancy specific DIC score has a sensitivity of 88 percent, a specificity of 96 percent, an LR+ of 22, and an LR-of 0.125. The treatment of DIC during pregnancy necessitates immediate attention to the underlying disease that caused the difficulty, including the patient's delivery, as well as repair of the hemostatic problem, which can be led by pregnancy-specific point-of-care tests. In low-resource countries, novel therapy approaches such as fibrinogen concentrate may help manage DIC in pregnancy (Erez, 2022a).

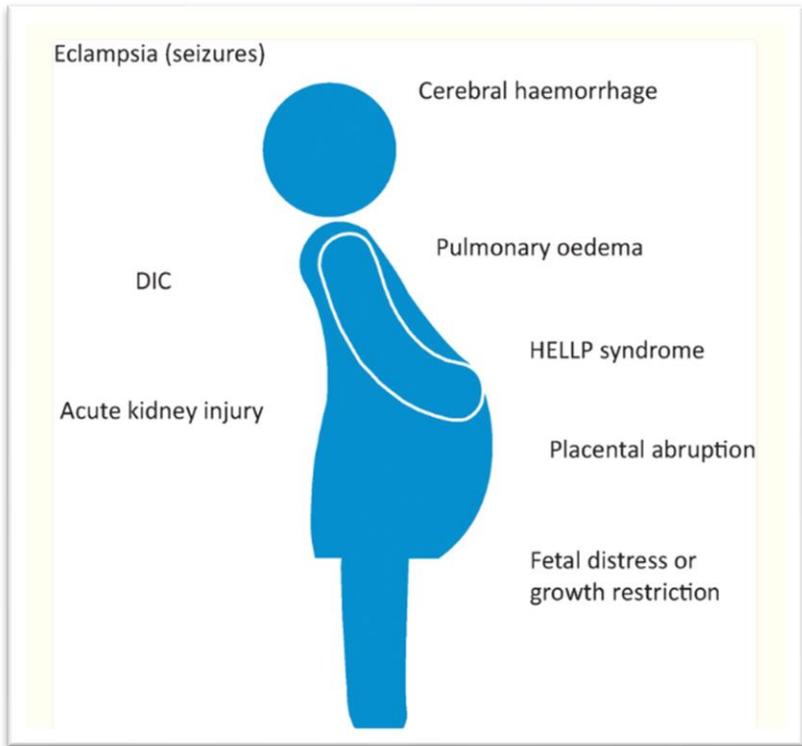


Fig. 1. Major complications of pre-eclampsia. DIC = disseminated intravascular coagulation; HELLP = haemolysis elevated liver enzymes low platelets (Narayan & Nelson-Piercy, 2017)

Nonovert DIC is a type of hemostatic failure that hasn't progressed to the point of decompensation. Pregnant patients can be identified at this point, which can help doctors predict who will have a severe obstetrical hemorrhage (Alhousseini et al., 2022). The fetus's demise in the womb is a sign of mother and perinatal health. This pathology is frequently worsened by DIC, which is induced by the stillbirth's intrauterine retention. With extended fetal detention (>8 days), antenatal mortality of the fetus causes pathological changes in the coagulation system, resulting in the development of DIC syndrome (Verdes et al., 2021).

2. Associated syndromes

DIC can be a complication of a variety of obstetrical diseases. HELLP syndrome is linked to advanced pre-eclampsia and can result in DIC in up to 39% of cases. Infection with the Coronavirus 2 of the Severe Acute Respiratory Syndrome (SARS-CoV-2) has also been associated to an excessive inflammatory/immune response as well as several phenotypic hemostatic derangements (Sanchez et al., 2021).

Anaphylactoid syndrome of pregnancy, also known as amniotic fluid embolism, occurs most commonly during childbirth and can lead to cardiorespiratory collapse and DIC (Kamata et al., 2020).

Acute fatty liver of pregnancy is an uncommon condition with no known cause that is usually diagnosed in the third trimester or shortly after delivery. The risk is estimated to be 1 in 6692–1 in 13,328. In the presence of clinical and laboratory symptoms such as nausea, vomiting, jaundice, increased serum transaminase levels, increased prothrombin time, and hypoglycemia, the obstetric team must have a high index of suspicion of this pathology. Early diagnosis, early delivery, and supportive care enhance maternal and perinatal outcomes dramatically. If this obstetric emergency is not diagnosed promptly, it can quickly develop to hepatic failure, DIC, haemorrhage, encephalopathy, multiple organ failure, and death (Yücesoy et al., 2005).

HELLP syndrome is a severe consequence of preeclampsia that worsens the prognosis of both the mother and the baby. It is defined as hemolysis, liver failure, and low platelets. It is frequently linked to the development of DIC syndrome (Batashki et al., 2009).

Endometrial tissue or endometrial-like tissue grows within the uterine myometrium in adenomyosis, a benign gynecological disorder. In patients with adenomyosis, just a few occurrences of DIC have been described. Although hysterectomy is recommended for women in their late reproductive years who have refractory severe uterine hemorrhage due to advanced uterine adenomyosis, conservative treatment is often preferred. Due to the social trend of late marriage, such cases have been on the rise recently. When a pregnancy is terminated, adenomyosis can result in significant bleeding and DIC. The overactive fibrinolysis system inside adenomyosis was thought to impact the neighboring endometrium, resulting in massive bleeding. Before considering hysterectomy to manage refractory uterine bleeding, consider nafamostat mesilate as an alternative, keeping in

mind the pathophysiology of excessive bleeding caused by uterine adenomyosis (Kimura et al., 2020).

Coagulopathies are obstetric problems that impact the pregnancy, labor, and puerperium periods. The DIC, which involves generalized activation of the coagulation system as well as activation of inflammatory cells, is one of the more severe and complex haemostatic illnesses. Patients whose pregnancy was complicated by SARS-CoV-2 infection developed DIC syndrome. Both the course of these cases and the literature review indicate that particular attention should be paid to coagulation system laboratory parameters, closely monitoring the foetal well-being, and, in the event of acute DIC development, it is recommended to deliver a baby and begin intensive therapy (Skalska-Swistek et al., 2022).

3. Diagnosis & Treatment

Patients with DIC may present to clinicians who are unfamiliar with certain elements of thrombosis and hemostasis. As a result, DIC diagnosis is frequently considered only after the patient has had uncontrollable bleeding or multi-organ failure, both of which are unsalvageable circumstances. The biggest challenge with DIC diagnosis, aside from clinical manifestations, is coagulation test abnormalities. Patients with DIC are thought to have a prolonged prothrombin time and partial thromboplastin time, as well as thrombocytopenia, reduced fibrinogen, and elevated D-dimers. Detecting DIC during pregnancy can be difficult, and it necessitates care and knowledge of the physiologic changes that occur during this time. It can be aided by a pregnancy-specific DIC score that includes three components: 1) fibrinogen concentrations; 2) prothrombin time difference – the difference in prothrombin time between the patient's plasma and the laboratory control; and 3) platelet count. The pregnancy specific DIC score has an 88 percent sensitivity, a 96 percent specificity, a positive probability ratio of 22, and a negative likelihood ratio of 0.125 at a threshold of 26 points. The treatment of DIC during pregnancy necessitates immediate attention to the underlying disease that caused the difficulty, including the patient's delivery, as well as repair of the hemostatic problem, which can be led by pregnancy-specific point-of-care tests (Erez et al., 2022b).

Erez et al., (2014) conducted a study to 1) determine the component needed to generate a validated DIC score during pregnancy. 2) To validate such scoring system in the identification of patients with clinical diagnosis of

DIC. All women who gave birth at the 'Soroka University Medical Center' throughout the study period and had blood coagulation tests such as total blood cell count, prothrombin time (seconds), partial thromboplastin time, fibrinogen, and D-dimers were included in the study. Based on ROC curve analysis, nomograms for pregnancy were created, and a DIC score was calculated. 1) Maternal plasma fibrinogen concentrations increased during pregnancy. 2) Maternal platelet count decreased gradually during gestation. 3) The prothrombin time and partial thromboplastin time values did not change with advancing gestation. 4) Prothrombin time difference had an area under the curve (AUC) of 0.96, and a prothrombin time difference ≥ 1.55 had an 87% sensitivity and 90% specificity for the diagnosis of DIC. 5) the platelet count had an AUC of 0.87, an 86% sensitivity and 71% specificity for the diagnosis of DIC. 6) fibrinogen concentrations had an AUC of 0.95 and a cutoff point ≤ 3.9 g/L had a sensitivity of 87% and a specificity of 92% for the development of DIC. 7) The pregnancy adjusted DIC score had an AUC of 0.975 and at a cutoff point of ≥ 26 had a sensitivity of 88%, a specificity of 96%, a LR(+) of 22 and a LR(-) of 0.125 for the diagnosis of DIC. As a conclusion, the positive likelihood ratio of this score suggests that a patient with a score of ≥ 26 has a high probability to have DIC.

Amniotic fluid embolism, commonly known as anaphylactoid syndrome of pregnancy, is an uncommon but life-threatening complication of pregnancy. DIC is associated with Anaphylactoid Syndrome of Pregnancy in around half of the cases. Recombinant factor VIIa has been utilized to treat DIC associated with Anaphylactoid syndrome of pregnancy on a few occasions in the past. Although recombinant factor VIIa has hazards, it can save lives when other treatments have failed (Frye et al., 2012).

Acute fatty liver during pregnancy, particularly when combined with DIC, can cause pituitary apoplexy and panhypopituitarism due to underlying coagulopathy. Because pituitary apoplexy is associated with a high mortality rate, clinical awareness and a strong index of suspicion are essential for detecting this illness. Hormone replacement therapy should be started as soon as possible to lower the risk of morbidity and mortality (Barvalia et al., 2015).

Jonard et al. (2016) examined the validity of two previously reported DIC diagnosis scores in pregnant women admitted to the critical care unit for a thrombotic or hemorrhagic complication of birth and postpartum. This was a population-based retrospective analysis of 154 individuals hospitalized to

an intensive care unit in a university hospital for severe delivery and postpartum problems. The International Society for Thrombosis and Hemostasis (ISTH) score was compared to a newly published score (tailored to physiological changes of pregnancy and based on three components: platelet count, prothrombin time differential, and fibrinogen) (based on four components: platelet count, fibrinogen, prothrombin time, and fibrin related marker). During the postpartum intensive care unit stay, both scores were calculated at delivery, intensive care unit admission (day 0), day 1 and day 2. The validity of both scores was determined by comparing them to the results of a blinded and consensual analysis conducted by two experts. Each score's sensitivity, specificity, and area under the curve (AUC) were determined using a generalized linear mixed model at each time and overall. The new score exhibited a sensitivity of 0.78, a specificity of 0.97 (p0.01), and a global AUC of 96 percent, compared to 0.31, 0.99, and 94 percent (p0.01) for the ISTH score. Between the two scores, the Kappa coefficient of correlation was 0.35. The lack of fibrinogen and fibrin-related peptides thresholds tailored to the physiological changes in coagulation generated by pregnancy explains the ISTH score's decreased sensitivity. In the subset of patients admitted to the intensive care unit after delivery for an acute particular problem, the new DIC score appears to be highly discriminating. Because of its low sensitivity, the ISTH score is not advised for pregnant women.

Nazarov & Yarmatov (2020) investigated the birth histories of 45 pregnant women in order to establish preventive intensive care strategies that ensure safe delivery in women with chronic DIC syndrome and consequently have a good influence on the mother and fetus' condition. All pregnant women were given comprehensive treatment, which included beta-blockers (atenalol, bisoprolol, metaprolol), calcium antagonists (nifedipine, amlodipine, corinfar), magnesium therapy, neurometabolic protection, and infusion therapy (refortan, stabizol, etc.). In a complex of critical care, pregnant women in the main group were given enoxaparin and heparin. All of the patients had a 44% decrease in platelet count, a 47% fall in prothrombin index, a 47% extension of prothrombin time and clotting time, and a 27% increase in hemoglobin levels. The coagulogram was examined in all pregnant women in stages: before birth, day 1, day 3, and day 5. The overall activity of blood coagulation factors that make up the internal pathway of hemostasis activation - VIII, IX, X, XI, XII - increases in the

third trimester during normal pregnancy, according to the literature and this research. All of the patients chose to have their babies. During the period, the clotting time was lengthened by 34% in 6 patients (26%) of the main group, while it did not change in the other patients. During labor and the early postpartum period, no problems were detected. In risk groups of pregnant women, the use of enoxaparin and heparin in a complex of intensive therapy reduces the chance of developing fatal complications, DIC of the syndrome, and also improves indicators of the mother's quality of life and the condition of the fetus.

Haematological interventions (low molecular weight heparin and unfractionated heparin), danaparoid sodium, synthetic protease inhibitor, antithrombin, human recombinant activated protein C, recombinant human soluble thrombomodulin, recombinant tissue factor pathway inhibitor, recombinant activated factor VIIa and any other types of haematological interventions) for treating DIC during pregnancy and postpartum are needed to be tested in randomised controlled trials assessing outcomes such as maternal death, perinatal death and safety via randomised controlled trials (Marti-Carvajal et al., 2011).

Literatures

- Alhousseini, A., Romero, R., Benschalom-Tirosh, N., Gudicha, D., Pacora, P., Tirosh, D., ... & Erez, O. (2022). Nonover disseminated intravascular coagulation (DIC) in pregnancy: a new scoring system for the identification of patients at risk for obstetrical hemorrhage requiring blood product transfusion. *The Journal of Maternal-Fetal & Neonatal Medicine*, 35(2), 242-257.
- Barvalia, U., Eliades, M., & Melhem, L. (2015). Concomitant Pituitary Apoplexy and Acute Fatty Liver of Pregnancy Complicated With Disseminated Intravascular Coagulation. *AACE Clinical Case Reports*, 1(4), e250-e254.
- Batashki, I., Milchev, N., Blagoeva, N., Markova, D., & Amaliev, G. (2009). HELLP syndrome, complicated with DIC syndrome in the third trimester of pregnancy. *Akusherstvo i Ginekologija*, 48(1), 48-52.
- Erez, O. (2017). Disseminated intravascular coagulation in pregnancy—Clinical phenotypes and diagnostic scores. *Thrombosis research*, 151, S56-S60.
- Erez, O. (2022a). Disseminated intravascular coagulation in pregnancy: New insights. *Thrombosis Update*, 6, 100083.
- Erez, O., Mastrolia, S. A., & Thachil, J. (2015). Disseminated intravascular coagulation in pregnancy: insights in pathophysiology, diagnosis and management. *American journal of obstetrics and gynecology*, 213(4), 452-463.
- Erez, O., Mastrolia, S. A., & Thachil, J. (2016). Disseminated Intravascular Coagulation in Pregnancy: Insights in Pathophysiology, Diagnosis, and Management. *Obstetric Anesthesia Digest*, 36(3), 125-126.
- Erez, O., Novack, L., Beer-Weisel, R., Dukler, D., Press, F., Zlotnik, A., ... & Mazor, M. (2014). DIC score in pregnant women—a population based modification of the International Society on Thrombosis and Hemostasis score. *PloS one*, 9(4), e93240.
- Erez, O., Othman, M., Rabinovich, A., Leron, E., Gotsch, F., & Thachil, J. (2022). DIC in Pregnancy—Pathophysiology, Clinical Characteristics, Diagnostic Scores, and Treatments. *Journal of Blood Medicine*, 13, 21.
- Frye, I. S., Sager, C., Daly, A., Barbot, P., Luce, E., Rinzler, L., & Forde, G. K. (2012). Recombinant Factor VIIa Utilized in Successful Treatment of Disseminated Intravascular Coagulation Secondary to Anaphylactoid Syndrome of Pregnancy. *University of Toronto Medical Journal*, 89(3).
- Jonard, M., Ducloy-Bouthors, A. S., & Fourier, F. (2016). Comparison of two diagnostic scores of disseminated intravascular coagulation in pregnant women admitted to the ICU. *PloS one*, 11(11), e0166471.
- Kadikar, S. K., Divan, F. J., Topiwala, U., & Agasiwala, S. (2021). Study of pregnancy with disseminated intravascular coagulation. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 10(11), 4220-4226.
- Kamata, M., Maruyama, T., Nishiguchi, T., & Iwasaki, S. (2020). Sudden onset of syncope and disseminated intravascular coagulation at 14 weeks of pregnancy: a case report. *BMC pregnancy and childbirth*, 20(1), 1-5.

- Kimura, F., Takahashi, A., Kitazawa, J., Yoshino, F., Katsura, D., Amano, T., & Murakami, T. (2020). Successful conservative treatment for massive uterine bleeding with non-septic disseminated intravascular coagulation after termination of early pregnancy in a woman with huge adenomyosis: case report. *BMC Women's Health*, 20(1), 1-6.
- Levi, M. (2009). Disseminated intravascular coagulation (DIC) in pregnancy and the peri-partum period. *Thrombosis Research*, 123, S63-S64.
- Marti-Carvajal, A. J., Comunián-Carrasco, G., & Peña-Martí, G. E. (2011). Haematological interventions for treating disseminated intravascular coagulation during pregnancy and postpartum. *Cochrane Database of Systematic Reviews*, (3).
- Narayan, B., & Nelson-Piercy, C. (2017). Medical problems in pregnancy. *Clinical Medicine*, 17(3), 251.
- Nazarov, F. Y., & Yarmatov, S. T. (2020). Optimization of methods for prevention and intensive therapy of complications in pregnant women with chronic syndrome of Disseminated Intravascular Coagulation. *Journal of Advanced Medical and Dental Sciences Research*, 8(9), 82-85.
- Sanchez, T., Roxo, M., Duarte, T., Spencer, L., & Matos, F. (2021). HELLP syndrome and disseminated intravascular coagulation (DIC) in COVID-19 pregnancy: Hemostatic balance challenge. *Anesthesia and Analgesia*, 1931-1931.
- Sharma, M. (2022). Chronic ectopic pregnancy complicated by septicemic shock and disseminated intravascular coagulation. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 11(1), 281-284.
- Skalska-Swistek, M., Huras, H., Jaworowski, A. P., Świstek, R., & Kołak, M. (2022). COVID-19 Infection Complicated by Disseminated Intravascular Coagulation during Pregnancy—Two Cases Report. *Diagnostics*, 12(3), 655.
- Verdes, D., Coşpormac, V., & Sârbu, Z. (2021). DIC syndrome in pregnancy caused by antenatal fetal death (literature review). In *Cercetarea în biomedicină și sănătate: calitate, excelență și performanță* (pp. 405-405).
- Yılmaz, M., & Aboalhasan, Y. (2022). Spontaneous Pregnancy Loss: A Review of Systematic Reviews and Meta-Analysis. *Current Approaches in Gynecology and Gyneco-Oncology*, pp. 21-42.
- Yücesoy, G., Özkan, S. Ö., Bodur, H., Çakiroğlu, Y., Calişkan, E., & Özeren, S. (2005). Acute fatty liver of pregnancy complicated with disseminated intravascular coagulation and haemorrhage: a case report. *International Journal of Clinical Practice*, 59, 82-84.

CHAPTER 18

FEMALE GENITALIA ANATOMY

Dr. Cemile ÖZCAN UÇAR¹

¹ Sultanbeyli State Hospital, İstanbul-TURKEY ORCHID: <http://orchid.org/000-0003-1407-2577> E-mail: cemileozcan7@hotmail.com

Overview:

Knowing the pelvic anatomy is one of the most basic requirements for the obstetrician and gynecologist. The basic information in anatomical structures never changes, but the knowledge of these structures is gradually expanding. The surgeon should have a very good command of normal anatomy, but should also be prepared for unusual cases.

1. Bone Pelvis

The pelvic skeleton consists of os coxae, os sacrum, and os coccyges. The two os coxae are fused anteriorly with the symphysis pubica. The pelvic cavity is called the *cavitas pelvis*. The pelvic cavity is divided into two parts *pelvis major* and *pelvis minor* by an imaginary line called *linea terminalis*. The upper opening of the pelvis is called *aperture pelvis superior* and the lower opening is called *aperture pelvis inferior*. The border of the *aperture pelvis superior* is formed by the *ala ossis ilii* on the sides and the floor of the os sacrum posteriorly. The border of the *aperture pelvis inferior* is formed by the *ischium-pubis arm* on the anterior-lateral sides, the *tuber ischiadicum* on the side, and the *os coccygis* on the dorsal side (Fig. 1: Standring, 2008).

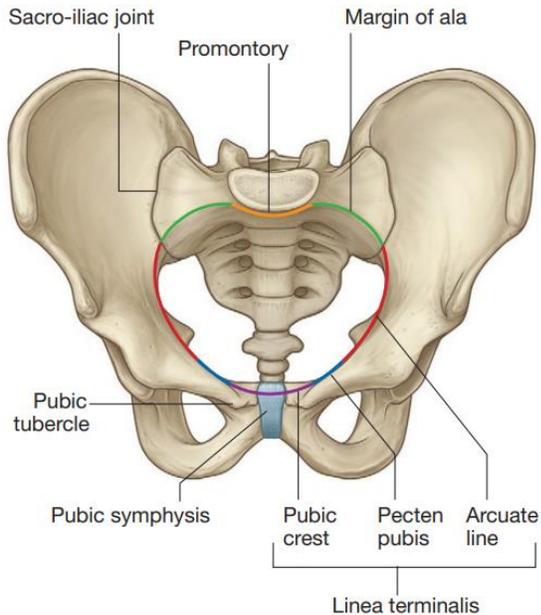


Figure 1: The Pelvis (Reproduced from Standring, 2008.)

The structure and diameters of the pelvis are important because of its role in childbirth in the female body. Pelvises can be categorized considering the diameter. However, in obstetric practice it is usually preferred to group pelvises in 4 main types: gynecoid, android, anthropoid, and platypelloid, where grouping is mainly based on the shape of the pelvic inlet (Maharaj, 2010).

Types of pelvis are calculated from the relationship between the length of the anterior–posterior diameter (APD) and the transverse diameter (TD) of the inlet. The main types of pelvis are (Fig 2: Hager, 1989):

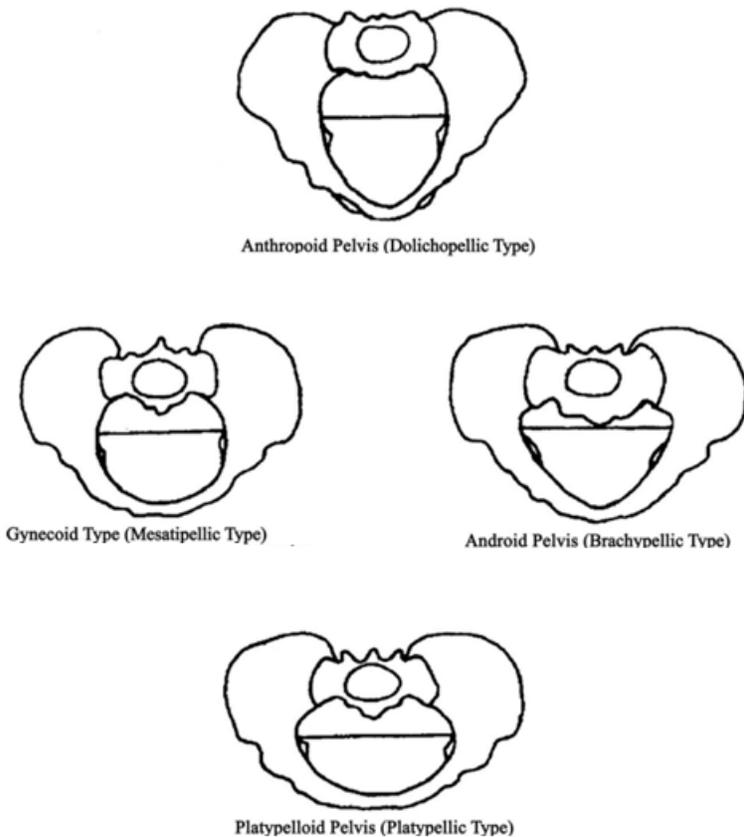


Figure 2: The Type of Pelvis (Reproduced from Hager, 1989)

- Gynecoid type pelvis: The aperture pelvis is superiorly oval in shape. It is the most common type in women.
- Anthropoid pelvis: Its antero-posterior diameter is larger than the transverse diameter. It is common in men.
- Android type pelvis: Apertura pelvis superior is heart-shaped. It is the most common type in men.
- Platypelloid pelvis: Apertura pelvis superior has a short antero-posterior diameter and a long transverse diameter (Hager LD, 1989)

2. Female Genital Organs

Female genital organs are divided into two parts as external and internal genital organs. The internal genital organs in the pelvic cavity consist of the ovary, tuba uterine, uterus and vagina (Fig. 3). The external genitalia, located below the diaphragma urogenitale and arcus pubicus, consist of mons pubis, labium majus pudendi, clitoris, bulbus vestibuli, and glands vestibularis major. All of the female external genitalia are also called the vulva (Yavagal S et al, 2011).

The internal genitalia

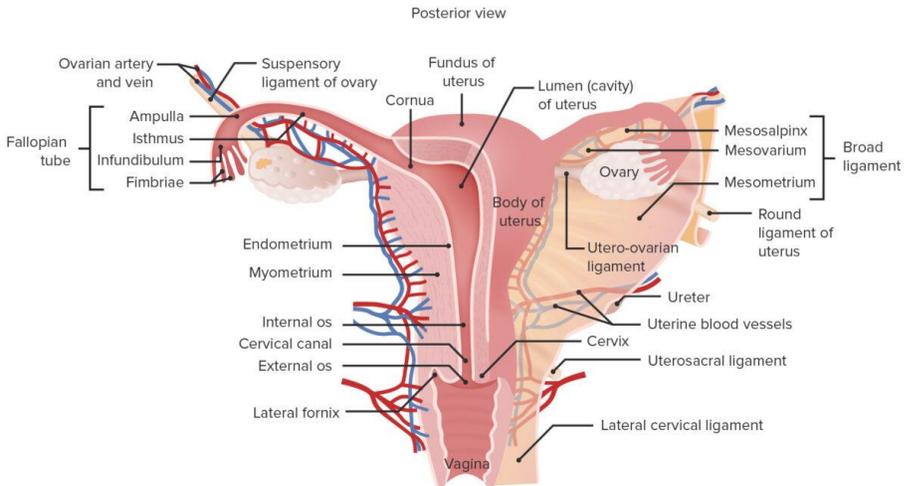


Figure 3: Female internal genital organs

The Ovaries

The ovary is a pair of organs located in the fossa ovarica on the lateral walls of the pelvis minor on the right and left. The ovaries, which correspond to the testicles in men, provide the development of the female reproductive cell, the ovum, as well as the production of progesterone and estrogen hormones. They are located between a. iliaca externa and a. iliaca interna in the fossa ovarica. Each ovarium is approximately 4 cm long, 2 cm wide and 0.8 cm thick. Its weight is 3-5 gr. It has two faces, facies lateralis and facialis medialis, two edges, margo liber and margo mesovaricus, and two ends, extremitas tubaria and extremitas uterine. The fimbria ovarica and the ligamentum ovarii suspensorium are attached to the tip of the extremitas tubaria. This ligament is continuous with an upwardly extending peritoneal plica and contains the arteria and vein ovarica. The extremitas uterine is attached to the cornu uteris of the uterus via the lig. ovarii proprium. At the anterior margin is the hilum ovarii. The vessels and nerves located between the two leaves of the mesovarium enter and exit the ovary from the hilum ovarii. Since no structure can hold onto the back edge, it is called margo liber; It is called margo mesovaricus because the mesovaricum attaches to the anterior margin (Arıncı and Elhan, 2014).

The fimbriae (finger-like projections) of the fallopian (uterine) tube covers the superior (tubal) pole. The superior pole is attached to the suspensory ligament of the ovary. It forms a basis for the ovary to the posterior pelvic wall, and in addition it behaves like a pipe for the ovarian vessels. Moreover, the vesicular appendix (hydatid of Morgagni) and the superior pole are related to each other. For completion, each vesicular appendix and the epoöphoron is connected to each other, where epoöphoron is a network of tubules residing in the mesosalpinx (superior aspect of the broad ligament of the uterus). Its inferior pole is in the direction towards the body of the uterus and connected to there with the help of the ligament of the ovary (different from the suspensory ligament of the ovary). The ligament of the ovary acts as the round ligament (both of which are derived from the gubernaculum). It secures each ovary to the cornu of the uterus. Moreover, each round ligament is also attached to the inner part of the labia majora.

The mesovarium is a double layer of peritoneum. Its function is to secure the ovary at its anterior surface to the posterior part of the broad ligament. The ovary is covered by a sheath of cuboidal epithelium and not peritoneum, excepting the mesovarium part. The posterior surface of the

ovary is exposed to the peritoneal cavity. The medial border of the ovary is in a relation with the uterosacral fold and the body of the uterus as well. Finally, the lateral surface of the ovary and the angle of the internal and external iliac vessels, the ureteric fold and the obturator nerve are related to each other.

The anterolateral surfaces of the abdominal aorta are divided into the ovarian arteries which are actually the direct branches. They are located just inferior to the renal arteries and arise bilaterally, and go on an inferolateral course. The ureters are crossed anteriorly by the arteries, on the surface of the psoas muscle group. Later it enters the suspensory ligament of the ovary in order to access the organ at its superior pole. Along its course throughout the ovary, several tubal branches are provided to the fallopian tube by the ovarian artery, before it anastomose with the ovarian branch of the uterine artery (branch of internal iliac artery).

On either side, the ovarian veins starts as a pampiniform plexus in the mesovarium before they coalesce in order to give two left and right ovarian veins. In the direction of their destination, they go through the suspensory ligament of the ovary. Throughout their path, the pair of veins on both sides fuses to form a single left and right ovarian vein. Each vein crosses their respective ureter and continues superomedially. The left ovary drains into the renal vein, while the right one into the inferior vena cava.

Both of the ovarian artery and the uterine artery supply blood to the ovary. The ovarian artery originates from the abdominal aorta below the renal artery or around L2 and consists a paired structure. The artery goes through the suspensory ligament of the ovary, and then enters the mesovarium. The ovarian artery may make an anastomosis with the uterine artery within the broad ligament (Ying J et al, 2019).

Drainage to the parametrium, cervix, mesosalpinx, and pampiniform plexus is provided by the ovarian vein which travels to the ovary by the suspensory ligament. It can be found to have anastomoses with the para-ovarian, uterine, vesical, rectal, and vulvar venous plexuses. The left ovarian vein drains down its contents into the left renal vein, while the right one empties directly into the inferior vena cava. The ovarian vein has a diameter of 5 mm on average (Tanaka Y et al, 2019).

The ovaries drain the majority of their lymph into the paraaortic lymph nodes, which arise around the level of L2. The lymph goes through the ovarian vessel to the paraaortic nodes near the bifurcation of the renal arteries and the aorta. However, researchers have noted two other pathways. The first one is the lymph which travels via lateral vessels reaching to hypogastric nodes, and then drain into the paraaortic nodes. The second one is the lymph following vessels close to the round ligament, and leads to the external iliac and inguinal lymph nodes (Hallas-Potts et al, 2019). Since these pathways provide a route of metastasis for ovarian cancer they are clinically important.

Two sources of sympathetic innervation of the ovary exist; one is through the ovarian plexus. The origin of the ovarian plexus is the renal plexus which also innervates parts of the fundus of the uterus. The suspensory ligament of the ovary carries this plexus to the ovaries. The second source of sympathetic innervation is through the superior ovarian nerve, carried within the ovarian ligament (Del Campo M et al, 2019). The parasympathetic innervation comes from the uterine (pelvic) plexus, which arise from the pelvic splanchnic nerves.

Fallopian Tube

The fallopian tube is 10 cm long and 3 mm in diameter. The main duty of the fallopian tube is transporting the egg from the ovary to the uterus and providing the connection between the ovary and the uterus. The fallopian tubes lie along the free edge of the ligamentum latum uteri. The part of the ligamentum latum uteri adjacent to the fallopian tube is called the mesosalpinx. Uterine, isthmus, ampulla, and infundibulum are the four main anatomical regions which compose the fallopian tube. The isthmus is neighbor to the uterine part. The ampulla which is the most common site of fertilization is lateral to the isthmus. The infundibulum, which resides in the most distal from the uterus, finishes at an abdominal ostium opening up into the peritoneal cavity and fimbriae, which catch the released oocyte during each menstrual cycle. The fimbria ovarica, supports the connection between the infundibulum and the ovary nearby. The fallopian tubes provide a space for fertilization to occur, and also function as a passageway for the ovum or gamete from the ovary to the uterus. (Eddy and Pauerstein, 1980).

Anastomoses between the ovarian and tubal branches of the ovarian artery and ascending branches of the uterine artery stemming from the arterial supply to the fallopian tube. The ovarian arteries branch off the abdominal aorta inferior to the origin of the renal arteries on each side. The uterine arteries arise from the internal iliac arteries, and the ascending branches travel superiorly towards the uterine horns while its descending branches travel inferiorly towards the superior vagina. The lateral fallopian tube is supplied by the ovarian arteries, while the medial fallopian tube is supplied by the ascending branches of the uterine artery. However, anastomoses between the two generally ensures that ischemia of any portion of the tube will not occur due to compromise of either.

The venous drainage flows to the tubal branches of the uterine and ovarian veins, in a similar configuration to the arterial supply. The right ovarian vein supplies drainage to the inferior vena cava (IVC), while the left ovarian vein supplies drainage to the left renal vein. The uterine veins drain into the internal iliac veins, which drain into the IVC.

The ovaries lymph drainage and the one of the fallopian tubes is similar to each other. Lymph flow is from the fallopian tubes to both the para-aortic (lumbar) lymph nodes and the pelvic lymph nodes (Ajithkumar et al, 2005).

Sympathetic efferent innervation originates from T11, T12, and L1. Afferent pain fibers for the fallopian tubes travel along the same pathway as Sympathetic efferent innervation. On the contrary, minor parasympathetic innervation is divided between vagal fibers of the ovarian plexus for the lateral part of the fallopian tube and medially from the pelvic splanchnic nerve from S1, S2, and S3. The most medial isthmus receives the densest innervation, and both innervation and musculature become sparser from proximal to the distal fallopian tube (Ezzati M, 2014)

Uterus

Uterus is 8 cm long, 5 cm wide and 2-3 cm thick, located between the bladder and rectum in the pelvic cavity. Its average weight is 30-40 gr. During pregnancy, the volume, shape and position of the uterus changes.

The uterus resides in the location in the female pelvis immediately posterior to the bladder and anterior to the rectum anatomically. Four main anatomic segments composes the female uterus. From superior to inferior

they are: fundus; a broad curved area in which fallopian tubes connects to the uterus, corpus (body); the main part of a uterus, it starts directly below the level of fallopian tubes and continues downward, isthmus; a lower neck region of the uterus, cervix; extends downwards from the isthmus and opens in the vagina (Chaudhry SR and Chaudhry K, 2021).

The uterus has 5 ligaments. However, only three of them contain carrier properties. The uterus carries mainly the muscle levator ani and three important ligaments. The three important ligaments that carry the uterus are the ligamentum transversum cervicis, ligamentum pubocervical and ligamentum sacrocervicalis (Arıncı and Elhan, 2014)

- The m. levator ani covers most of the pelvis outlet. This muscle and the fascia diaphragmatis pelvis superior covering the upper surface of this muscle are the most important structures that carry the pelvic organs.
- Lig.transversum cervicis(colli)(lig. cardinale; Mackenrodt ligament): These fibers, consisting of connective tissue covering the upper part of the vagina and the lower part of the uterus, come together at the lateral edges of these organs and end by adhering to the lateral wall of the pelvis. A. vaginalis is closely located near to this ligament, and the bond between vaginalis and the ligament gets stronger due to this issue. Smooth muscle fibers is also contained.
- Lig. pubocervicalis (lig. uterovesicalis): It is two ribbon-shaped ligaments that connect the posterior aspect of the pubis to the cervix uteri. This ligament also attaches to the bladder, where it passes from the sides. These fibers are also called lig. pubovesicalis.
- Lig. sacrocervicalis (lig. uterosacralis): It is a fibromuscular ligament that is a continuation of the posterior part of the lig. transversum cervicis and connects the cervix uteri to the sacrum. These ligaments form the folds on the sides of excavatio rectouterina.
- Lig. latum uteri: It is called the two-leaf peritoneum that extends between the lateral edge of the uterus and the lateral walls of the pelvis. Tuba uterina is located on its free upper edge. It is divided into 3 sections. The part close to the uterus is called the

mesometrium, the part close to the tuba uterina is called the mesosalpinx and the part close to the ovary is called the mesovarium. The connective tissue between its two leaves is called the parametrium.

- Lig. teres uteri: It attaches to the upper parts of the uterus between the two leaves of the lig. latum uteri, just below the entrance of the tuba uterina. It passes over the lig. inguinale and enters the anulus inguinalis. Its fibers blend into the connective tissue of the labium majora.

The blood starts to rise from the anterior branch of the internal iliac artery, flows through the uterine and ovarian arteries and finally reaches the uterus. Uterine arteries are the main blood vessels that supply blood to the uterus. The arcuate arteries, which branch into the radial arteries, are the main branches for the blood supply entering the myometrium. Basal and spiral arteries are the other branches for the blood after the entry to the level of endometrium (Chaudhry SR and Chaudhry K, 2021).

Different parts of the uterus are supplied by the uterine arteries which play a crucial role in maintaining blood supply during menstrual cycles and in pregnancy. Along with the ovarian and fallopian tube lymphatic drainage, the fundal area of the uterus chiefly drains into para-aortic lymph nodes. Along the round ligament, some part of it drains into superficial inguinal lymph nodes. The lower portions of the uterus drain into external and internal iliac lymph nodes along uterine blood vessels.

The autonomic nervous system, sympathetic, and parasympathetic nervous system supply nerve to the internal pelvic organs. Autonomic T11 and T12 innervate the uterus, and sympathetic nerve supply for the uterus is provided by the hypogastric plexus, while the parasympathetic supply is received from S2 to S4. The uterus and cervix are not sensitive to cutting and burning. So there is no need for anesthesia for the cervix to be cauterized during therapeutic procedures. However, the uterus and cervix are sensitive to stretch (distension), and pain occurs during normal vaginal delivery due to dilation of the cervix. (Tong and Huo, 1991).

The uterus is located between the urinary bladder anteriorly and the rectum posteriorly. The average dimensions of the uterus in an adult female are 8 cm long, 5 cm across, and 4 mm thick. The volume of the uterine

cavity is 80 mL to 200 mL on average. The body, the cervix, and the fundus are the three main segments of uterus.

Three tissue layers consist the uterus, which are the following:

- Endometrium: the inner lining and composed of the functional (superficial) and basal endometrium. Reproductive hormones are related to the functional layer. When this layer sheds, menstrual bleeding occurs. If there is damage to the basal endometrium, the formation of adhesions and fibrosis (Asherman syndrome) may occur.
- Myometrium: the muscle layer and consists smooth muscle cells.
- Serosa/Perimetrium: the thin outer layer consisting epithelial cells.

The long axis of the cervix is usually not in line with the long axis of the body of the uterus. Usually, the long axis of the body of the uterus is tilted forward over the long axis of the cervix, which is called ante flexion of the uterus. Retroflexion stands for a backward tilt at this level. In 80 percent of women, a forward tilt occurs and the long axis of the uterus lies at the right angle to the long axis of the vagina. A backward tilt of the uterus over the vagina occurs in 20 percent of women, where they are called respectively; anteversion and retroversion (Fidan U et al, 2017).

The uterus may naturally lie in different positions such as anteverted/retroverted, ante flexed/retro flexed, or midline, and it may be rotated (especially during pregnancy). The uterus most commonly lies in an ante flexed and anteverted position in 50% of women.

When the uterus is in a retroverted/retro flexed or "tipped" position, it may cause pelvic pain, dyspareunia, minor incontinence, fertility difficulty, and difficulty inserting tampons. In pregnancy, this may lead to uterine incarceration.

The uterus may also vary in size and shape depending on the reproductive phase of the female and response to the female sex hormones.

- Pre-pubertal age: Uterus is small, and the cervix is longer than the body. The cervix to body ratio is 2:1.
- Reproductive age: Mature size, the body is bigger than the cervix, and the cervix to body ratio is 1:2.

- Post-menopausal: The uterus is atrophic, the body size is smaller than the cervix. The cervix to body ratio is 2:1.

Vagina

The vagina is a muscular canal of approximately 7.5 cm in length that extends from the uterus to the vestibule of the external genitalia. It runs in the midline in a plane almost parallel to that of the lower sacrum, and meets the cervix at an angle varying from 45 to 90, depending on the degree of bladder distension. Cervical protrusion into the proximal vagina creates a circular cul-de-sac referred to as the vaginal fornix (Deutsch and Gosink, 1982).

It contains the vaginal orifice, external urethral meatus, vestibular bulbs, and the openings of the greater vestibular glands (also known as Bartholin's glands). The vaginal orifice is below the opening of the urethra and is characterized by the presence of the hymen (a circumferential hairless skin with variable shape) (Standrings, 2008).

The artery that provides blood supply to the vagina is arteria vaginalis. Arteria vaginalis is one of the branches of arteria arteria iliaca interna (hypogastric artery). Arteria vaginalis anastomoses with branches of arteria uterine, arteria vesicalis inferior and arteria rectalis media. For this reason, the branches of these arteries also contribute to the nutrition of the vagina.

The vaginal venous plexus is a group of veins draining blood from the vagina. It lies around the sides of the vagina. Its blood is eventually into the internal iliac veins.

The lymph drainage of the vagina: Nodi iliaci externi and interni, Nodi iliaci interni and Nodi inguinales profundi.

Nerves of the vagina: Plexus uterovaginalis, Plexus hypogasticus inferior (plexus pelvicus) and Nerve pudendus.

The external genitalia (Vulva)

The female external genitalia, or vulva, include the mons pubis, labia majora and minora, clitoris, vestibule, vestibular bulbs, greater (Bartholin) and lesser vestibular glands, Skene glands, and the distal urethral and vaginal openings. (Fig. 4)

External genitalia are abundantly supplied with blood. The branches of the a. pudenda interna and a. pudenda externa supply the skin of the external genitalia. The remaining part is fed by a. bulbi vestibuli(vaginae), a.

perinalis and a. clitoridis, which are branches of a. pudenda interna. The veins open into the v. vaginalis and v. vesicalis inferior via the plexus pudendalis.

Lymphs of external genitalia nodi inguinales superficiales and profundi.

Nerves of external genitalia are n. ilioinguinalis, genital branch of n. genitofemoralis, n. cutaneus femoris posterior, perineal branch of n. pudendus. It also receives its autonomous branches from the plexus uterovaginalis.

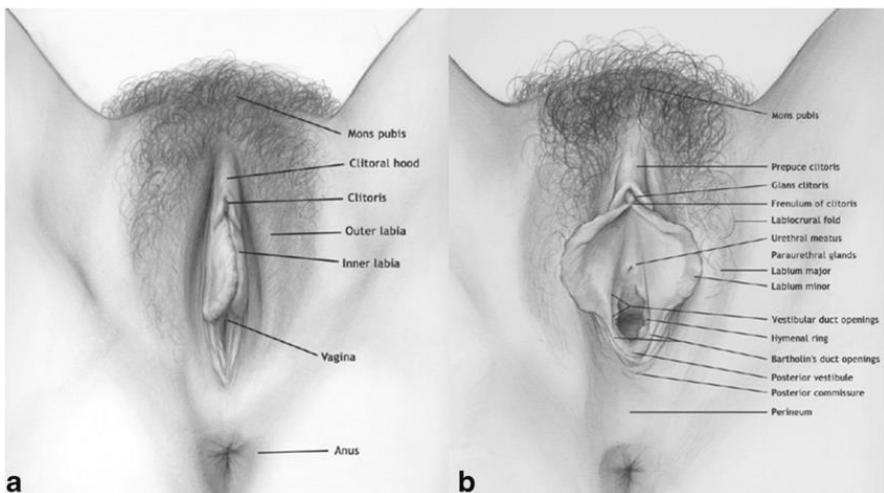


Figure 4: Female external genital organs

Mons Pubis

The raised area in front of the symphysis pubica is called the mons pubis. The subcutaneous fat tissue gives the swelling of the mons pubis. Adults have hairs called pubes in this area (Standrings, 2008).

Labium Majora

It is a pair of thick skin folds located at the entrance of the vestibulum vaginae. The labium majora, which is the equivalent of the scrotum skin in men, is about 8 cm long and 2-2.5 cm high. It extends from the mons pubis anteriorly to the perineum posteriorly. Labium majora has two sides, inner and outer. The outer surface, like the scrotum, is darker than the skin of the

neighboring region, due to its excess pigment, and there are hairs on it. Its inner surface is flat and contains large fat follicles. League. The teres uteri passes through the canalis inguinalis and connects the uterus to the skin of the labium majora and the fat-connective tissue inside. The right and left ends of the labium majora unite anteriorly to form the commissura labium anterior and posteriorly the commissura labium posterior. The 2.5-3 cm section between the commissura labium posterior and the anus is called the perineum. The space between the labium majora is called the rima pudenda (Williams and Bannister, 2008).

Labium minora

It is two small skin folds 3-4 cm long and 1-1.5 cm high, located between the labium majora. It is the equivalent of the skin of the penis in men. It does not contain adipose tissue. In nullipares, their posterior ends unite in a section called fourchette (Putz and Pabst, 2008). It does not have hair and sweat glands on its outer surface, but it does have oil glands.

Clitoris

The clitoris is an erectile structure, homolog to the male penis, formed by two corpora cavernosa and the glans, covered by the prepuce. (O'Connell and Lancey, 2005) The clitoris begins as a 3-3.5 cm long crus clitoris attached to the ischium-pubis arms and is covered by the muscle ischiocavernosus. As the crus clitoris extends towards the pubis, they approach each other and unite in front of the pubis to form the corpus clitoridis (2.5-3 cm).

The free end of the corpus clitoridis is called the glans clitoridis. The ligament hanging the clitoris is called the lig. suspensorium clitoridis. The clitoris is surrounded by a connective tissue sheath called the fascia clitoridis. It is very sensitive to contact, pressure and heat (Arıncı and Elhan, 2014)

The urethra lies surrounded by this complex with the body directly anterior to it, flanked superficially by the bulbs and deeply by the crura.

The ducts of Skene's glands open into the urethra and the lateral sides of the ostium urethra externum.

Vestibular Bulbs

The corpus spongiosum in men is the equivalent of the posterior part of the penis. The vestibular bulbs (recently renamed “bulbs of the clitoris”) are two erectile organs situated laterally to the vaginal orifice directly beneath the skin of the labia minora and joined together (pars intermedia) and extended to the base of the glans (O’Connell and Lancey, 2005).

Gl. Vestibularis Major (Bartholin Gland)

The male glands are the equivalent of bulbourethralis and are a pair of left and right glands. These two small (0.5 cm in diameter), pea-shaped glands are located on the lateral sides of the ostium vaginae and are adjacent to the posterior parts of the vestibular bulbs. Each gland opens into the groove between the labium minora and the hymen by a 2 cm long duct (O’Connell and Lancey, 2005).

REFERENCES

- Standrings (2008). *Gray's Anatomy: The Anatomical Basis of Clinical Practice*, 40th edn. Churchill Livingstone-Elsevier, New York.
- Maharaj D (2010). Assessing cephalopelvic disproportion: back to the basics. *Obstet Gynecol Surv.* 65:387–395.
- Hager LD. (1989). The evolution of sex differences in the hominid bony pelvis. PhD Dissertation. University of California at Berkeley.
- Yavagal S, De Farias TF, Medina CA et al. (2011). Normal vulvovaginal, perineal and pelvic anatomy with reconstructive considerations. *Semin Plast Surg* 25; 121-129.
- Arıncı K, Elhan A (2014). *Anatomi*, 6th. Güneş Tıp, Ankara.
- Ying J, Feng J, Hu J, Wang S, Han P, Huang Y, Zhao W, Qian J. (2019). Can ovaries be preserved after an ovarian arteriovenous disconnection? One case report and a review of surgical treatment using Da Vinci robots for aggressive ovarian fibromatosis. *J Ovarian Res.* 12(1):52.
- Tanaka Y, Tsuboyama T, Yamamoto K, Terai Y, Ohmichi M, Narumi Y (2019). A case of torsion of a normal ovary in the third trimester of pregnancy: MRI findings with emphasis on asymmetry in the diameter of the ovarian veins. *Radiol Case Rep.* 14(3):324-327.
- Hallas-Potts A, Dawson JC, Herrington CS. (2019). Ovarian cancer cell lines derived from non-serous carcinomas migrate and invade more aggressively than those derived from high-grade serous carcinomas. *Sci Rep.* 9(1):5515.
- Del Campo M, Piquer B, Witherington J, Sridhar A, Lara HE. (2019). Effect of Superior Ovarian Nerve and Plexus Nerve Sympathetic Denervation on Ovarian-Derived Infertility Provoked by Estradiol Exposure to Rats. *Front Physiol.* 10:349.
- Eddy CA, Pauerstein CJ. (1980). Anatomy and physiology of the fallopian tube. *Clin Obstet Gynecol.* 1177-93.
- Ajithkumar TV, Minimole AL, John MM, Ashokkumar OS. (2005). Primary fallopian tube carcinoma. *Obstet Gynecol Surv.* 60(4):247-52.
- Ezzati M, Djahanbakhch O, Arian S, Carr BR. (2014). Tubal transport of gametes and embryos: a review of physiology and pathophysiology. *J Assist Reprod Genet.* 31(10):1337-47.
- Chaudhry SR, Chaudhry K. *StatPearls* [Internet] (2021). StatPearls Publishing; Treasure Island.
- Tong XK, Huo RJ. (1991). The anatomical basis and prevention of neurogenic voiding dysfunction following radical hysterectomy. *Surg Radiol Anat.* 13(2):145-8.
- Fidan U, Keskin U, Ulubay M, Öztürk M, Bodur S. (2017). Value of vaginal cervical position in estimating uterine anatomy. *Clin Anat.* 30(3):404-408.
- Deutsch AL, Gosink BB. (1982). Normal female pelvic anatomy. *Semin Roentgenol.* 17(4):241-50.
- Williams PL, Bannister LH (2008). *Gray's Anatomy of the Human Body*, Churchill Livingstone, New York.

- .Putz R, Pabst R (2008). Sobotta Atlas of Human Anatomy, 14th edn. Urban Fischer-Elsevier, Munich, Germany.
- O'Connell HE, De Lancey JOL (2005). Clitoral anatomy in nulliparous, healthy, premenopausal volunteers using unenhanced magnetic Resonance Imaging. *J Urol* 173: 2060–2063.

CHAPTER 19

BLOOD TRANSFUSION IN OBSTETRICS: AN OVERVIEW

Dr. Gülsüm DOĞAN¹

¹ Siirt training and research hospital, obstetrics and gynecology department, Siirt, Turkey ORCID ID: 0000-0003-2836-1302
Corresponding author: glsmdgn214@gmail.com

1. Introduction

Blood transfusion, defined as the transfer of blood from one person's circulation to that of another for medicinal purposes, is a relatively new concept. It was only during and shortly after WWII that it became a widespread realistic option (Learoyd, 2012). Nutritional anemia and obstetric problems are the primary causes of blood and blood product transfusions in poor nations (Vasava et al., 2020). One-fourth of the 99 percent of maternal mortality in underdeveloped nations is related to postpartum hemorrhage (Rahman et al., 2017). Postpartum haemorrhage (bleeding after childbirth) is the major cause of maternal death globally (Say et al., 2014; Yılmaz, xxx).

Safe blood is essential for providing comprehensive emergency obstetric care and lowering maternal mortality. Many countries suffer from a shortage of blood, which disproportionately affects women and children who require life-saving blood transfusions. Although preventing postpartum bleeding by treating underlying anemia and infectious illnesses is important, it is insufficient in the case of obstetric hemorrhage. Alternative methods of giving safe blood in times of bleeding should be prioritized in the developing world, with a particular focus on quick testing, warm whole blood donation, and autologous blood transfusion (Schantz-Dunn & Nawal, 2011).

In obstetrics, blood transfusions should be given to save the patient's life. Severe blood loss can cause hypovolemic shock, which necessitates a blood transfusion right away to avoid organ failure and death. Blood and blood component transfusions must be treated as if they were drugs. They should only be used after carefully assessing the benefits and hazards, as well as in the proper dose, indication, and regimen (Reshma & Sreelatha, 2019).

Peripartum hemorrhage is still one of the leading causes of maternal death around the world. In extreme situations, treatment may entail the administration of packed red blood cells, and patient blood management may drastically reduce it (Zdanowicz et al., 2021). In Obstetrics & Gynecology, blood transfusion is an important element of patient care. The backbone of this discipline of medicine is the blood transfusion facility. Blood is a valuable commodity since it must be collected from humans and is expensive. It must be used with caution. Blood is normally prescribed based on the clinician's assessment of blood loss and the patient's health. Blood transfusion practices at a tertiary care center must be reviewed on a regular

basis in the modern era of evidence-based medicine. In obstetric cases, three indications are equally distributed: anemia compromising pregnancy, obstetric haemorrhage, and postpartum correction of anemia. In Gynecology, the majority of patients receive blood transfusions prior to surgery to address anemia caused by irregular uterine hemorrhage. Whole blood transfusions were given to the majority of the participants to correct anemia. Inappropriate blood transfusion practices, such as the use of blood transfusion for preoperative correction of anemia in elective surgery and the use of whole blood for anemia correction, must be changed. Alternative methods for reducing the need for blood transfusions should be used more frequently (Anjali et al., 2015).

Blood and blood component transfusions are routine in obstetric wards, but they are not without risk. Non-haemolytic transfusion responses occur four times out of every hundred transfusions, but haemolytic transfusion events occur once out of every 40,000. The majority of donated blood is separated into its constituent parts: packed red cells, platelets, and fresh frozen plasma or cryoprecipitate. Autotransfusion, pre-autologous blood storage, oxygen-carrying blood substitutes, and intraoperative cell salvage are some of the alternatives to blood transfusion. Despite the hazards of transfusions, obstetricians frequently transfuse blood and blood products to their patients in an excessively aggressive manner. Placenta praevia, postpartum blood loss, and surgery-related acute blood loss are the most common causes of acute blood loss in obstetrics. A consultant obstetrician, anaesthetist, haematologist, and the blood bank must be involved as soon as possible. There are no set guidelines for when red cell transfusions should be started, and the decision is solely based on clinical and haematological factors (Nigam et al., 2013).

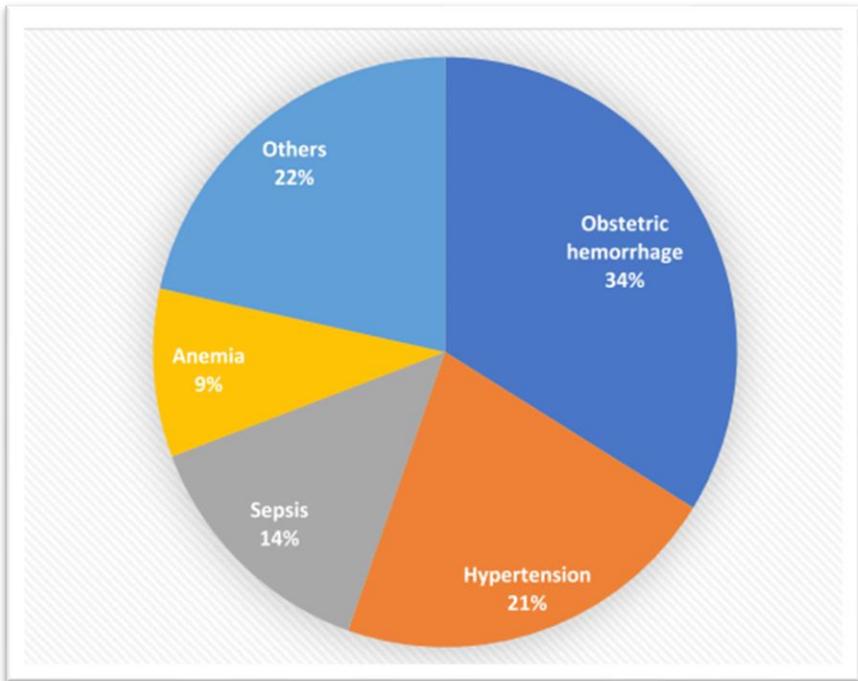


Fig 1. Primary causes of maternal mortality (Sitaula et al., 2021)

Obstetric haemorrhage, particularly postpartum haemorrhage, is still a leading cause of significant bleeding and maternal mortality. Due to physiological changes and comorbid diseases, assessing blood loss and determining the proper demand is difficult during pregnancy. Many parameters have been used to determine the need for blood and its components, as well as the transfusion of blood and its components. In order to generate practice guidelines, infrastructure, economic, social, and religious constraints in blood banking and donation must be addressed. Because of changes in maternal physiology, the possibility of alloimmunization, and infections in the foetus, transfusion in obstetric patients is difficult. While there are both emergent and non-emergent indications for transfusion in obstetrics, the foundation of transfusion practice is that it should be appropriate, that is, not provided when not needed and not ignored when needed (Jadon & Bagai, 2014).

2. Physiological changes in pregnancy

With the typical blood loss after delivery, a rise in red cell mass (20-30%) and a disproportionately larger increase in plasma volume (50%) helps the patient stay haemodynamically stable. Increased fibrinogen and factors VII, VIII, and IX, as well as an increase in the natural anticoagulants Protein A, Protein C, and Antithrombin III, prevail in pregnancy, resulting in a hypercoagulable state. The activity of the fibrinolytic system reduces. Plasminogen levels rise, while plasminogen inhibitor type II levels rise in tandem, dampening its activity. The fall in platelet levels, known as gestational thrombocytopenia, is an exception to the typical increase in coagulation factors (Jadon & Bagai, 2014).

Massive obstetric bleeding necessitates immediate red blood cell and coagulation factor transfusions. Because the pathophysiology of major obstetric hemorrhage is so varied, the shock index alone may not be enough to determine blood transfusion. Between January 1, 2009, and July 31, 2011, Era et al. (2015) evaluated the records of 80 emergency referral patients who got blood transfusions at our hospital. In patients with dilutional coagulopathy, the shock index exhibited a significant positive association with blood transfusion volume for red blood cell concentrate and fresh frozen plasma, but a higher correlation was detected with fibrinogen level and JSOG DIC score (Japan Society of Obstetrics and Gynecology disseminated intravascular coagulation score). The strongest correlations in patients with consumptive coagulopathy were seen between red blood cell concentrate transfusion volume and fibrinogen level, followed by fresh frozen plasma transfusion volume and JSOG DIC score, then fibrinogen level. Only fibrinogen level was found to be substantially linked with both red blood cell concentrate and fresh frozen plasma massive transfusion in multivariate analysis. The fibrinogen level was the strongest predictor of the requirement for blood transfusion following a large maternal hemorrhage among shock indicators (Era et al., 2015).

In surgical patients, blood transfusion is thought to be immunosuppressive. Maternal age, gestational age, preterm labor, and artificial delivery were all risk factors for blood transfusion. Blood transfusion is linked to a broad suppression of Th cells as well as an enhanced IL-10 response. The findings reveal that blood transfusion is associated to immunomodulation in obstetric haemorrhage patients,

implying that more strict blood transfusion criteria should be considered in obstetric haemorrhage patients (Jiao & Zheng, 2019).

Indications of blood transfusion in obstetrics are 1) Anaemia of pregnancy and haemoglobinopathies. 2) Obstetric haemorrhage. 3) Surgeries where significant blood loss is expected. The need for a transfusion is avoided when anemia is treated early, and maternal mortality is reduced. Transfusion should not be decided solely on the basis of haemoglobin estimation, as healthy and clinically stable women do not need blood transfusions even if their Hb is less than 7 g/dl. To summarize, if Hb is less than 6 g/dl and birth is expected in four weeks, transfusion is required. When Hb is less than 7 g/dl during labor or the postpartum period, blood transfusion is only recommended if the patient has a history of bleeding or is at risk of bleeding owing to a medical condition (Jadon & Bagai, 2014).

3. Risks

Despite significant improvements in the safety of the blood supply, there are still infectious and noninfectious dangers to the patient. Noninfectious transfusion reactions are more common than infectious transfusion consequences (Lavoie, 2011). A structured approach to the adoption of a quality management system is required for the effective establishment and maintenance of satisfactory standards in pre-transfusion testing. Missed incompatibilities and immediate or delayed haemolytic transfusion responses can come from technical errors, clerical errors, the use of non-validated techniques or equipment, and non-compliance with established procedures (Stainsby et al., 2006).

The majority of serious adverse effects are caused by acute blood transfusion responses. A better prognosis can be achieved by being aware of the numerous clinical signs of acute and delayed transfusion responses, as well as the capacity to detect significant reactions quickly. Evidence-based medicine has revolutionized the clinical practice landscape today in order to reduce harmful transfusion reactions. Recognizing unpleasant outcomes when under anaesthesia is always difficult. Unnecessary blood transfusions can be avoided using better blood conservation procedures during surgery and reduced blood loss anaesthetic techniques. Infectious problems have been reduced to nearly non-existent levels due to improved and newer blood screening procedures. Most non-infectious problems can be prevented by universal leukoreduction of red blood cells, selection of potential donors

such as using only male donors' plasma, and restriction of red blood cell storage (Sahu & Hemlata, 2014). Blood transfusion is a life-saving procedure in some obstetric and gynecological situations, however it comes with the danger of a transfusion reaction and infection transmission. For the safety of the patients, proper usage of blood and blood products is essential (Chowdhury et al., 2016).

In order to assess and update blood transfusion practices, audit and education are required. Despite the existence of established recommendations on the appropriate use of blood components, erroneous usage of blood components without justification continues (Kandasamy et al., 2020).

Using high-quality national monitoring data from China's National Maternal Near Miss Surveillance System, Xie et al., (2021) screened for the incidence, trends, risk factors, and primary reasons for obstetric massive blood transfusion, as well as the outcomes following obstetric massive blood transfusion. The transfusion of 5 units of red blood cells or 1000 mL of whole blood was regarded as a massive blood transfusion. Large blood transfusion cases per 10,000 pregnancies were used to calculate the incidence of massive blood transfusion. Obstetric massive blood transfusion occurred in 27 626 cases, equating to a rate of 23.68 per 10,000 births in China from 2012 to 2019 (14.03–29.59 per 10,000 births, p for trend 0.001). From a biological standpoint, amniotic fluid embolism, uterine atony, abnormal placenta, severe anemia, ectopic pregnancy, abortion, caesarean section, advanced mother age, and multiparous were all linked to obstetric large blood transfusion. While uterine atony, severe anemia, and placenta previa are the top three complications that lead to obstetric massive blood transfusion in the Chinese population, uterine atony, severe anemia, and placenta previa are the top three complications that lead to obstetric massive blood transfusion in the Chinese population. Overall, the secular trends of hysterectomy incidence (25.07 percent –9.92 percent) and MMR during hospitalization (21.41–7.48) among women who received major blood transfusions were decreasing. Researchers concluded that more attention should be paid to education on the importance of the antenatal visit, evidence-based transfusion practice, and females who are multiparous and have advanced age, amniotic fluid embolism, uterine atony, severe anemia, and placenta previa to reduce the incidence of obstetric massive blood transfusion.

The capacity to anticipate risk variables for blood transfusion following postpartum hemorrhage could improve the effectiveness of life-saving interventions in postpartum hemorrhage patients. Xing et al. (2019) looked at risk factors and developed a rating system for blood transfusion risk in obstetric patients. The data of 14,112 women who gave birth between January 1, 2015, and December 31, 2015, was evaluated. A total of 392 (2.9%) of the 13,328 patients had blood transfusions. Polyembryony, thrombocytopenia, anemia, placenta preeclampsia, previa, uterine scarring, placental implantation, uterine rupture, stillbirth, retained placenta, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) were all found to be significantly associated to perinatal transfusion after multivariable adjustment. Transfusion risk was not linked to heart disease or hemophilia.

A thorough understanding of blood and blood product transfusion is required to make it available to those who are truly in need while also reducing the financial burden. The physicians' compliance with blood transfusion standards determines the appropriateness of blood and blood products use. Anemia, followed by maternal hemorrhage, is still a common reason for blood and blood product transfusions. Anemia prevention measures should be implemented. Obstetric hemorrhage is a life-threatening emergency that cannot always be avoided or avoided. It is necessary to establish several techniques to avoid transfusion responses (Madhushree et al., 2018).

Gulucu and Uzun (2022) studied obstetric patients who received blood transfusions at a gynecology and obstetrics clinic. The study comprised obstetric patients who had a blood transfusion during the peripartum phase. There were a total of 213 individuals that required blood transfusions. Patients who gave birth in our clinic had a 2.5 percent overall blood transfusion rate. The most common indications for blood transfusion in the patients included in the study were uterine atony (50.7%) and chronic anemia (32.9%). All transfusion patients had a prenatal Hb of 9.8 and a postpartum Hb of 8.2. The pre-transfusion mean Hb, RBC, Hct, and Plt values were 7, 3.9, 30.3, and 245.2, respectively, while the post-transfusion mean Hb, RBC, Hct, and Plt values were 9, 3.52, 27.5, and 215.1, respectively. The profit-loss relationship should be customized and explicitly illustrated before it is applied to the patient, according to the researchers, due to blood replacement, supply challenges, and transfusion complications.

Staying up to date on current guidelines for pharmacological, hematological, and surgical interventions, as well as having an active blood transfusion center in the healthcare provider, is critical in reducing maternal mortality and morbidity rates in unpredictable obstetric situations that cause bleeding.

Pregnancy poses a unique difficulty since immunological responses differ between pregnant and non-pregnant women. Regular prenatal checks should be prioritized in order to maximize hemoglobin levels at the time of delivery and to identify high-risk patients. To limit blood loss, active management of the third stage of labor is essential (Shridevi & Patil, 2019).

4. Assessment of blood loss

Assessment of blood loss by vital signs monitoring is unreliable in pregnancy, due to the increased maternal plasma volume. The high cardiac output and relative haemodilution allow for a substantial volume of blood loss in a pregnant woman before hypotension and a drop in haemoglobin/haematocrit occur. The examination could also be a farce, since huge volumes of blood loss could be hidden in the uterine cavity. Preeclampsia, thrombocytopenia, and the HELLP syndrome are all comorbid diseases that can cause catastrophic bleeding. While the hypercoagulable state of pregnancy helps to prevent blood loss, it also puts the mother at risk for pulmonary embolism and disseminated intravascular coagulopathy. In order to prevent infections and avoid Haemolytic Disease of the Foetus and Newborn in current and future pregnancies, the foetus must be kept in mind while addressing acute haemorrhagic situations (Jadon & Bagai, 2014).

The need for blood transfusion in obstetrics and gynecology has decreased as a result of new pharmacological medications and surgical developments compared to the past. Previously, the most prevalent reason for blood transfusion was obstetrical bleeding. This pattern appears to be shifting (Singh et al., 2018).

Literatures

- Anjali, K., Varsha, K., Sulabha, J., Anuja, B., Bhavana, K., & Savita, S. (2015). Blood transfusion in Obstetrics and Gynaecology: A retrospective analysis. *Panacea J Med Sci*, 5(3), 109-12.
- Chowdhury, F., Akhter, S., Islam, A., Rayen, J., Begum, N., & Begum, F. (2016). Evaluation of blood transfusion practices in obstetrics and gynecology in a tertiary hospital in Bangladesh. *Journal of Bangladesh College of Physicians and Surgeons*, 34(1), 9-14.
- Era, S., Matsunaga, S., Matsumura, H., Murayama, Y., Takai, Y., & Seki, H. (2015). Usefulness of shock indicators for determining the need for blood transfusion after massive obstetric hemorrhage. *Journal of Obstetrics and Gynaecology Research*, 41(1), 39-43.
- Gulucu, S., & Uzun, K. E. (2022). Evaluation of blood transfusion rate in obstetric patients. *Ginekologia Polska*. DOI: 10.5603/GP.a2021.0261
- Jadon, A., & Bagai, R. (2014). Blood transfusion practices in obstetric anaesthesia. *Indian journal of anaesthesia*, 58(5), 629.
- Jiao, C., & Zheng, L. (2019). Blood transfusion-related immunomodulation in patients with major obstetric haemorrhage. *Vox Sanguinis*, 114(8), 861-868.
- Kandasamy, D., Selvarajan, A. K., & Jeyakumar, J. D. (2020). Outcome of audit and education on blood transfusion practice in obstetrics setting. *Hematology, Transfusion and Cell Therapy*.
- Lavoie, J. (2011). Blood transfusion risks and alternative strategies in pediatric patients. *Pediatric Anesthesia*, 21(1), 14-24.
- Learoyd, P. (2012). The history of blood transfusion prior to the 20th century—part 1. *Transfusion Medicine*, 22(5), 308-314.
- Madhushree, D., Metgud, M. C., & Patil, K. (2018). Retrospective analysis of all patients undergoing blood transfusion in obstetrics at a Tertiary Care Hospital, Belgaum: A cross-sectional study. *Indian Journal of Health Sciences and Biomedical Research (KLEU)*, 11(2), 116.
- Nigam, A., Prakash, A., & Saxena, P. (2013). Blood transfusion in obstetrics. *Kathmandu University Medical Journal*, 11(4), 355-359.

- Rahman, A., Akhter, S., Nisha, M. K., Islam, S. S., Ashraf, F., Rahman, M., ... & Anwar, I. (2017). Can mHealth improve access to safe blood for transfusion during obstetric emergency?. *International journal of women's health*, 9, 235.
- Reshma, L., & Sreelatha, S. (2019). Role of blood transfusion in obstetrics. *Tropical Journal of Obstetrics and Gynaecology*, 36(3), 330.
- Sahu, S., & Hemlata, A. V. (2014). Adverse events related to blood transfusion. *Indian journal of anaesthesia*, 58(5), 543.
- Say, L., Chou, D., Gemmill, A., Tunçalp, Ö., Moller, A. B., Daniels, J., ... & Alkema, L. (2014). Global causes of maternal death: a WHO systematic analysis. *The Lancet global health*, 2(6), e323-e333.
- Schantz-Dunn, J., & Nawal, M. (2011). The use of blood in obstetrics and gynecology in the developing world. *Reviews in obstetrics and gynecology*, 4(2), 86.
- Shridevi, A. S., & Patil, G. L. (2019). Blood transfusion needs among obstetric patients in a tertiary care hospital: a prospective observational study. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 8(11), 4244-4250.
- Singh, R. K., Anne, S., & Ravindran, S. P. (2018). Changing trends of blood transfusion requirement in obstetrics and gynaecology. *Int J Reprod Contracept Obstet Gynecol*, 7, 2018-22.
- Sitaula, S., Basnet, T., Agrawal, A., Manandhar, T., Das, D., & Shrestha, P. (2021). Prevalence and risk factors for maternal mortality at a tertiary care centre in Eastern Nepal-retrospective cross sectional study. *BMC Pregnancy and Childbirth*, 21(1), 1-8.
- Stainsby, D., Jones, H., Asher, D., Atterbury, C., Boncinelli, A., Brant, L., ... & Cohen, H. (2006). Serious hazards of transfusion: a decade of hemovigilance in the UK. *Transfusion medicine reviews*, 20(4), 273-282.
- Vasava, D. C., Thaker, R. V., Tyagi, A. A., & Patel, F. P. (2020). Analysis of transfusion of blood and blood products and their utilization pattern at department of obstetrics of tertiary care hospital. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 9(1), 261-266.

- Xie, Y., Liang, J., Mu, Y., Liu, Z., Wang, Y., Dai, L., ... & Wang, X. (2021). Incidence, trends and risk factors for obstetric massive blood transfusion in China from 2012 to 2019: an observational study. *BMJ open*, 11(9), e047983.
- Xing, Z., He, Y., Ji, C., Xu, C., Zhang, W., Li, Y., ... & Zheng, L. (2019). Establishing a perinatal red blood cell transfusion risk evaluation model for obstetric patients: a retrospective cohort study. *Transfusion*, 59(5), 1667-1674.
- Yılmaz, M. (xxx). Postpartum kanamalar. *Bölüm* 29:341-351.
- Zdanowicz, J. A., Schneider, S., Mueller, M., Tschudi, R., & Surbek, D. (2021). Red blood cell transfusion in obstetrics and its implication for patient blood management: a retrospective analysis in Switzerland from 1998 to 2016. *Archives of gynecology and obstetrics*, 303(1), 121-128.

CHAPTER 20

ALLOIMMUNIZATION IN PREGNANCY: A REVIEW

Dr. Gülsüm DOĞAN¹

¹ Siirt training and research hospital, obstetrics and gynecology department Siirt, Turkey ORCID ID: 0000-0003-2836-1302
Corresponding author: glsmdgn214@gmail.com

1. Introduction

Despite major advances in the production, storage, and transfusion of platelet products, transfusion refractoriness remains a significant clinical concern, affecting up to 14% of hematological patients getting platelet transfusions. Leukoreduction can greatly reduce the rate of human leukocyte antigen alloimmunization, which is a key cause of immunological platelet refractoriness. Pathogen reduction does not reduce human leukocyte antigen alloimmunization, despite encouraging preclinical data. Human leukocyte antigen-selected platelet transfusions are usually used to treat patients with alloimmune refractoriness to human leukocyte antigen. Low human leukocyte antigen expression or human leukocyte antigen-universal platelets are two future approaches for preventing and treating human leukocyte antigen alloimmune refractoriness (Saris & Pavenski, 2020).

Transfusion of red blood cells is essential for addressing acute and chronic difficulties in sickle cell disease; nevertheless, it is complicated by alloimmunization of red blood cells, iron overload, transfusion responses, and infection. Several studies have found an increased incidence of alloantibodies in sickle cell disease patients who have been transfused, particularly for the Rh and Kell antigens. As a result, the National Institutes of Health Expert Panel and British Society for Haematology guidelines for red blood cell transplants advocate primary matching for C/c, E/e, and K antigens in addition to ABO/RhD. The evidence for these recommendations, however, was regarded as insufficient, and our understanding of alloimmunization in sickle cell disease is still developing (Fasano et al., 2019).

2. Pregnancy

During pregnancy, alloimmunization, also known as isoimmunization, occurs when the mother produces IgG antibodies against paternally inherited antigens in the foetus/newborn. Due to the production of maternal alloantibodies against the red blood cell antigen, neutrophils, and platelets cell antigens during pregnancy, various alloimmune disorders such as haemolytic disease of the foetus and newborn (HDFN), neonatal alloimmune neutropenia, and foetal and neonatal alloimmune thrombocytopenia occur. Recent research suggests that, in addition to antibodies against platelet antigens, maternal anti-HLA (anti-human leukocyte antigen) class I alloantibodies may be the cause of foetal and neonatal alloimmune

thrombocytopenia. On the contrary, research have shown that HLA-C, a classical HLA class I molecule, and HLA-G, a nonclassical HLA molecule, play essential roles in placentation and maternal immune system modulation throughout pregnancy, resulting in acceptance of the semi allogeneic fetus. So far, the majority of studies have focused on alloimmunization in pregnancy as it relates to the Rh antigen (Singh et al., 2019). Red blood cell alloantibodies have been associated to considerable perinatal morbidity and mortality in pregnant women (Ngoma et al., 2016).

The incompatibility of maternal and fetal erythrocytes causes haemolytic disease of the fetus and newborn (HDFN). Alloimmunization of red blood cells is a well-known cause of HDFN. The range of alloimmunization differs around the world due to demographic variation. Despite prenatal and postnatal prevention, there is a substantial chance of D antigen sensitization in D negative women. Regardless of rhesus type, all pregnant women should be tested for abnormal antibodies (Karim et al., 2015). Physicians caring for women of childbearing age face a difficulty when it comes to alloimmunization to red blood cell antigens. Antibodies can develop as a result of exposure to non-self red blood cell antigens during transfusion during pregnancy. If the antigen is carried by a future pregnancy, maternal antibodies may assault the fetal red blood cells, resulting in red cell loss and clinically severe HDFN. HDFN can cause intrauterine fetal death due to high output cardiac failure, effusions, and ascites, a condition known as "hydrops fetalis." Once a mother has been diagnosed with a clinically significant red blood cell alloantibody, serial antibody titers and ultrasounds of the fetus's middle cerebral artery are utilized to determine whether in-utero transfusions are necessary (Webb & Delaney, 2018).

Anti-D is still the most powerful HDFN antibody (Scheffer et al., 2011). However, the widespread use of rhesus (Rh)-D immunoglobulin - "rhogam" - to protect against anti-D alloimmunization has resulted in an increase in alloimmunization due to antibodies against other red blood cells (ACOG, 2006) Minor red blood cell antibodies are divided into 29 systems, including Kell (K, k, Jsa, Jsb), Rh (C, c, Cw, E, e), Duffy (Fya, Fyb), and Kidd (Jka, Jkb), among others (Koelewijn et al., 2009). Anti-kell antibodies have been linked to severe anemia, hydrops fetalis, and fetal mortality in the past. Furthermore, regardless of antibody titer, anti-kell antibody can cause severe anemia due to its ability to inhibit bone marrow as well as destroy red blood cells (Van Wamelen et al., 2007). In the vast majority of patients, anti-

kell, anti-c, and to a lesser extent other Rh antibodies (C, Cw, E, e) produce severe HDFN (Scheffer et al., 2011).

Though whole blood and its components are an important element of modern medicine, they come with hazards, one of which is the development of antibodies against one or more erythrocyte antigens when exposed to the antigen through transfusion, pregnancy, or transplantation. Alloimmunization (owing to genetic differences in donor-recipient or mother-fetus RBC antigen) is extremely difficult and severely restricts the utility of transfusion. As a result, pregnant women should be screened for clinically significant antibodies (Sultana et al., 2022).

Rh alloimmunization occurs during pregnancy when maternal red blood cells that lack the Rh antigen (RhD negative) are exposed to RhD positive red blood cells through the placenta, causing the maternal immune system to become activated. Sensitization is the development of antibodies against RhD positive blood cells as a result of this. Sensitization of the mother's blood occurs not just through the placenta, but also as a result of blood transfusions, miscarriage, and ectopic pregnancy, as well as procedures like amniocentesis. In the therapy of hemolytic illness of the fetus and infant, the identification of maternal alloimmunization against red cell antigens is critical (Al-Dughaishi et al., 2016).

Antibody screening should be considered for high-risk pregnancies and prenatal patients with a history of blood transfusion (Sankaralingam et al., 2016). For accurate detection of RhIG in pregnant women, proper classification of RhD phenotypes is recommended. However, due to differences in serologic testing, distinguishing between RhD-negative and RhD-positive phenotypes is challenging in the case of D variants (Bub et al., 2018).

Despite using anti-D immunoglobulin to prevent RhD alloimmunization in RhD negative women throughout pregnancy and after the birth of a RhD positive child, antigen RhD is still the second most common cause of maternal erythrocyte alloimmunization. Non-D antigens of the Rh system, antigens of the Kell system, and seldom seen antigens of the MNS and Kidd blood systems induce the remaining clinically significant alloimmunizations (Holuskova et al., 2013).

Hyperhemolytic Syndrome or Hyperhemolytic Transfusion Reaction (HHTR), a life-threatening subtype of Delayed Hemolytic Transfusion Reaction, is defined by the destruction of both transfused and autologous

erythrocytes, as shown by a drop in post-transfusion hemoglobin below pre-transfusion levels. Clinicians must have a high index of suspicion for HHTR, especially since the best treatments for prevention and treatment are still being developed. Early detection of HHTR, which leads to the discontinuation of future transfusions and the commencement of immunosuppressive treatment, can save lives, especially in clinical circumstances where therapeutic alternatives are limited, such as during pregnancy (Bezirgiannidou et al., 2016). Prenatal diagnosis of alloimmunization is the perfect example of constructive effort by a diagnosis in order to identify cases in need of therapy to decrease morbidity and increase survival with the least number of invasive procedures and reducing the risks associated with them prior to the onset of immunoglobulin antiD, many of the fetuses of mothers negative for the antigen "D" developing severe disease, history of prenatal diagnosis of alloimmunization is the perfect example of constructive effort by a diagnosis (Lambertino & Villegas, 2014).

During pregnancy, alloimmunization from blood transfusions, transplants, or circulating fetal cells is a major problem. Some people who have been exposed to a substance produce alloantibodies, while others do not, showing that genetic risk factors differ (Seielstad et al., 2018).

3. Biologic mechanisms

During pregnancy, tissue antigens from the fetus and/or placenta prime maternal immune cells to divide and differentiate, resulting in alloimmunization. Pregnancy alloimmunization causes the production of anti-HLA antibodies in many women, which can last for decades and prevent transplantation by restricting donor compatibility. Memory B cells that can rapidly develop anti-HLA antibodies after transplantation, as well as pathogenic memory T cells, may be generated by pregnancy alloimmunization, posing a hazard to graft survival. However, new evidence suggests that pregnancy also affects the development of anergic, malfunctioning, and regulatory T cells, which may or may not be involved in increased graft rejection. As a result, some of the immunological processes involved in maternal immunologic tolerance of the fetus may survive afterwards and influence the allograft response (Porrett, 2018).

Pregnancy demands physiological exposure to foreign fetal alloantigens, as well as frequent re-exposure. There is evidence of both

alloimmunization and increased tolerance phenotypes in the after of pregnancy. The increase of fetal-specific maternal CD8+ T lymphocytes during pregnancy and their maintenance as an active memory pool after parturition are primed by pregnancy. Antigen re-encounter in non-reproductive situations causes cytolysis and the potential for vigorous secondary growth. In contrast, fetal antigen re-stimulation during later pregnancy causes CD8+ T cell functional exhaustion, which is associated with elevated PD-1 and LAG-3 expression. Neutralization of PD-L1/LAG-3 activates fetal-specific CD8+ T lymphocytes, resulting in fetal wastage during secondary but not main pregnancy. Thus, CD8+ T lymphocytes with fetal alloantigen specificity survive in mothers after pregnancy, and their unique susceptibility to functional exhaustion maintains protection against fetal wasting in subsequent pregnancies (Kinder et al., 2020).

4. Management and prevention

To assess the paternal RHD zygosity more accurately, quantitative polymerase chain reaction can be employed instead of serology. In cases when the paternal RHD genotype is unknown or heterozygous, modern DNA techniques can now determine the fetal blood type using cell-free fetal DNA in maternal plasma. Serial Doppler assessment of the middle cerebral artery's peak systolic velocity has become the gold standard for detecting fetal anemia and determining the need for the first intrauterine transfusion. The peak systolic velocity in the middle cerebral artery can be utilized to time the second transfusion, but its application in determining when to execute following treatments requires more research. According to new research, intrauterine transfusion results in a normal neurologic outcome in 94% of cases, while severe hydrops fetalis may be linked to a higher risk of disability. On the horizon is recombinant Rh immune globulin. In the future, cell-free fetal DNA genotyping for fetal RHD genotyping could be used to determine whether patients should get antenatal Rh immune globulin (Moise Jr & Argoti, 2012).

Maternal red blood cell alloimmunization is the most common cause of fetal anemia. The use of an indirect antiglobulin test to look for maternal antibodies allows for AI screening during pregnancy. Fetal genotyping (for Rh-D, Rh-c, Rh-E, and Kell), quantification (for anti-rhesus antibodies), and antibody titration, as well as ultrasound surveillance, are all undertaken in the context of alloimmunization (Ghesquiere et al., 2018). Alloimmunization

of red blood cells during pregnancy is still a big issue. Antibodies to D have historically been the most common cause of severe hemolysis, but other antibodies are also relevant. Anti-D was the most strongly related with severe hemolysis, necessitating phototherapy or exchange transfusions, of all clinically significant antibodies (Bollason et al., 2017).

The most common cause of prenatal and neonatal anemia is red blood cell alloimmunization. In the second and third trimesters of pregnancy, alloimmunizations with anti-PP1Pk or anti-P may result in recurrent miscarriages and hemolytic illness of the fetus and newborn. The physiopathology and precocity of vaccinations against P and PP1Pk antigens differ from those against other antigens. PE in combination with IVIg appears to be an effective treatment for anti-PP1Pk or anti-P fetomaternal incompatibility (Lepine et al., 2021). An increased chance of alloimmunization is linked to a mother's history of intravenous drug consumption. During pregnancy, one out of every 30 intravenous drug abusers may be diagnosed with an alloantibody. Needle-sharing is one plausible mechanism for intravenous drug abuse–related alloimmunization; however, other factors such as poor obstetric care, a lack of Rh immunoglobulin, or a failure to recognize early pregnancy loss cannot be ruled out (Lappen et al., 2016).

Over the last few decades, the market for therapeutic plasma products has grown significantly. Antihemophilic factors, intravenous immune globulin, albumin, plasma protein fraction, hyperimmune globulins, and other speciality products are among these. With the expansion of this industry, health organizations have progressively shifted responsibility for product management from the blood bank or physician's office to the pharmacy. RhIG is a human plasma derivative that targets RhO-positive red blood cells (also called D antigen). The widespread use of RhIG in the United States and other countries has significantly reduced the occurrence of hemolytic disease of the fetus and newborn (HDFN), a devastating condition caused by D-antigen sensitization of a pregnant woman via exposure to fetal red blood cells (usually during placental detachment during labor) that results in a maternal immune response that leads to severe hemolysis in the fetus. Routine RhIG administration between 26 and 30 weeks of pregnancy and again within 72 hours of delivery has been shown to be highly effective in preventing maternal Rh alloimmunization, with very low rates of D-antigen sensitization (ranging from 0 to 2.2 percent) reported in multiple

studies of at-risk women. The four RhIG medicines now on the market in the United States have similar clinical indications but differ in some ways. Pharmacists can help other doctors understand the rationale for using RhIG, the key distinctions between products, and the best time to start RhIG therapy. Routine RhIG therapy to women at risk of Rh alloimmunization has proven to be clinically efficacious, making HDFN a rare clinical occurrence. The RhIG products on the market are not all the same, and they should be thoroughly examined to verify that they are administered safely (Aitken & Tichy 2015).

Because blood cells are not particularly immunogenic, transfusion only causes antibody formation on rare occasions. Alloimmunization against red blood cells, platelets, and/or leukocytes is more likely during pregnancy due to immunological changes. Antigenic stimuli for immunization against red blood cells are fetal-maternal hemorrhage during pregnancy or in relation to birth, but other mechanisms, such as trophoblast-derived microparticles, may also play a role in the generation of antibodies against platelets. Antibody-mediated immune suppression has been successfully utilized to prevent RhD vaccination for over four decades. The results of a mouse model of fetal and neonatal alloimmune thrombocytopenia (FNAIT) indicate that the same concept could be used to prevent FNAIT. A consortium supported by the European Union is currently working on a hyperimmune anti-human platelet antigen 1a (HPA-1a) immunoglobulin G. The goal is to give the drug to nonimmunized HPA-1a-negative mothers after they give birth to an HPA-1a-positive child to prevent HPA-1a immunization. Plasma from women who have previously given birth to a child with FNAIT caused by anti-HPA-1a will be utilized to purify the anti-HPA-1a. It's feasible that a treatment to prevent FNAIT will be accessible within this decade if the findings of the planned phase III trial are positive (Kjeldsen-Kragh & Skogen, 2013).

Due to the rarity and mildness of fetal/newborn hemolytic syndrome caused by Jra immunization, only regular obstetrical care is suggested for pregnant women exposed to the Jra antigen. Even in pregnant women exposed to some antigens for which only regular obstetrical care is suggested, PSV-MCA (peak systolic velocity of the fetal middle cerebral artery) should be examined for the diagnosis of fetal anemia (Masumoto et al., 2010).

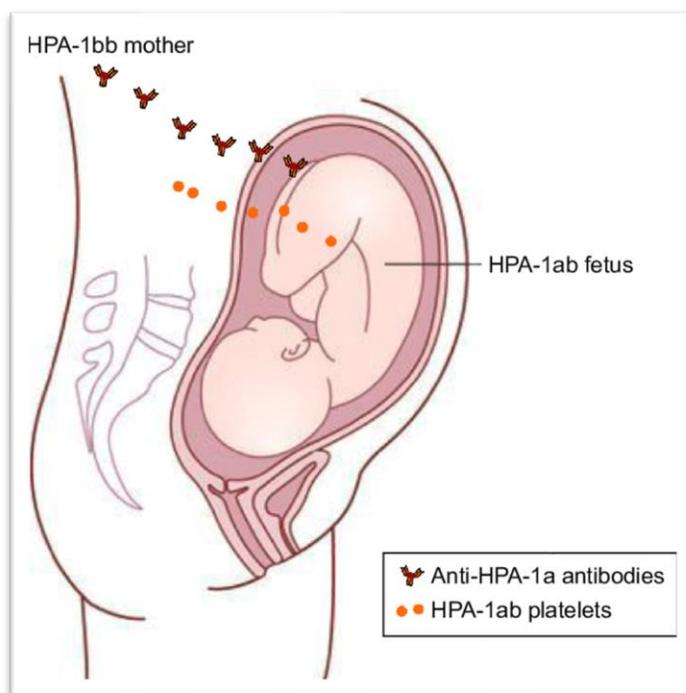


Fig. 1. Pathophysiology of HPA-1 alloimmunization in mothers. Notes: Fetal platelets/fetal platelet antigen may enter the maternal blood in an HPA-1bb mother who is pregnant with an HPA-1ab fetus, causing the mother to produce anti-HPA-1a antibodies (Tiller et al., 2017).

Rhesus and Kell antigen antibodies have been linked to severe hemolytic illness of the fetus and newborn (HDFN), which necessitates intrauterine red blood cell transfusion. Early in pregnancy, a combination of therapeutic plasma exchange and intravenous immune globulin, followed by intrauterine transfusion later in pregnancy, is effective in managing severe maternal red blood cell alloimmunization and HDFN. In difficult cases of HDFN, intrauterine transfusion with entirely phenotypically matched red blood cell units may assist prevent future red blood cell alloimmunization (Nwogu et al., 2018).

Antibodies against red blood cells Antigen for Rhesus D (RhD) can be produced during pregnancy in a RhD-negative woman carrying a RhD-positive fetus, especially after a fetomaternal haemorrhage during delivery or any surgery that could cause fetomaternal haemorrhage. While the first baby

is normally unaffected, subsequent RhD-positive newborns may develop haemolytic disease of the fetus/newborn (HDFN). Incompatibility with RhD is one of the most common causes of HDFN. Anti-D is given to RhD-negative mothers at 28 or 30 weeks of pregnancy, and within 72 hours of potential maternal exposure to fetal red cells, to reduce the risk of HDFN. Intramuscular and intravenous formulations of AnitD are currently available. Okwundu and Afolabi (2013) investigated the efficacy and effectiveness of intramuscular anti-D IgG vs. intravenous anti-D IgG in preventing RhD alloimmunization in RhD-negative pregnant women. Anti-D was equally efficacious when administered intramuscularly and intravenously. Anti-D injections can be given intramuscularly or intravenously. The available preparations, the dose to be provided, and the patients' preferences will all influence whether intramuscular or intravenous administration is chosen.

Literatures

- ACOG. (2006). American College of Obstetricians and Gynecologists Practice Bulletin No. 75: Management of alloimmunization during pregnancy. *Obstetrics and gynecology*, 108(2), 457-464.
- Aitken, S. L., & Tichy, E. M. (2015). RhOD immune globulin products for prevention of alloimmunization during pregnancy. *American Journal of Health-System Pharmacy*, 72(4), 267-276.
- Al-Dughaiishi, T., Al Harrasi, Y., Al-Duhli, M., Al-Rubkhi, I., Al-Riyami, N., Al-Riyami, A. Z., ... & Gowri, V. (2016). Red cell alloimmunization to Rhesus antigen among pregnant women attending a tertiary care hospital in Oman. *Oman medical journal*, 31(1), 77.
- Bezirgiannidou, Z., Christoforidou, A., Kontekaki, E., Anastasiadis, A. G., Papamichos, S. I., Menexidou, H., ... & Mantadakis, E. (2016). Hyperhemolytic Syndrome complicating a delayed hemolytic transfusion reaction due to anti-P1 alloimmunization, in a pregnant woman with HbO-Arab/ β -thalassemia. *Mediterranean Journal of Hematology and Infectious Diseases*, 8(1).
- Bollason, G., Hjartardottir, H., Jonsson, T., Gudmundsson, S., Kjartansson, S., & Halldorsdottir, A. M. (2017). Red blood cell alloimmunization in pregnancy during the years 1996-2015 in Iceland: a nation-wide population study. *Transfusion*, 57(11), 2578-2585.
- Bub, C. B., Aravechia, M. G., Costa, T. H., Kutner, J. M., & Castilho, L. (2018). RHD alleles among pregnant women with serologic discrepant weak D phenotypes from a multiethnic population and risk of alloimmunization. *Journal of Clinical Laboratory Analysis*, 32(1), e22221.
- Fasano, R. M., Meyer, E. K., Branscomb, J., White, M. S., Gibson, R. W., & Eckman, J. R. (2019). Impact of red blood cell antigen matching on alloimmunization and transfusion complications in patients with sickle cell disease: a systematic review. *Transfusion Medicine Reviews*, 33(1), 12-23.
- Ghesquiere, L., Garabedian, C., Coulon, C., Verpillat, P., Rakza, T., Wibaut, B., ... & Debarge, V. (2018). Management of red blood cell alloimmunization in

- pregnancy. *Journal of Gynecology Obstetrics and Human Reproduction*, 47(5), 197-204.
- Holuskova, I., Lubušký, M., Studničková, M., & Prochazka, M. (2013). Incidence of erythrocyte alloimmunization in pregnant women in olomouc region. *Ceska gynekologie*, 78(1), 56-61.
- Karim, F., Moiz, B., & Kamran, N. (2015). Risk of maternal alloimmunization in Southern Pakistan—A study in a cohort of 1000 pregnant women. *Transfusion and Apheresis Science*, 52(1), 99-102.
- Kinder, J. M., Turner, L. H., Stelzer, I. A., Miller-Handley, H., Burg, A., Shao, T. Y., ... & Way, S. S. (2020). CD8+ T cell functional exhaustion overrides pregnancy-induced fetal antigen alloimmunization. *Cell reports*, 31(12), 107784.
- Kjeldsen-Kragh, J., & Skogen, B. (2013). Mechanisms and prevention of alloimmunization in pregnancy. *Obstetrical & Gynecological Survey*, 68(7), 526-532.
- Koelewijn, J. M., Vrijkotte, T. G. M., de Haas, M., Van Der Schoot, C. E., & Bonsel, G. J. (2009). Risk factors for the presence of non-rhesus D red blood cell antibodies in pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology*, 116(5), 655-664.
- Lambertino, J. R., & Villegas, S. M. (2014). Rh alloimmunization in pregnant women, a look to diagnosis and therapeutic approach. *Ginecología y Obstetricia de México*, 82(11), 744-754.
- Lappen, J. R., Stark, S., Gibson, K. S., Prasad, M., & Bailit, J. L. (2016). Intravenous drug use is associated with alloimmunization in pregnancy. *American Journal of Obstetrics and Gynecology*, 215(3), 344-e1.
- Lepine, M. S., Goua, V., Debouverie, O. S., Giraud, C., Rafat, C., Thonier, V., ... & Maisonneuve, E. (2021). Multidisciplinary management of anti-PP1Pk or anti-P alloimmunization during pregnancy: A new case with anti-P and a literature review. *Transfusion*, 61(6), 1972-1979.

- Masumoto, A., Masuyama, H., Sumida, Y., Segawa, T., & Hiramatsu, Y. (2010). Successful management of anti-Jra alloimmunization in pregnancy: a case report. *Gynecologic and obstetric investigation*, 69(2), 81-83.
- Moise Jr, K. J., & Argoti, P. S. (2012). Management and prevention of red cell alloimmunization in pregnancy: a systematic review. *Obstetrics & Gynecology*, 120(5), 1132-1139.
- Ngoma, A. M., Mutombo, P. B., Ikeda, K., Nollet, K. E., Natukunda, B., & Ohto, H. (2016). A systematic review of red blood cell alloimmunization in pregnant women in Africa: time to do better. *ISBT Science Series*, 11(1), 62-69.
- Nwogu, L. C., Moise Jr, K. J., Klein, K. L., Tint, H., Castillo, B., & Bai, Y. (2018). Successful management of severe red blood cell alloimmunization in pregnancy with a combination of therapeutic plasma exchange, intravenous immune globulin, and intrauterine transfusion. *Transfusion*, 58(3), 677-684.
- Okwundu, C. I., & Afolabi, B. B. (2013). Intramuscular versus intravenous anti-D for preventing Rhesus alloimmunization during pregnancy. *Cochrane Database of Systematic Reviews*, (1).
- Porrett, P. M. (2018). Biologic mechanisms and clinical consequences of pregnancy alloimmunization. *American Journal of Transplantation*, 18(5), 1059-1067.
- Sankaralingam, P., Jain, A., Bagga, R., Kumar, P., & Marwaha, N. (2016). Red cell alloimmunization in RhD positive pregnant women and neonatal outcome. *Transfusion and Apheresis Science*, 55(1), 153-158.
- Saris, A., & Pavenski, K. (2020). Human leukocyte antigen alloimmunization and alloimmune platelet refractoriness. *Transfusion Medicine Reviews*, 34(4), 250-257.
- Scheffer, P. G., Van Der Schoot, C. E., Page-Christiaens, G. C. M. L., & De Haas, M. (2011). Noninvasive fetal blood group genotyping of rhesus D, c, E and of K in alloimmunised pregnant women: evaluation of a 7-year clinical experience. *BJOG: An International Journal of Obstetrics & Gynaecology*, 118(11), 1340-1348.
- Seielstad, M., Page, G. P., Gaddis, N., Lanteri, M., Lee, T. H., Kakaiya, R., ... & NHLBI REDS-III Study Investigators. (2018). Genomewide association

- study of HLA alloimmunization in previously pregnant blood donors. *Transfusion*, 58(2), 402-412.
- Singh, M., Rajak, J., Kadam, S., & Rajadhyaksha, S. B. (2019). Alloimmunization and Role of HLA in Pregnancy. *Complications of Pregnancy*.
- Sultana, A., Ujjan, I. D., Khan, M. S., Memon, K. A., Asif, R., & Noureen, A. (2022). Red Cell Alloimmunization in Multi-Transfused Pregnant Women. *Annals of the Romanian Society for Cell Biology*, 26(01), 196-206.
- Tiller, H., Husebekk, A., Ahlen, M. T., Stuge, T. B., & Skogen, B. (2017). Current perspectives on fetal and neonatal alloimmune thrombocytopenia—increasing clinical concerns and new treatment opportunities. *International journal of women's health*, 9, 223.
- Van Wamelen, D. J., Klumper, F. J., De Haas, M., Meerman, R. H., van Kamp, I. L., & Oepkes, D. (2007). Obstetric history and antibody titer in estimating severity of Kell alloimmunization in pregnancy. *Obstetrics & Gynecology*, 109(5), 1093-1098.
- Webb, J., & Delaney, M. (2018). Red blood cell alloimmunization in the pregnant patient. *Transfusion medicine reviews*, 32(4), 213-219.

CHAPTER 21

PLACENTA ACCRETA SPECTRUM

Dr. Sıtkı ÖZBİLGEÇ¹

¹ Necmettin Erbakan University, Meram Faculty of Medicine, Department of Gynecological Oncology, Konya, Turkey orcid no: 0000-0002-4776-4791 sozbilgec@yahoo.com

Introduction

Placental adhesion disorder that develops due to pathological invasion of placental trophoblasts to the myometrium, sometimes to uterine serosa and adjacent tissues is called Placenta accreta spectrum (PAS)(Belfort, 2010; Jauniaux, Chantraine, Silver, & Langhoff-Roos, 2018; Jauniaux, Collins, & Burton, 2018; Timor-Tritsch & Monteagudo, 2012). Since the placenta does not separate spontaneously in these patients, manual interventions to displace the placenta may cause severe bleeding. The pathogenesis of most instances of PAS is notion to be placental implantation at an area of faulty decidualization resulting from preexisting harm to the interface between the endometrium and the myometrium. The placenta previa following a previous cesarean delivery is the major risk factor for PAS.

Definitions

PAS is a wide term that refers to three distinct subtypes:

Placenta accreta:

The myometrium is attached to the anchoring placental villi rather than the decidua.

Placenta increta:

The myometrium is penetrated by anchoring placental villi.

Placenta percreta:

Through the myometrium, anchoring placental villi penetrate the uterine serosa or neighboring organs (Picture 1).

Picture 1



The International Federation of Gynecology and Obstetrics (FIGO) Expert Consensus Panel on Placenta Accreta Spectrum Disorders Diagnosis and Management developed a categorization system for PAS (Jauniaux, Ayres-de-Campos, Langhoff-Roos, Fox, & Collins, 2019):

- Grade 1- atypically adherent placenta: an adherent or Creta placenta
- Grade 2- unusually invasive placenta: increta
- Grade 3- unusually invasive placenta: percreta
- subtype 3a – occurs only in the uterine serosa

- subtype 3b – the invasion of the urine bladder
- subtype 3c – the invasion of other pelvic organs/tissues

Prevalence

In a 2019 comprehensive study, 7001 instances of PAS were identified among roughly 5.8 million births, resulting in an overall pooled prevalence of 0.17 percent.(Jauniaux, Bunce, Grønbeck, & Langhoff-Roos, 2019). Placenta accreta is substantially more prevalent than placenta increta and percreta. The forms and frequency of aberrant placentation were also determined in the same systematic study. (Jauniaux, Ayres-de-Campos, et al., 2019):

- **Placenta accreta** – 63%
- **Placenta increta** – 15%
- **Percreta percreta** – 22%

Pathogenesis

Although the pathophysiology of PAS is unknown with confidence, mounting evidence supports the hypothesis that PAS is caused by decidua and/or myometrium abnormalities. (Einerson et al., 2020). The first notion was that after surgery at the endometrial-myometrial interface, the faulty decidua in this location enabled the placental anchoring villi to connect directly to and/or invade the myometrium. (Khong, 2008; Tantbirojn, Crum, & Parast, 2008) More recently, the pathogenesis of uterine remodeling after scar formation has been implicated. (Jauniaux, Hussein, Elbarmelgy, Elbarmelgy, & Burton, 2022). Scar placentation increases the perfusion of the subplacental and intervillous circulations in this model, leading to the increasing fibrinoid deposition at the whole uteroplacental interface in this location. The thick fibrinoid deposition bends the Nitabuch membrane and is the primary cause of aberrant placental attachment at the scar site; this process occurs in the absence of villous implantation deep inside the myometrium underneath the accreta location.

The parameters that control the level of pathologic "invasion" (e.g., accreta vs increta versus percreta) are not well characterized, but they imply that a myometrial invasion of trophoblast does not occur. Large and deep myometrial abnormalities are often connected with the scar not reepithelializing normally(Ben-Nagi, Walker, Jurkovic, Yazbek, & Aplin,

2009). In certain instances, partial or total dehiscence of a uterine scar provides direct passage for extravillous trophoblast to the deeper myometrium, serosa, and beyond (Tantbirojn et al., 2008).

Clinical Features

Risk factors:

The primary risk factor for developing a PAS is placenta previa after a previous cesarean birth. In a prospective analysis of 723 women with placenta previa who had a cesarean birth, the prevalence of PAS grew in direct proportion to the number of cesarean deliveries (Silver et al., 2006):

- 3 percent of first (primary) cesarean births
- Cesarean birth for the second time, 11%
- Third cesarean delivery, 40%
- 61 percent of fourth cesarean births
- Cesarean birth for the fifth or subsequent time, 67 percent

Other risk factors include a history of uterine surgery (e.g., myomectomy into the uterine cavity, hysteroscopic removal of intrauterine adhesions, cornual resection of ectopic pregnancy, dilation and curettage, and endometrial ablation (Kohn et al., 2018), greater than 35 years of maternal age, multiparity, a history of pelvic irradiation, manual placenta removal, postpartum endometritis, infertility and/or infertility treatments (e.g., cryopreserved embryo transfer), and perhaps numerous gestations (Baldwin et al., 2018; Esh-Broder, Ariel, Abas-Bashir, Bdolah, & Celnikier, 2011; Fitzpatrick et al., 2012; Hayashi, Nakai, Satoh, & Matsuda, 2012; Kaser et al., 2015; Miller, Leonard, Fox, Carusi, & Lyell, 2021; Nageotte, 2014; Salmanian et al., 2020; Silver et al., 2015; Timor-Tritsch, Monteagudo, Cali, Vintzileos, et al., 2014).

Cesarean scar pregnancy has been regarded as a risk factor for PAS, however, given their identical histology, these two disorders may constitute a continuum of the same illness (Pekar-Zlotin et al., 2017; Timor-Tritsch, Monteagudo, Cali, Palacios-Jaraquemada, et al., 2014; Timor-Tritsch, Monteagudo, Cali, Vintzileos, et al., 2014).

Notably, the sex ratio linked with PAS is skewed toward female fetuses, in contrast to the typical sex ratio in the general population, which is skewed toward male fetuses. (James, 1995; Khong, Healy, & McCloud, 1991).

Clinical presentation:

In a perfect scenario, PAS would be suspected initially as a result of abnormalities on an obstetric ultrasound examination performed when the patient is asymptomatic. It is often detected during prenatal sonographic screening of women who have a previal placenta or a low anterior placenta and have had previous uterine surgery. In women with fewer obvious risk factors for aberrant placental attachment, it may be discovered incidentally during regular ultrasound evaluation, and occasionally the diagnosis is found only after placental delivery(Carusi et al., 2020).

The initial clinical sign of PAS is often extensive, life-threatening bleeding that occurs during manual placental separation attempts. In contrast to a simply retained placenta, a portion or the whole placenta stays securely connected to the uterine cavity, preventing the development of a plane of separation. If placental tissue has infiltrated the anterior serosa or bladder, severe bleeding may ensue during efforts to dissect the bladder away from the lower uterine tract.

However, in the situation of placenta previa, it may show as prenatal hemorrhage.

Possible laboratory findings:

- **Biomarkers:**

There is no clinical benefit biomarker. Although a high maternal serum alpha-fetoprotein (MSAFP) level (more than two or two and a half multiples of the median) has been found in individuals with aberrant placental implantation, this result is inconsistent and not diagnostic in and of itself. Additionally, a normal MSAFP does not rule out the diagnosis(Hung et al., 1999; Kupferminc, Tamura, Wigton, Glassenberg, & Socol, 1993; C. Zelop et al., 1992).

- **Hematuria:**

Hematuria during pregnancy may be caused by a placenta percreta with bladder invasion. A study of the literature revealed that 17 (31%) of 54 instances of placenta percreta entering the bladder were linked with hematuria(Washecka & Behling, 2002).

Consequences:

When attempting to remove the placenta during delivery, the absence of a normal plane of cleavage between the placental basal plate and the uterine wall leads to significant bleeding. The bleeding is more severe with more invasive placentation due to the placental bed's increased hypervascularity (ie, local neovascularization and vasodilation) (Glaze et al., 2008; Mehrabadi et al., 2015; C. M. Zelop, Harlow, Frigoletto, Safon, & Saltzman, 1993). Massive bleeding may result in disseminated intravascular coagulopathy, adult respiratory distress syndrome, renal failure, unexpected surgery, or death, as well as transfusion-related complications.

• **Peripartum hysterectomy and associated complications:**

In a systematic evaluation of 7001 PAS patients, 52.2 percent (95 percent confidence interval [CI] 38.3-66.4) needed a peripartum hysterectomy and 46.9 percent (95 percent CI 34.0-59.9) required blood transfusion (Jauniaux, Bunce, et al., 2019).

Other than transfusion, the most prevalent morbidity in a group of 356 patients with PAS was bladder damage, which occurred in 5% of cases (Morlando et al., 2021). Complications such as urinary tract injury, genitourinary fistula, bowel damage, thrombotic event, wound infection, hemorrhagic shock, cardiac arrest, and renal failure occurred in 2% of patients.

• **Increased maternal morbidity with more invasive placentation:**

Composite maternal morbidity is notably significant with placenta percreta [86 against 27 percent with accreta (Marcellin et al., 2018)].

• **Neonatal morbidity:**

It seems as if preterm delivery and small for gestational age newborns are more prevalent in pregnancies complicated by PAS (Gielchinsky et al., 2004). The neonatal outcome is highly associated with gestational age at delivery but does not seem to be changed much by placental invasion depth (accreta vs percreta)(Seet, Kay, Wu, & Terplan, 2012).

- **Mortality:**

Although maternal and perinatal mortality are rare in case studies from tertiary care facilities with multispecialty competence, these findings are prone to selection bias (Shamshirsaz et al., 2015; Warshak et al., 2010). There were no maternal fatalities in a cohort of 442 patients with suspected PAS from 2008 to 2019 in the International Society of PAS database, despite blood loss of up to 20,000 mL and 88 patients with placental invasion into the bladder or beyond (eg, pelvic sidewall) (van Beekhuizen et al., 2021).

Postpartum placental histology:

Postpartum histology reveals placental villi attached directly to or entering the myometrium without an intermediate decidual plate. The placenta is classified as an accreta, increta, or percreta, depending on the level of myometrial invasion (superficial, deep, or entering the whole uterine wall) since the degree of villous adhesion or invasion is not always uniform (Jauniaux, Collins, et al., 2018). In the absence of hysterectomy, the diagnosis of localized accreta may be verified by identifying these characteristics in uterine curettings or adhering to myometrium fragments.

Prenatal screening and diagnosis:

Prenatal screening and diagnosis are critical in order to inform the patient about the probable placental anomaly and to design a suitable delivery location and strategy. Preoperative preparation, which includes the availability of surgical and radiological competence, transfusion components, and proper equipment, enhances result. In a meta-analysis (11 trials, 700 pregnancies), women who were identified with PAS before to birth had considerably less blood loss (mean difference 0.9 L) and required fewer red cell transfusions (mean difference 1.5 units) than women who were diagnosed postpartum. (Buca et al., 2018).

Candidates and screening method:

Between about 18 and 24 weeks of gestation, women with a Previa or a low anterior placenta and a history of uterine surgery should have a complete transabdominal and transvaginal sonographic assessment of the interface between the placenta and myometrium.

Prenatal diagnosis:

Prenatal diagnosis of PAS is most probable in individuals with placenta previa or a low-lying placenta after one or more prior cesarean births, as well as imaging investigations indicating aberrant implantation, as mentioned below. When imaging investigations indicate normal placental implantation, the diagnosis may be fairly ruled out.

The most accurate diagnostic sonographic findings are placental lacunae (which look as intraplacental sonolucent gaps) and disruption of the interface between the bladder wall and uterine serosa (ie, bladder line). The movement of color Doppler evidence of turbulent ("chaotic") lacunar flow and/or bridging vessels is a significant confirming result. If ultrasound studies are inconclusive or ambiguous [e.g., when the region of concern is not the anterior lower uterine segment, as is the case following myomectomy (Levine, Hulka, Ludmir, Li, & Edelman, 1997)], magnetic resonance imaging (MRI) may be used to further clarify the diagnosis if it affects patient management; however, the utility of the additional information gained by MRI is unknown.

Ultrasound findings:

The following transabdominal and transvaginal sonographic findings have been related with PAS in the second and third trimesters; not all of the findings need to be present (Comstock, 2005; Finberg & Williams, 1992; Guy, Peisner, & Timor-Tritsch, 1990). Numerous observations may be masked by the posterior placental position.

- **Multiple lacunae in the placenta:**

Multiple large, irregular intraplacental sonolucent areas (ie, placental lacunae) in the core of a lobule or cotyledon next to the implicated myometrium substitute for typical placental homogeneity, giving the placenta a "moth-eaten" look. PAS is more likely to occur when there are more than three big lacunae with uneven boundaries and a high velocity and/or turbulent flow (>15 cm/s). Lacunae had a sensitivity of around 75, 89, and 76 percent for recognizing placenta accreta, increta, and percreta, respectively, and specificities of roughly 97, 98, and 99 percent (Pagani et al., 2018).

A normal placenta may include vascular lakes, which are generally a few tiny, sonolucent areas with a consistent form and normal myometrial thickness. In PAS, on the other hand, the placental lacunae are more frequent and irregular in form, and the underlying myometrium may be thinned. While a partial hydatidiform mole resembles a "Swiss cheese," the sonolucent gaps are tiny, dispersed throughout the placenta, and devoid of blood flow.

- **Disruption of the bladder line:**

Disruption or loss of the typically continuous white line marking the bladder wall-uterine serosa interface (referred to as the "bladder line") may be caused by placental percreta or neovascularity associated with placental accreta or increta.

- **Loss of the clear zone:**

The usual hypoechoic space behind the placenta (referred to as the "clean space" or "clear zone") may be absent or abnormal. Direct pressure from the ultrasonography probe and bladder filling might mask this symptom (Jauniaux, Collins, et al., 2018).

- **Myometrial thinning:**

The retroplacental myometrium may be very thin (less than 1 mm) as a result of a previous hysterectomy scar or placental invasion. When the placenta covers the area of thinning, it is critical to seek for further symptoms of PAS. For instance, if the placenta is seen spreading into the myometrium (ie, percreta), it is undoubtedly an invasive placenta. However, sonographic differentiation of placenta accreta from increta might be difficult (or perhaps impossible) due to the thin myometrium obstructing evaluation of invasion depth.

- **Abnormal vascularity:**

Vessels extending from the placenta through the myometrium into the bladder or through the serosa in other locations are a definite marker of placenta percreta.

- **Improper uterine contour:**

An abnormal uterine contour may occur when a section of the uterus linked to an abnormally adherent placenta expands into the bladder as a result of the underlying thin myometrium's weakness. This condition is sometimes referred to as placental bulging.

- **Exophytic mass:**

A focal mass that penetrates the uterine serosa and often extends into the bladder is indicative of placenta percreta.

Color Doppler:

When combined with the other ultrasonography findings discussed above, color Doppler is effective for confirming the diagnosis of PAS. The following are specific findings on color Doppler ultrasonography that support this diagnosis (Berkley & Abuhamad, 2013; Chou, Ho, & Lee, 2000; Comstock & Bronsteen, 2014; Shih et al., 2009; Twickler et al., 2000):

- Turbulent lacunar blood flow (>15 cm/sec)
- Bridging vessels
- Diffuse or focal intraparenchymal flow
- Hypervascularity of serosa-bladder interface
- Prominent subplacental venous complex

Bridging vessels are placental vessels that extend beyond the serosa and into the bladder via the myometrium (or other organs). They should not be confused with bladder varices, which are enlargements of the maternal bladder veins that are often seen during normal pregnancy.

Utility of additional imaging techniques:

The role of the following imaging techniques in diagnosis of PAS has not been clearly determined.

Magnetic resonance imaging (MRI):

In three clinical situations, MRI may be more useful than ultrasound because the bladder can't be used to help clear up the placental-myometrial interface. MRI can also help determine the depth of the myometrial and parametrial involvement, and if the placenta is anterior to the bladder, how

far it is from the bladder. This area isn't well seen by transvaginal ultrasound. (Kirkinen, Helin-Martikainen, Vanninen, & Partanen, 1998; Maldjian et al., 1999).

The following MRI findings, are the most reliable indicators of placenta accreta.(Jha et al., 2020):

- Uterine bulging into the bladder ("placental/uterine bulge")
- Interruption of the bladder wall
- Loss of retroplacental hypointense line on T2W images
- Abnormal vascularization of the placental bed
- Dark intraplacental bands on T2W imaging ("T2-dark bands")
- Myometrial thinning
- Focal exophytic mass

Three-dimensional power Doppler ultrasound:

PAS has been effectively assessed using three-dimensional ultrasonography(Cali, Giambanco, Puccio, & Forlani, 2013; Shih et al., 2009). Diagnostic criteria include:

- Intraplacental vascularization is irregular, with convoluted confluent arteries across the placental breadth.
- The uterine serosa-bladder wall contact is hypervascular.

First-trimester ultrasound examination:

PAS might be considered if ultrasound examination before to 9 weeks indicates gestational sac implantation in the lower anterior section of the uterus, especially in the niche of the previous cesarean birth scar(Cali et al., 2020; Comstock, Lee, Vettraino, & Bronsteen, 2003; Doulaveris et al., 2020; Happe et al., 2020; Rac et al., 2016; Stirnemann et al., 2011).

MANAGEMENT

Introduction

Management of individuals with placenta accreta spectrum disorders (PAS; placenta accreta, increta, or percreta) differs significantly("Obstetric Care Consensus No. 7: Placenta Accreta Spectrum," 2018; Silver et al., 2015).

Prenatal care:

Prenatal treatment is provided according to standard recommendations for managing placenta previa-accreta in individuals with this condition:

- Correction of anemia due to iron deficiency, if present.
- Between 23 and 34 weeks of gestation, antenatal betamethasone is used to treat pregnancies at elevated risk of delivery within seven days (eg, antepartum bleeding).
- If vaginal bleeding develops when the patient is RhD negative, anti-D immune globulin should be administered.
- Attempt to avoid pelvic examinations and strenuous physical exercise. Numerous therapists advocate for abstinence from sexual activity, despite the fact that any benefit is untested.
- Consider hospitalization during the third trimester if vaginal bleeding, contractions, or living in a rural location from a PAS center of excellence. Women who are asymptomatic may be observed as outpatients if they are educated correctly and can be admitted to the hospital quickly if symptoms emerge (Collins et al., 2019).

Autologous blood donation is often ineffective since the majority of patients who need transfusion after birth require more units than a prenatal donor can safely contribute.

Nonstress tests and/or biophysical profile scores are not regularly conducted but are utilized in pregnancies with established reasons (eg, fetal growth restriction, preeclampsia).

Serial sonographic examinations of the placenta are often ineffective after a diagnosis of PAS. However, an ultrasonography performed between 32 and 34 weeks of gestation can properly detect the placenta and assist in determining the possibility of bladder involvement. This data is beneficial for surgical planning and execution. (Merrill, Sultan, & Sharawi, 2021).

Preparation for delivery

Components of preoperative planning:

It is critical to develop a preoperative plan for women at high risk of PAS. The goal is to educate (via informed consent) and plan for activities

that will reduce the likelihood of substantial postpartum hemorrhage, as well as its considerable morbidity and mortality. Cesarean hysterectomy is routinely performed since the placenta cannot be removed otherwise and subinvolution frequently results in postpartum hemorrhage if left in situ. Specifically, the following components of preoperative planning and care should be addressed (Belfort, 2010):

- **Informed consent:**

The possibilities of intraoperative complications and interventions must be told to the patient (eg, severe hemorrhage, blood transfusion, injury to or partial resection of bladder and bowel, hysterectomy to control bleeding, risk of postoperative vesicovaginal fistula).

- **Multidisciplinary care team:**

The management and delivery of treatment by a multidisciplinary team in a tertiary care hospital improves outcomes and decreases complication rates (Bartels et al., 2018; Eller et al., 2011; Schwickert et al., 2021; Shamshirsaz et al., 2015). A multidisciplinary meeting should be arranged including all key care participants at least two weeks prior to the intended delivery date to ensure that the necessary arrangements and implementation planning are in order.

The multidisciplinary team includes specialists in perinatology, anesthesiologists, neonatologists, interventional radiologists, pathologists, and blood bank and nursing personnel. It is vital to have a surgeon in the operating room with substantial expertise conducting wide parametrial dissection and retroperitoneal exploration in case hemorrhage management, bladder resection and/or isolation, and partial resection and/or reimplantation of the ureters are necessary. This experience is common among some obstetrician-gynecologists, as well as general surgeons, urologists, and vascular surgeons. When bladder involvement is anticipated or the surgeon does not possess the necessary surgical competence, a urogynecologist, urologist, or gynecologic oncologist should be contacted.

If the planned delivery location is unable to provide a multidisciplinary team and related resources, the patient should be transferred to a tertiary center capable of managing significant intraoperative bleeding and providing fast postoperative critical care.

Scheduled delivery:

Delivery should be scheduled within a time period when the necessary personnel and facilities are easily accessible. In overall, scheduled delivery results in less intraoperative blood loss than urgent delivery, (Eller, Porter, Soisson, & Silver, 2009; Tikkanen, Paavonen, Loukovaara, & Stefanovic, 2011; Warshak et al., 2010), while emergency delivery in a center of excellence may provide equivalent outcomes (Schwickert et al., 2021). However, a considerable number of patients, especially those with placenta percreta, have complications that need an early delivery (Bowman, Manuck, Eller, Simons, & Silver, 2014; Shamshirsaz et al., 2018).

- **Cesarean hysterectomy:**

Preoperatively, in the majority of instances, a firm choice about conservative treatment or cesarean hysterectomy should be taken. In most cases, if the prenatal diagnosis of PAS is pretty certain based on imaging examinations and/or clinical risk factors (Eller et al., 2009; "Obstetric Care Consensus No. 7: Placenta Accreta Spectrum," 2018; Oyelese & Smulian, 2006; Wong, Hutton, Zuccollo, Tait, & Pringle, 2008), it is recommended that the uterus be surgically removed and the placenta remain intact (placental implantation at the site of prior uterine surgery). This method minimizes the risk of blood loss and its related problems (Eller et al., 2009; Warshak et al., 2010). The administration of PAS, on the other hand, is moving toward a more conservative management style.

- **Intravenous access:**

At least two intravenous catheters with a big diameter (14 gauge) should be inserted peripherally. A central line provides little added benefit to many patients, and hence is not inserted frequently. A fast infuser is advantageous for rapidly giving warmed blood products and fluids.

- **Monitoring:**

It is not uncommon for invasive arterial monitoring to be conducted (Einerson & Weiniger, 2021). Additionally, cardiac output monitors and transthoracic or transesophageal echocardiography may be used (TEE).

- **Thromboembolism prophylaxis:**

Pneumatic compression devices should be inserted due to the increased risk of postpartum venous thrombosis associated with surgery, significant bleeding, and blood transfusion.

- **Blood products:**

It must be ensured that a comprehensive supply of blood products is accessible at all times. The blood bank should be notified, and there should be enough red blood cells, fresh frozen plasma, cryoprecipitate, and platelets available at the time of delivery; the median estimated blood loss varies between 2.5 and 7.8 liters at the time of delivery (Eller et al., 2009; Pri-Paz et al., 2013; Shamshirsaz et al., 2015; Tikkanen et al., 2011). It is impossible to predict the amount of blood loss that will occur during pregnancy. (Wright et al., 2011).

- **Drugs:**

- Tranexamic acid reduces the risk of postpartum bleeding-related death by slowing the breakdown of fibrin.
- The use of recombinant VIIa to reduce obstetric haemorrhage is being investigated; however, its use especially for placental accreta bleeding has not been extensively documented.

Bladder catheter and ureteral stents:

To ensure the integrity of the urinary system is not compromised, it is recommended to have a three-way Foley catheter and ureteral stenting devices on hand in case they are necessary. This is critical in circumstances when bladder resection is required.

- **Anesthesia:**

The most often used kind of anaesthesia is general anaesthesia (Lilker, Meyer, Downey, & Macarthur, 2011).

- **Positioning:**

It is possible to have greater access to the vaginal and cervix by placing the patient in a lithotomy posture or by placing his or her legs flat on the table, but this is not recommended (Collins et al., 2019).

- **Postoperative care:**

If an intensive care unit bed is required for postoperative care, it should be made available as soon as possible.

Endovascular intervention for hemorrhage control:

It may be necessary to perform preventive endovascular intervention with a balloon catheter placed in both internal iliac arteries, uterine artery embolization, or a combination of the two procedures in order to reduce bleeding during or after delivery.

Delivery

Timing:

When difficulties such as early prelabor rupture of the membranes, preterm labor, or antepartum hemorrhage occur in a large number of patients, it is necessary to deliver the baby sooner rather than later than anticipated. Women who are bleeding actively should be delivered immediately in order to receive prenatal betamethasone (Gyamfi-Bannerman, 2018).

The optimal gestational age for planned birth is debatable, and there is a dearth of high-quality evidence. A compromise must be struck between the dangers of preterm birth and the possibility of complications, such as hemorrhage, forcing an emergency delivery under less than optimal circumstances.

- The American College of Obstetricians and Gynecologists recommend scheduled delivery between 34+0 and 35+6 weeks of gestation for stable (no bleeding or premature labour) patients, in accordance with. ("Obstetric Care Consensus No. 7: Placenta Accreta Spectrum," 2018).
- For women who are at high risk of having an emergency birth before 34 weeks, planned delivery before 34 weeks may be suitable, although emergency delivery at centers of excellence continues to provide good outcomes (Pri-Paz et al., 2013; Shamshirsaz et al., 2018).

Betamethasone is taken during pregnancy in accordance with established standards.

Procedure

Cesarean hysterectomy:

The use of a vertical midline skin incision or a Cherney incision is suggested, although in instances when the risk of intraoperative complications is low, a transverse incision (e.g., Pfannenstiel) (eg, posterior placenta not extending to the serosa) (Collins et al., 2019). Before commencing the uterine incision, the pelvis is examined for signs and symptoms of percreta, as well as the presence of any collateral blood flow in the area.

Using intraoperative ultrasound to map the placental edge and determine the best placement for the hysterotomy incision, which should avoid transecting the placenta, may be advantageous. An incision at least two fingerbreadths above the placental border is made during the vertical hysterotomy. Leaving a myometrial gap between the placenta and the incision helps to prevent the placenta from being disturbed during the uterine opening or closing. Conservative methods are seldom helpful and jeopardise the patient by delaying hysterectomy in situations when the placenta accreta has been disrupted after delivery and is bleeding. Large amounts of bleeding during the wait might set off a downward spiral of hypoperfusion of all organ systems, hypothermia, coagulopathy, and metabolic acidosis, among other things.

Following the infant's birth, the chord is severed, the uterine incision is immediately closed to minimise blood loss, and a hysterectomy is done. Even when a percreta is not extrauterine, the surgery is often challenging due to substantial parametrial vascular engorgement and friable tissues. Separately, the management of peripartum hysterectomy is explored.

Prophylactic oxytocin is not commonly given after delivery of the newborn since it may result in partial placental detachment and increased haemorrhage. (Collins et al., 2019). However, if the placenta has been removed partially or fully, or if bleeding is already profuse, uterotonic medicines should be administered. Postpartum haemorrhage is addressed individually.

Internal iliac (hypogastric) artery ligation is not recommended because it is time-consuming, operator-dependent, unsuccessful (without hysterectomy) at managing pelvic bleeding in up to 60% of cases (Clark, Phelan, Yeh, Bruce, & Paul, 1985; Papp et al., 2006), and prohibits further use of selective pelvic angiography and embolization be necessary for the future

Management of placenta percreta with bladder invasion:

Placenta percreta invading the bladder may need partial cystectomy. In one analysis of 54 instances of placenta percreta entering the bladder, 24 of the 54 patients had partial cystectomy (44 percent) (Sentilhes, Ambroselli, et al., 2010). When the bladder is implicated, it is best to visit a urogynecologist, urologist, or gynecologic oncologist. Cystoscopy or deliberate cystotomy during surgery is often beneficial in determining the extent of bladder and perhaps ureteral involvement (Palacios Jaraquemada, Pesaresi, Nassif, & Hermosid, 2004).

Conservative management of placenta accreta

Potential candidates:

Uterine conservation may be considered in the following situations:

- Patients who are adamant about preserving their fertility. Such patients should get intensive counselling on the risks of bleeding, infection, the potential necessity for intra- or postoperative life-saving hysterectomy, and even death, as well as the possibility of unsatisfactory pregnancy outcomes (including recurrence or haemorrhage) (Chandrabaran, Rao, Belli, & Arulkumaran, 2012; Clausen, Lönn, & Langhoff-Roos, 2014) in future pregnancies.
- When it is believed that hysterectomy has an unacceptably high risk of bleeding or harm to other organs, which may be minimised by keeping the placenta in place (Teixidor Viñas, Belli, Arulkumaran, & Chandrabaran, 2015).
- When it is believed that placental excision is probable due to localised accreta or a fundal or posterior placenta.

Uterine conservation with the placenta left in situ:

The placenta is left in situ after birth of the infant in this procedure (dubbed expectant management). The umbilical cord is ligated at the placental insertion site; the hysterotomy is closed conventionally; and uterotonic medicines, compression sutures, intrauterine balloon tamponade, uterine artery embolization, and/or uterine artery ligation are employed in various combinations. This is done prophylactically in certain circumstances and as required to treat postpartum haemorrhage in others(Collins et al., 2019; Fox et al., 2015) . According to the American College of Obstetricians and Gynecologists' committee view, this method should be used only in exceptional circumstances or as part of an authorised clinical study in fully informed patients(Collins et al., 2019). However, this strategy is gaining traction, and further data will become accessible in the near future.

Delayed hysteroscopic excision of placental remains has been effectively utilised to speed placental resolution or to treat persistent bleeding and/or pelvic discomfort after placental resolution, although experience is limited(Hequet et al., 2013; Legendre, Zoulovits, Kinn, Senthiles, & Fernandez, 2014; Rein et al., 2011).

Delayed-interval hysterectomy is another possibility, especially for women with percreta placenta, although experience with this procedure is limited(Lee et al., 2017; Rupley, Tergas, Palmerola, & Burke, 2016; Schmeler et al., 2005; Zuckerwise et al., 2020) and specialists advise against it(Collins et al., 2019). Clinicians familiar with the method recommend it only in the most severe, possibly life-threatening instances of placenta percreta or when prompt hysterectomy is deemed unsafe due to the amount of placental invasion or a lack of sufficient resources.(Zuckerwise et al., 2020). The experience with this strategy has been inconsistent, and there is a dearth of high-quality data comparing the benefits and downsides of this approach to scheduled caesarean hysterectomy.

Adjunctive treatment with methotrexate is contraindicated: There is no persuasive evidence that leaving the placenta in place improves any result, and there is abundant evidence of drug-related risks (eg, pancytopenia, nephrotoxicity)(Collins et al., 2019).

A comprehensive evaluation of ten cohort studies and fifty case series or case reports involving 434 individuals with PAS handled conservatively demonstrated the protracted course and severe hazards of uterine conservation with the placenta remained in situ (eg, expectant management,

uterine artery embolization, methotrexate therapy, hemostatic sutures, arterial ligation, balloon tamponade) (Steins Bisschop, Schaap, Vogelvang, & Scholten, 2011). The following short-term results were reported, however not all studies had data for all outcomes:

- 53 percent of women have severe vaginal bleeding.
- Sepsis: 6%
- 19% of women undergo a secondary hysterectomy (range 6 to 31 percent)
- Death rate: 0.3% (range 0 to 4 percent)
- 67 percent of subsequent pregnancies (range 15 to 73 percent)

Uterine conservation with placental resection:

In two clinical circumstances, uterine conservation with placental excision may be effective without posing an unacceptable risk:

- **Focal accreta:**

Focal accreta may be suspected prenatally or discovered intrapartum as a result of bleeding and/or a partly retained placenta after birth. Several papers exist reporting effective uterine conservation in these instances(Chandrahara et al., 2012; Clausen et al., 2014; Palacios Jaraquemada et al., 2004). Women with a clearly defined focal region of morbidly adherent placenta (adherent area equal to 50% of the anterior surface of the uterus(Collins et al., 2019)] and an accessible border of healthy myometrium are candidates for this method(Fox et al., 2015). Desire for future pregnancy is not required, since the surgery is anticipated to be less invasive than a caesarean hysterectomy. The bleeding sites are oversewn or a tiny wedge of uterine tissue containing the focally adhered placenta is removed (placental-myometrial en bloc excision and repair).

The triple P surgery is another method of conserving the uterus while doing placental excision(Teixidor Viñas et al., 2015). This procedure entails devascularization of the pelvis and the excision of a portion of the uterus(Teixidor Viñas et al., 2015). It has only been recorded in a few instances, and its effectiveness is unknown.

- **Fundal or posterior placenta accreta:**

In contrast to anterior placenta accreta, the authors' experience indicates that uterine conservation may be viable with posterior or fundal accreta, since haemorrhage after placenta accreta removal is more easily managed medically, by interventional radiology, or with conservative surgery. If bleeding cannot be successfully managed with these additional techniques, a (relatively) simple hysterectomy remains a possibility.

Recurrence of the condition in subsequent pregnancies:

PAS occurred in 22 and 29% of subsequent pregnancies of women who were effectively handled conservatively, respectively (Provansal et al., 2010; Sentilhes, Kayem, et al., 2010). Women who want to conceive again should be aware of this risk and seek early prenatal care from a maternal-fetal medicine expert to help diagnosis and therapy.

Unexpected placenta accreta

During caesarean section:

Some occurrences of placenta accreta are discovered after caesarean delivery, most often with a repeat caesarean birth. When the surgeon enters the peritoneal cavity, he or she may diagnose PAS if one or more of the following are observed:

- Invasion of the lower uterine section, serosa, or bladder by placental tissue.
- Vascularity is increased and convoluted along the serosa of the lower uterine section. In the peritoneum, vessels may flow cranio-caudally.
- A bluish/purple lower uterine segment that bulges toward the pelvic sidewalls.

It is critical to differentiate these results from a typical placenta connected under a uterine window (uterine scar dehiscence). The uterine tissue and arteries seem normal in these circumstances.

PAS is indicated after delivery of the newborn if gentle tension on the umbilical chord pushes the uterine wall forward without separating the

placenta, and the uterus separate from the placental bed contracts. If the diagnosis is in doubt, moderate digital examination for cleavage planes may be undertaken; the lack of a plane is diagnostic.

Management:

If PAS is suspected prior to hysterotomy, it is critical to prevent or limit manipulation of the uterus or potential extrauterine placental extension sites (e.g., the posterior bladder wall), since this might induce life-threatening bleeding. It's concurred with an expert study that recommended the following course of action in the absence of a viable foetus (Silver et al., 2015):

- If the patient is not bleeding profusely, the mother and foetus are stable, and the resources necessary to manage these challenging situations are unavailable immediately, the uterus may be wrapped with warm packs and further operation deferred until adequate staff and other resources are available.
- If the patient is not bleeding profusely, the mother and foetus are stable, and assembling these resources locally is not feasible, the abdomen should be closed and the patient quickly transferred to a facility capable of managing these patients, although the risk of massive haemorrhage during transport must be considered.

If the woman is bleeding profusely and/or the baby is compromised, the best alternative is to deliver through hysterotomy away from the placenta, followed by closure of the hysterotomy and leaving the placenta alone until suitable people and resources for maternal care are available. Intraoperative ultrasonography employing a probe with a sterile cover may be used to determine the placement of the placenta. If an ultrasound inspection is not possible, a hysterotomy in the posterior uterus or fundus is usually sufficient to avoid the placenta.

Women who are bleeding profusely or are otherwise unstable must be handled ideally within the constraints of their clinical context and available resources. This involves fluid and blood product resuscitation, normal surgical haemorrhage control methods, and pressure on bleeding sites (e.g., digital, abdominopelvic packs); infrarenal aortic compression or aortic cross-clamping may be employed to try to control life-threatening haemorrhage.

Direct pressure on a percreta should be avoided or used sparingly since it might enlarge the bleeding area. A large-scale transfusion procedure is advantageous.

Separately, the intraoperative care of women who have significant bleeding during caesarean birth is reviewed in depth. Key principles include keeping the patient warm, rapidly transfusing red cells to restore or maintain adequate circulatory volume and tissue oxygenation, reversing or preventing coagulopathy with fresh frozen plasma and platelets (e.g., a 1:1:1 or 1:2:4 ratio of packed red blood cells, fresh frozen plasma, and platelets), and reversing electrolyte imbalances, particularly hypocalcemia (Erfani et al., 2019; "Obstetric Care Consensus No. 7: Placenta Accreta Spectrum," 2018).

During vaginal birth:

A localised or full placenta accreta is sometimes discovered after manual removal of a retained placenta following vaginal birth. There is no cleavage plane between the myometrium and the whole placenta or localised portions of the placenta in these circumstances. Hemorrhage with life-threatening consequences is possible. These patients should receive proper fluids and transfusions while preparing for laparotomy and surgical treatment (hysterectomy or localised resection), as indicated above.

Administration of postoperative care:

If necessary, an intensive care unit bed should be made available for postoperative treatment. These patients may need ventilator support owing to pulmonary edoema caused by large fluid resuscitation or fluid changes, or due to severe lung damage caused by transfusion (Silver et al., 2015). Certain patients need the use of vasopressors and invasive hemodynamic monitoring. Postoperative bleeding is possible, and interventional radiology's ability to do angiographic embolization of deep pelvic arteries, so preventing reoperation, might significantly improve patient care.

REFERENCES

- Baldwin, H. J., Patterson, J. A., Nippita, T. A., Torvaldsen, S., Ibiebele, I., Simpson, J. M., & Ford, J. B. (2018). Antecedents of Abnormally Invasive Placenta in Primiparous Women: Risk Associated With Gynecologic Procedures. *Obstet Gynecol*, *131*(2), 227-233. doi:10.1097/aog.0000000000002434
- Bartels, H. C., Rogers, A. C., O'Brien, D., McVey, R., Walsh, J., & Brennan, D. J. (2018). Association of Implementing a Multidisciplinary Team Approach in the Management of Morbidly Adherent Placenta With Maternal Morbidity and Mortality. *Obstet Gynecol*, *132*(5), 1167-1176. doi:10.1097/aog.0000000000002865
- Belfort, M. A. (2010). Placenta accreta. *Am J Obstet Gynecol*, *203*(5), 430-439. doi:10.1016/j.ajog.2010.09.013
- Ben-Nagi, J., Walker, A., Jurkovic, D., Yazbek, J., & Aplin, J. D. (2009). Effect of cesarean delivery on the endometrium. *Int J Gynaecol Obstet*, *106*(1), 30-34. doi:10.1016/j.ijgo.2009.02.019
- Berkley, E. M., & Abuhamad, A. Z. (2013). Prenatal diagnosis of placenta accreta: is sonography all we need? *J Ultrasound Med*, *32*(8), 1345-1350. doi:10.7863/ultra.32.8.1345
- Bowman, Z. S., Manuck, T. A., Eller, A. G., Simons, M., & Silver, R. M. (2014). Risk factors for unscheduled delivery in patients with placenta accreta. *Am J Obstet Gynecol*, *210*(3), 241.e241-246. doi:10.1016/j.ajog.2013.09.044
- Buca, D., Liberati, M., Cali, G., Forlani, F., Caisutti, C., Flacco, M. E., . . . D'Antonio, F. (2018). Influence of prenatal diagnosis of abnormally invasive placenta on maternal outcome: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*, *52*(3), 304-309. doi:10.1002/uog.19070
- Cali, G., Giambanco, L., Puccio, G., & Forlani, F. (2013). Morbidly adherent placenta: evaluation of ultrasound diagnostic criteria and differentiation of placenta accreta from percreta. *Ultrasound Obstet Gynecol*, *41*(4), 406-412. doi:10.1002/uog.12385
- Calí, G., Timor-Tritsch, I. E., Forlani, F., Palacios-Jaraquemada, J., Monteagudo, A., Kaelin Agten, A., . . . D'Antonio, F. (2020). Value of first-trimester ultrasound in prediction of third-trimester sonographic stage of placenta accreta spectrum disorder and surgical outcome. *Ultrasound Obstet Gynecol*, *55*(4), 450-459. doi:10.1002/uog.21939
- Carusi, D. A., Fox, K. A., Lyell, D. J., Perlman, N. C., Aalipour, S., Einerson, B. D., . . . Shamshirsaz, A. A. (2020). Placenta Accreta Spectrum Without Placenta Previa. *Obstet Gynecol*, *136*(3), 458-465. doi:10.1097/aog.0000000000003970
- Chandharan, E., Rao, S., Belli, A. M., & Arulkumaran, S. (2012). The Triple-P procedure as a conservative surgical alternative to peripartum hysterectomy for placenta percreta. *Int J Gynaecol Obstet*, *117*(2), 191-194. doi:10.1016/j.ijgo.2011.12.005
- Chou, M. M., Ho, E. S., & Lee, Y. H. (2000). Prenatal diagnosis of placenta previa accreta by transabdominal color Doppler ultrasound. *Ultrasound Obstet Gynecol*, *15*(1), 28-35. doi:10.1046/j.1469-0705.2000.00018.x

- Clark, S. L., Phelan, J. P., Yeh, S. Y., Bruce, S. R., & Paul, R. H. (1985). Hypogastric artery ligation for obstetric hemorrhage. *Obstet Gynecol*, 66(3), 353-356.
- Clausen, C., Lönn, L., & Langhoff-Roos, J. (2014). Management of placenta percreta: a review of published cases. *Acta Obstet Gynecol Scand*, 93(2), 138-143. doi:10.1111/aogs.12295
- Collins, S. L., Alemdar, B., van Beekhuizen, H. J., Bertholdt, C., Braun, T., Calda, P., . . . Chantraine, F. (2019). Evidence-based guidelines for the management of abnormally invasive placenta: recommendations from the International Society for Abnormally Invasive Placenta. *Am J Obstet Gynecol*, 220(6), 511-526. doi:10.1016/j.ajog.2019.02.054
- Comstock, C. H. (2005). Antenatal diagnosis of placenta accreta: a review. *Ultrasound Obstet Gynecol*, 26(1), 89-96. doi:10.1002/uog.1926
- Comstock, C. H., & Bronsteen, R. A. (2014). The antenatal diagnosis of placenta accreta. *Bjog*, 121(2), 171-181; discussion 181-172. doi:10.1111/1471-0528.12557
- Comstock, C. H., Lee, W., Vettraino, I. M., & Bronsteen, R. A. (2003). The early sonographic appearance of placenta accreta. *J Ultrasound Med*, 22(1), 19-23; quiz 24-16. doi:10.7863/jum.2003.22.1.19
- Doulaveris, G., Ryken, K., Papatomas, D., Estrada Trejo, F., Fazzari, M. J., Rotenberg, O., . . . Dar, P. (2020). Early prediction of placenta accreta spectrum in women with prior cesarean delivery using transvaginal ultrasound at 11 to 14 weeks. *Am J Obstet Gynecol MFM*, 2(4), 100183. doi:10.1016/j.ajogmf.2020.100183
- Einerson, B. D., Comstock, J., Silver, R. M., Branch, D. W., Woodward, P. J., & Kennedy, A. (2020). Placenta Accreta Spectrum Disorder: Uterine Dehiscence, Not Placental Invasion. *Obstet Gynecol*, 135(5), 1104-1111. doi:10.1097/aog.0000000000003793
- Einerson, B. D., & Weiniger, C. F. (2021). Placenta accreta spectrum disorder: updates on anesthetic and surgical management strategies. *Int J Obstet Anesth*, 46, 102975. doi:10.1016/j.ijoa.2021.102975
- Eller, A. G., Bennett, M. A., Sharshiner, M., Masheter, C., Soisson, A. P., Dodson, M., & Silver, R. M. (2011). Maternal morbidity in cases of placenta accreta managed by a multidisciplinary care team compared with standard obstetric care. *Obstet Gynecol*, 117(2 Pt 1), 331-337. doi:10.1097/AOG.0b013e3182051db2
- Eller, A. G., Porter, T. F., Soisson, P., & Silver, R. M. (2009). Optimal management strategies for placenta accreta. *Bjog*, 116(5), 648-654. doi:10.1111/j.1471-0528.2008.02037.x
- Erfani, H., Shamshirsaz, A. A., Fox, K. A., Rezaei, A., Hui, S. R., Shamshirsaz, A. A., . . . Belfort, M. A. (2019). Severe hypocalcemia during surgery for placenta accreta spectrum: The case for empiric replacement. *Acta Obstet Gynecol Scand*, 98(10), 1326-1331. doi:10.1111/aogs.13636
- Esh-Broder, E., Ariel, I., Abas-Bashir, N., Bdolah, Y., & Celnikier, D. H. (2011). Placenta accreta is associated with IVF pregnancies: a retrospective chart review. *Bjog*, 118(9), 1084-1089. doi:10.1111/j.1471-0528.2011.02976.x

- Finberg, H. J., & Williams, J. W. (1992). Placenta accreta: prospective sonographic diagnosis in patients with placenta previa and prior cesarean section. *J Ultrasound Med*, 11(7), 333-343. doi:10.7863/jum.1992.11.7.333
- Fitzpatrick, K. E., Sellers, S., Spark, P., Kurinczuk, J. J., Brocklehurst, P., & Knight, M. (2012). Incidence and risk factors for placenta accreta/increta/percreta in the UK: a national case-control study. *PLoS One*, 7(12), e52893. doi:10.1371/journal.pone.0052893
- Fox, K. A., Shamshirsaz, A. A., Carusi, D., Secord, A. A., Lee, P., Turan, O. M., . . . Belfort, M. A. (2015). Conservative management of morbidly adherent placenta: expert review. *Am J Obstet Gynecol*, 213(6), 755-760. doi:10.1016/j.ajog.2015.04.034
- Gielchinsky, Y., Mankuta, D., Rojansky, N., Laufer, N., Gielchinsky, I., & Ezra, Y. (2004). Perinatal outcome of pregnancies complicated by placenta accreta. *Obstet Gynecol*, 104(3), 527-530. doi:10.1097/01.aog.0000136084.92846.95
- Glaze, S., Ekwilanga, P., Roberts, G., Lange, I., Birch, C., Rosengarten, A., . . . Ross, S. (2008). Peripartum hysterectomy: 1999 to 2006. *Obstet Gynecol*, 111(3), 732-738. doi:10.1097/AOG.0b013e31816569f2
- Guy, G. P., Peisner, D. B., & Timor-Tritsch, I. E. (1990). Ultrasonographic evaluation of uteroplacental blood flow patterns of abnormally located and adherent placentas. *Am J Obstet Gynecol*, 163(3), 723-727. doi:10.1016/0002-9378(90)91056-i
- Gyamfi-Bannerman, C. (2018). Society for Maternal-Fetal Medicine (SMFM) Consult Series #44: Management of bleeding in the late preterm period. *Am J Obstet Gynecol*, 218(1), B2-b8. doi:10.1016/j.ajog.2017.10.019
- Happe, S. K., Rac, M. W. F., Moschos, E., Wells, C. E., Dashe, J. S., McIntire, D. D., & Twickler, D. M. (2020). Prospective First-Trimester Ultrasound Imaging of Low Implantation and Placenta Accreta Spectrum. *J Ultrasound Med*, 39(10), 1907-1915. doi:10.1002/jum.15295
- Hayashi, M., Nakai, A., Satoh, S., & Matsuda, Y. (2012). Adverse obstetric and perinatal outcomes of singleton pregnancies may be related to maternal factors associated with infertility rather than the type of assisted reproductive technology procedure used. *Fertil Steril*, 98(4), 922-928. doi:10.1016/j.fertnstert.2012.05.049
- Hequet, D., Morel, O., Soyer, P., Gayat, E., Malartic, C., & Barranger, E. (2013). Delayed hysteroscopic resection of retained tissues and uterine conservation after conservative treatment for placenta accreta. *Aust N Z J Obstet Gynaecol*, 53(6), 580-583. doi:10.1111/ajo.12138
- Hung, T. H., Shau, W. Y., Hsieh, C. C., Chiu, T. H., Hsu, J. J., & Hsieh, T. T. (1999). Risk factors for placenta accreta. *Obstet Gynecol*, 93(4), 545-550. doi:10.1016/s0029-7844(98)00460-8
- James, W. H. (1995). Sex ratios of offspring and the causes of placental pathology. *Hum Reprod*, 10(6), 1403-1406. doi:10.1093/humrep/10.6.1403
- Jauniaux, E., Ayres-de-Campos, D., Langhoff-Roos, J., Fox, K. A., & Collins, S. (2019). FIGO classification for the clinical diagnosis of placenta accreta spectrum disorders. *Int J Gynaecol Obstet*, 146(1), 20-24. doi:10.1002/ijgo.12761

- Jauniaux, E., Bunce, C., Grønbeck, L., & Langhoff-Roos, J. (2019). Prevalence and main outcomes of placenta accreta spectrum: a systematic review and meta-analysis. *Am J Obstet Gynecol*, 221(3), 208-218. doi:10.1016/j.ajog.2019.01.233
- Jauniaux, E., Chantraine, F., Silver, R. M., & Langhoff-Roos, J. (2018). FIGO consensus guidelines on placenta accreta spectrum disorders: Epidemiology. *Int J Gynaecol Obstet*, 140(3), 265-273. doi:10.1002/ijgo.12407
- Jauniaux, E., Collins, S., & Burton, G. J. (2018). Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. *Am J Obstet Gynecol*, 218(1), 75-87. doi:10.1016/j.ajog.2017.05.067
- Jauniaux, E., Hussein, A. M., Elbarmelgy, R. M., Elbarmelgy, R. A., & Burton, G. J. (2022). Failure of placental detachment in accreta placentation is associated with excessive fibrinoid deposition at the utero-placental interface. *Am J Obstet Gynecol*, 226(2), 243.e241-243.e210. doi:10.1016/j.ajog.2021.08.026
- Jha, P., Pöder, L., Bourgioti, C., Bharwani, N., Lewis, S., Kamath, A., . . . Masselli, G. (2020). Society of Abdominal Radiology (SAR) and European Society of Urogenital Radiology (ESUR) joint consensus statement for MR imaging of placenta accreta spectrum disorders. *Eur Radiol*, 30(5), 2604-2615. doi:10.1007/s00330-019-06617-7
- Kaser, D. J., Melamed, A., Bormann, C. L., Myers, D. E., Missmer, S. A., Walsh, B. W., . . . Carusi, D. A. (2015). Cryopreserved embryo transfer is an independent risk factor for placenta accreta. *Fertil Steril*, 103(5), 1176-1184.e1172. doi:10.1016/j.fertnstert.2015.01.021
- Khong, T. Y. (2008). The pathology of placenta accreta, a worldwide epidemic. *J Clin Pathol*, 61(12), 1243-1246. doi:10.1136/jcp.2008.055202
- Khong, T. Y., Healy, D. L., & McCloud, P. I. (1991). Pregnancies complicated by abnormally adherent placenta and sex ratio at birth. *Bmj*, 302(6777), 625-626. doi:10.1136/bmj.302.6777.625
- Kirkinen, P., Helin-Martikainen, H. L., Vanninen, R., & Partanen, K. (1998). Placenta accreta: imaging by gray-scale and contrast-enhanced color Doppler sonography and magnetic resonance imaging. *J Clin Ultrasound*, 26(2), 90-94. doi:10.1002/(sici)1097-0096(199802)26:2<90::aid-jcu7>3.0.co;2-d
- Kohn, J. R., Shamshirsaz, A. A., Popek, E., Guan, X., Belfort, M. A., & Fox, K. A. (2018). Pregnancy after endometrial ablation: a systematic review. *Bjog*, 125(1), 43-53. doi:10.1111/1471-0528.14854
- Kupferminc, M. J., Tamura, R. K., Wigton, T. R., Glassenberg, R., & Socol, M. L. (1993). Placenta accreta is associated with elevated maternal serum alpha-fetoprotein. *Obstet Gynecol*, 82(2), 266-269.
- Lee, P. S., Kempner, S., Miller, M., Dominguez, J., Grotegut, C., Ehrisman, J., . . . Secord, A. A. (2017). Multidisciplinary approach to manage antenatally suspected placenta percreta: updated algorithm and patient outcomes. *Gynecol Oncol Res Pract*, 4, 11. doi:10.1186/s40661-017-0049-6
- Legendre, G., Zoulovits, F. J., Kinn, J., Senthiles, L., & Fernandez, H. (2014). Conservative management of placenta accreta: hysteroscopic resection of

- retained tissues. *J Minim Invasive Gynecol*, 21(5), 910-913. doi:10.1016/j.jmig.2014.04.004
- Levine, D., Hulka, C. A., Ludmir, J., Li, W., & Edelman, R. R. (1997). Placenta accreta: evaluation with color Doppler US, power Doppler US, and MR imaging. *Radiology*, 205(3), 773-776. doi:10.1148/radiology.205.3.9393534
- Lilker, S. J., Meyer, R. A., Downey, K. N., & Macarthur, A. J. (2011). Anesthetic considerations for placenta accreta. *Int J Obstet Anesth*, 20(4), 288-292. doi:10.1016/j.ijoa.2011.06.001
- Maldjian, C., Adam, R., Pelosi, M., Pelosi, M., 3rd, Rudelli, R. D., & Maldjian, J. (1999). MRI appearance of placenta percreta and placenta accreta. *Magn Reson Imaging*, 17(7), 965-971. doi:10.1016/s0730-725x(99)00035-1
- Marcellin, L., Delorme, P., Bonnet, M. P., Grange, G., Kayem, G., Tsatsaris, V., & Goffinet, F. (2018). Placenta percreta is associated with more frequent severe maternal morbidity than placenta accreta. *Am J Obstet Gynecol*, 219(2), 193.e191-193.e199. doi:10.1016/j.ajog.2018.04.049
- Mehrabadi, A., Hutcheon, J. A., Liu, S., Bartholomew, S., Kramer, M. S., Liston, R. M., & Joseph, K. S. (2015). Contribution of placenta accreta to the incidence of postpartum hemorrhage and severe postpartum hemorrhage. *Obstet Gynecol*, 125(4), 814-821. doi:10.1097/aog.0000000000000722
- Merrill, J., Sultan, P., & Sharawi, N. (2021). Advances in anesthetic and obstetric management of patients with placenta accreta spectrum. *Curr Opin Anaesthesiol*, 34(3), 260-268. doi:10.1097/aco.0000000000000985
- Miller, H. E., Leonard, S. A., Fox, K. A., Carusi, D. A., & Lyell, D. J. (2021). Placenta Accreta Spectrum Among Women With Twin Gestations. *Obstet Gynecol*, 137(1), 132-138. doi:10.1097/aog.0000000000004204
- Morlando, M., Schwickert, A., Stefanovic, V., Gziri, M. M., Pateisky, P., Chalubinski, K. M., . . . Collins, S. L. (2021). Maternal and neonatal outcomes in planned versus emergency cesarean delivery for placenta accreta spectrum: A multinational database study. *Acta Obstet Gynecol Scand*, 100 Suppl 1, 41-49. doi:10.1111/aogs.14120
- Nageotte, M. P. (2014). Always be vigilant for placenta accreta. *Am J Obstet Gynecol*, 211(2), 87-88. doi:10.1016/j.ajog.2014.04.037
- Obstetric Care Consensus No. 7: Placenta Accreta Spectrum. (2018). *Obstet Gynecol*, 132(6), e259-e275. doi:10.1097/aog.0000000000002983
- Oyelese, Y., & Smulian, J. C. (2006). Placenta previa, placenta accreta, and vasa previa. *Obstet Gynecol*, 107(4), 927-941. doi:10.1097/01.aog.0000207559.15715.98
- Pagani, G., Cali, G., Acharya, G., Trisch, I. T., Palacios-Jaraquemada, J., Familiari, A., . . . D'Antonio, F. (2018). Diagnostic accuracy of ultrasound in detecting the severity of abnormally invasive placentation: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*, 97(1), 25-37. doi:10.1111/aogs.13238
- Palacios Jaraquemada, J. M., Pesaresi, M., Nassif, J. C., & Hermosid, S. (2004). Anterior placenta percreta: surgical approach, hemostasis and uterine repair. *Acta Obstet Gynecol Scand*, 83(8), 738-744. doi:10.1111/j.0001-6349.2004.00517.x

- Papp, Z., Tóth-Pál, E., Papp, C., Sziller, I., Gávai, M., Silhavy, M., & Hupuczi, P. (2006). Hypogastric artery ligation for intractable pelvic hemorrhage. *Int J Gynaecol Obstet*, 92(1), 27-31. doi:10.1016/j.ijgo.2005.08.022
- Pekar-Zlotin, M., Melcer, Y., Levinsohn-Tavor, O., Tovbin, J., Vaknin, Z., & Maymon, R. (2017). Cesarean Scar Pregnancy and Morbidly Adherent Placenta: Different or Similar? *Isr Med Assoc J*, 19(3), 168-171.
- Pri-Paz, S., Fuchs, K. M., Gaddipati, S., Lu, Y. S., Wright, J. D., & Devine, P. C. (2013). Comparison between emergent and elective delivery in women with placenta accreta. *J Matern Fetal Neonatal Med*, 26(10), 1007-1011. doi:10.3109/14767058.2013.766711
- Provansal, M., Courbiere, B., Agostini, A., D'Ercole, C., Boubli, L., & Bretelle, F. (2010). Fertility and obstetric outcome after conservative management of placenta accreta. *Int J Gynaecol Obstet*, 109(2), 147-150. doi:10.1016/j.ijgo.2009.12.011
- Rac, M. W., Moschos, E., Wells, C. E., McIntire, D. D., Dashe, J. S., & Twickler, D. M. (2016). Sonographic Findings of Morbidly Adherent Placenta in the First Trimester. *J Ultrasound Med*, 35(2), 263-269. doi:10.7863/ultra.15.03020
- Rein, D. T., Schmidt, T., Hess, A. P., Volkmer, A., Schöndorf, T., & Breidenbach, M. (2011). Hysteroscopic management of residual trophoblastic tissue is superior to ultrasound-guided curettage. *J Minim Invasive Gynecol*, 18(6), 774-778. doi:10.1016/j.jmig.2011.08.003
- Rupley, D. M., Tergas, A. I., Palmerola, K. L., & Burke, W. M. (2016). Robotically assisted delayed total laparoscopic hysterectomy for placenta percreta. *Gynecol Oncol Rep*, 17, 53-55. doi:10.1016/j.gore.2016.05.009
- Salmanian, B., Fox, K. A., Arian, S. E., Erfani, H., Clark, S. L., Aagaard, K. M., . . . Shamshirsaz, A. A. (2020). In vitro fertilization as an independent risk factor for placenta accreta spectrum. *Am J Obstet Gynecol*, 223(4), 568.e561-568.e565. doi:10.1016/j.ajog.2020.04.026
- Schmeler, K. M., Mayo-Smith, W. W., Peipert, J. F., Weitzen, S., Manuel, M. D., & Gordinier, M. E. (2005). Adnexal masses in pregnancy: surgery compared with observation. *Obstet Gynecol*, 105(5 Pt 1), 1098-1103. doi:10.1097/01.AOG.0000157465.99639.e5
- Schwickert, A., van Beekhuizen, H. J., Bertholdt, C., Fox, K. A., Kayem, G., Morel, O., . . . Braun, T. (2021). Association of peripartum management and high maternal blood loss at cesarean delivery for placenta accreta spectrum (PAS): A multinational database study. *Acta Obstet Gynecol Scand*, 100 Suppl 1, 29-40. doi:10.1111/aogs.14103
- Seet, E. L., Kay, H. H., Wu, S., & Terplan, M. (2012). Placenta accreta: depth of invasion and neonatal outcomes. *J Matern Fetal Neonatal Med*, 25(10), 2042-2045. doi:10.3109/14767058.2012.678429
- Sentilhes, L., Ambroselli, C., Kayem, G., Provansal, M., Fernandez, H., Perrotin, F., . . . Bretelle, F. (2010). Maternal outcome after conservative treatment of placenta accreta. *Obstet Gynecol*, 115(3), 526-534. doi:10.1097/AOG.0b013e3181d066d4
- Sentilhes, L., Kayem, G., Ambroselli, C., Provansal, M., Fernandez, H., Perrotin, F., . . . Goffinet, F. (2010). Fertility and pregnancy outcomes following

- conservative treatment for placenta accreta. *Hum Reprod*, 25(11), 2803-2810. doi:10.1093/humrep/deq239
- Shamshirsaz, A. A., Fox, K. A., Erfani, H., Clark, S. L., Shamshirsaz, A. A., Nassr, A. A., . . . Belfort, M. A. (2018). Outcomes of Planned Compared With Urgent Deliveries Using a Multidisciplinary Team Approach for Morbidly Adherent Placenta. *Obstet Gynecol*, 131(2), 234-241. doi:10.1097/aog.0000000000002442
- Shamshirsaz, A. A., Fox, K. A., Salmanian, B., Diaz-Arrastia, C. R., Lee, W., Baker, B. W., . . . Belfort, M. A. (2015). Maternal morbidity in patients with morbidly adherent placenta treated with and without a standardized multidisciplinary approach. *Am J Obstet Gynecol*, 212(2), 218.e211-219. doi:10.1016/j.ajog.2014.08.019
- Shih, J. C., Palacios Jaraquemada, J. M., Su, Y. N., Shyu, M. K., Lin, C. H., Lin, S. Y., & Lee, C. N. (2009). Role of three-dimensional power Doppler in the antenatal diagnosis of placenta accreta: comparison with gray-scale and color Doppler techniques. *Ultrasound Obstet Gynecol*, 33(2), 193-203. doi:10.1002/uog.6284
- Silver, R. M., Fox, K. A., Barton, J. R., Abuhamad, A. Z., Simhan, H., Huls, C. K., . . . Wright, J. D. (2015). Center of excellence for placenta accreta. *Am J Obstet Gynecol*, 212(5), 561-568. doi:10.1016/j.ajog.2014.11.018
- Silver, R. M., Landon, M. B., Rouse, D. J., Leveno, K. J., Spong, C. Y., Thom, E. A., . . . Mercer, B. M. (2006). Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol*, 107(6), 1226-1232. doi:10.1097/01.aog.0000219750.79480.84
- Steins Bisschop, C. N., Schaap, T. P., Vogelvang, T. E., & Scholten, P. C. (2011). Invasive placentation and uterus preserving treatment modalities: a systematic review. *Arch Gynecol Obstet*, 284(2), 491-502. doi:10.1007/s00404-011-1934-6
- Stirnemann, J. J., Mousty, E., Chalouhi, G., Salomon, L. J., Bernard, J. P., & Ville, Y. (2011). Screening for placenta accreta at 11-14 weeks of gestation. *Am J Obstet Gynecol*, 205(6), 547.e541-546. doi:10.1016/j.ajog.2011.07.021
- Tantbirojn, P., Crum, C. P., & Parast, M. M. (2008). Pathophysiology of placenta accreta: the role of decidua and extravillous trophoblast. *Placenta*, 29(7), 639-645. doi:10.1016/j.placenta.2008.04.008
- Teixidor Viñas, M., Belli, A. M., Arulkumaran, S., & Chandraran, E. (2015). Prevention of postpartum hemorrhage and hysterectomy in patients with morbidly adherent placenta: a cohort study comparing outcomes before and after introduction of the Triple-P procedure. *Ultrasound Obstet Gynecol*, 46(3), 350-355. doi:10.1002/uog.14728
- Tikkanen, M., Paavonen, J., Loukovaara, M., & Stefanovic, V. (2011). Antenatal diagnosis of placenta accreta leads to reduced blood loss. *Acta Obstet Gynecol Scand*, 90(10), 1140-1146. doi:10.1111/j.1600-0412.2011.01147.x
- Timor-Tritsch, I. E., & Monteagudo, A. (2012). Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. *Am J Obstet Gynecol*, 207(1), 14-29. doi:10.1016/j.ajog.2012.03.007

- Timor-Tritsch, I. E., Monteagudo, A., Cali, G., Palacios-Jaraquemada, J. M., Maymon, R., Arslan, A. A., . . . Mittal, K. R. (2014). Cesarean scar pregnancy and early placenta accreta share common histology. *Ultrasound Obstet Gynecol*, *43*(4), 383-395. doi:10.1002/uog.13282
- Timor-Tritsch, I. E., Monteagudo, A., Cali, G., Vintzileos, A., Viscarello, R., Al-Khan, A., . . . Dar, P. (2014). Cesarean scar pregnancy is a precursor of morbidly adherent placenta. *Ultrasound Obstet Gynecol*, *44*(3), 346-353. doi:10.1002/uog.13426
- Twickler, D. M., Lucas, M. J., Balis, A. B., Santos-Ramos, R., Martin, L., Malone, S., & Rogers, B. (2000). Color flow mapping for myometrial invasion in women with a prior cesarean delivery. *J Matern Fetal Med*, *9*(6), 330-335. doi:10.1002/1520-6661(200011/12)9:6<330::aid-mfm1002>3.0.co;2-o
- van Beekhuizen, H. J., Stefanovic, V., Schwickert, A., Henrich, W., Fox, K. A., M, M. H. G., . . . Duvkot, J. J. (2021). A multicenter observational survey of management strategies in 442 pregnancies with suspected placenta accreta spectrum. *Acta Obstet Gynecol Scand*, *100 Suppl 1*(Suppl 1), 12-20. doi:10.1111/aogs.14096
- Warshak, C. R., Ramos, G. A., Eskander, R., Benirschke, K., Saenz, C. C., Kelly, T. F., . . . Resnik, R. (2010). Effect of predelivery diagnosis in 99 consecutive cases of placenta accreta. *Obstet Gynecol*, *115*(1), 65-69. doi:10.1097/AOG.0b013e3181c4f12a
- Washecka, R., & Behling, A. (2002). Urologic complications of placenta percreta invading the urinary bladder: a case report and review of the literature. *Hawaii Med J*, *61*(4), 66-69.
- Wong, H. S., Hutton, J., Zuccollo, J., Tait, J., & Pringle, K. C. (2008). The maternal outcome in placenta accreta: the significance of antenatal diagnosis and non-separation of placenta at delivery. *NZ Med J*, *121*(1277), 30-38.
- Wright, J. D., Pri-Paz, S., Herzog, T. J., Shah, M., Bonanno, C., Lewin, S. N., . . . Devine, P. (2011). Predictors of massive blood loss in women with placenta accreta. *Am J Obstet Gynecol*, *205*(1), 38.e31-36. doi:10.1016/j.ajog.2011.01.040
- Zelop, C., Nadel, A., Frigoletto, F. D., Jr., Pauker, S., MacMillan, M., & Benacerraf, B. R. (1992). Placenta accreta/percreta/increta: a cause of elevated maternal serum alpha-fetoprotein. *Obstet Gynecol*, *80*(4), 693-694.
- Zelop, C. M., Harlow, B. L., Frigoletto, F. D., Jr., Safon, L. E., & Saltzman, D. H. (1993). Emergency peripartum hysterectomy. *Am J Obstet Gynecol*, *168*(5), 1443-1448. doi:10.1016/s0002-9378(11)90779-0
- Zuckerwise, L. C., Craig, A. M., Newton, J. M., Zhao, S., Bennett, K. A., & Crispens, M. A. (2020). Outcomes following a clinical algorithm allowing for delayed hysterectomy in the management of severe placenta accreta spectrum. *Am J Obstet Gynecol*, *222*(2), 179.e171-179.e179. doi:10.1016/j.ajog.2019.08.035

CHAPTER 22

THROMBOPHILIAS IN PREGNANCY: AN OVERVIEW

Dr. Yasmin ABOALHASAN¹

¹ Department of Obstetrics and Gynecology, Siirt University, Siirt, Turkey
Orcid: 0000-0002-6231-9223 Corresponding author: yasminaboalhasan@gmail.com

1. Introduction

Thrombophilia is a set of hereditary disorders characterized by irregular blood clotting. Thrombophilia is a term used by doctors to describe patients who have abnormal thrombosis (Voicu et al., 2020). Thrombophilias are diseases that are either genetic or acquired that predispose patients to thrombosis. Patients with venous thrombosis and their family are frequently tested for thrombophilia; however, such testing rarely provides useful information and can even harm patients (Stevens et al., 2016).

Venous thromboembolism, which usually includes deep vein thrombosis, pulmonary embolism, or both, is a complex and multifactorial disorder in which a number of potential causes interact and eventually combine to raise an individual's risk to a certain level, resulting in the development of venous occlusive disorders. Thrombophilia is characterized as a predisposition to venous thromboembolism due to an underlying hypercoagulable state caused by genetic or acquired blood coagulation or fibrinolysis problems. Inherited (or genetically determined) and acquired thrombophilia are the two types of thrombophilia. Defects in natural anticoagulants such as antithrombin, protein C, and protein S, as well as elevated clotting factor values (particularly factor VIII) and prothrombotic polymorphisms in genes encoding for factor V (i.e. factor V Leiden) and prothrombin, are among the former. Antiphospholipid antibody syndrome, malignancy, acquired elevations of coagulation factors or acquired reductions of natural inhibitors, or hyperhomocysteinemia are the most common of the latter conditions (Montagnana et al., 2017).

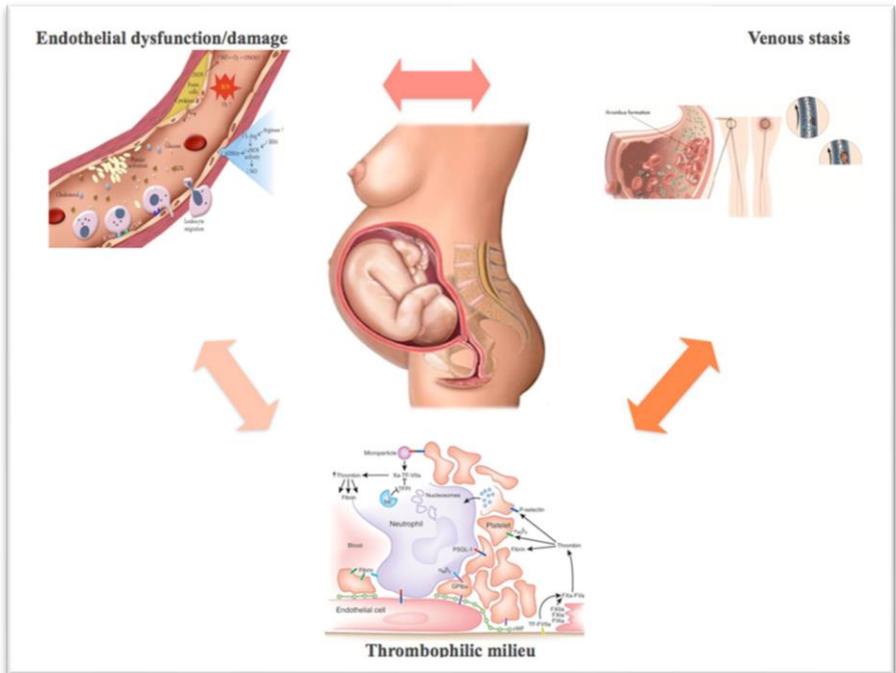


Fig. 1. Virchow's triad in pregnancy. Mechanical venous stasis generated by a pregnant uterus increases coagulable disposition and enhances pregnant women's already higher thrombophilic milieu, as well as endothelial dysfunction/damage, all of which contribute to an elevated risk of venous thromboembolic events during pregnancy (Conti et al., 2014).

Thrombophilia is a blood coagulation disease that raises the risk of venous thromboembolism. Thromboembolism, arterial thrombosis, and pregnancy complications have all been tested for in the last few decades, and the practice has evolved from testing specific populations, resulting in high perceived risks, to broad testing for a variety of conditions, including venous thromboembolism, arterial thrombosis, and pregnancy complications (Middeldorp, 2016). The term thrombophilia refers to a group of diseases that are linked to an increased risk of developing venous thromboembolism. Antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, and myeloproliferative disease are acquired forms of thrombophilia, whereas factor V Leiden variant (G1691A), prothrombin gene (PGA) variant (G20210A), protein C deficiency, protein S deficiency, and antithrombin deficiency are inherited forms (Arachchillage & Makris, 2019).

2. Thrombophilia in pregnancy

For a couple attempting to have a family, a diagnosis of recurrent pregnancy loss can be one of the most difficult moments. While aneuploidy and structural or functional anomalies of the reproductive system may account for some recurrent pregnancy losses, many patients are left with no explanation and, more crucially, no clear therapeutic strategy for conception and live birth. While many of these couples turn to assisted reproductive technology, failed cycles, particularly after the transfer of euploid embryos, may result in further physical, emotional, psychological, and financial stress (Piazza & Grandone, 2021).

Recurrent pregnancy loss, which is defined as three or more miscarriages in a row, affects 1% of all women, with no cause found in half of the instances (Rai & Regan, 2006). Given the importance of sufficient uteroplacental circulation on fetal development and survival, inherited and acquired thrombophilias have been investigated as a possible cause of pregnancy loss (Skeith et al., 2016).

Recurrent losses and pregnancy-related difficulties generate tremendous stress to both couples and health care providers who are hoping for a healthy pregnancy outcome. When it comes to the presence and strength of links between inherited thrombophilia and these problems, the data is mixed. A complete thrombophilia screen is costly, and there is presently no proven effective treatment for women who have recurrent miscarriage and inherited thrombophilia. Women with recurrent miscarriage and placenta-related problems are usually treated with antithrombotic medication, which is based on the concept of microvascular thrombosis of the placenta. For women with recurrent pregnancy losses or late pregnancy complications, inherited thrombophilia testing is not required outside of a clinical trial. Even if a heritable thrombophilic defect is discovered in women with recurrent miscarriages or late pregnancy problems, the presence of thrombophilia markers does not always mean that extra therapy is needed during pregnancy (Arachchillage & Makris, 2019).

Pregnancy increases the risk of venous thromboembolism by four to five times compared to non-pregnant women. Despite the growing use of heparin prophylaxis in high-risk patients, pulmonary embolism remains the greatest cause of maternal death in the Western world. However, there is little research on how to use thromboprophylaxis to its full potential. Thrombophilia, an inherited or acquired tendency for venous

thromboembolism, is linked to pregnancy difficulties such recurrent miscarriage and preeclampsia (Middeldorp et al., 2022). Congenital thrombophilia, a condition marked by protein shortages such as antithrombin, protein C, and protein S, is a leading cause of venous thromboembolism. Congenital thrombophilia is nevertheless a major cause of venous thromboembolism in pregnant patients as well as in young or middle-aged patients without any underlying diseases (Ikejiri et al., 2017).

3. Risks

Immunologic factors play a role in certain miscarriages, but the precise causes of recurrent pregnancy loss remain unknown. A disturbance of maternal–fetal immune homeostasis can lead to miscarriages and recurrent pregnancy loss. One of the most important processes in the fetus's appropriate growth and development is the remodeling of the maternal uterine spiral arteries. For appropriate placentation, a enough oxygen supply is required, which is achieved by suitable vascular modifications. Because the fetus can express paternal antigens and, in some situations, antigens from a gamete donor, the development of fetal tissues can pose an immunologic challenge. The maternal immune system actively responds to fetal antigens, and misregulation of this crosstalk could cause miscarriages and recurrent pregnancy loss. Because acquired thrombophilia is the most common cause of recurrent pregnancy loss owing to thrombophilia, antiphospholipid antibody syndrome should be the focus of screening and treatment (Alecsandru et al., 2021).

Antithrombin, protein C, or protein S deficiency, as well as homozygous factor V Leiden, should be considered for antepartum, postpartum, or both thrombosis prophylaxis. On the basis of thrombophilia and family history alone, women with heterozygous factor V Leiden, heterozygous prothrombin G20210A mutation, or compound heterozygous factor V Leiden and prothrombin G20210A mutation should not be offered thrombosis prophylaxis. These findings should be taken into account in future guidance on the risk of Venous thromboembolism during pregnancy (Croles et al., 2017).

Although thrombophilic gene polymorphism is recognized to be a risk factor for recurrent pregnancy loss, few research have validated its relevance in the risk of recurrent pregnancy loss. The diagnosis of thrombophilic genes polymorphisms is helpful in determining the causes of recurrent pregnancy

loss, as this complex disease can also be influenced by acquired variables such as reproduction-related risk factors and prolonged immobilization (Barut et al., 2018). The difficulty of repeated pregnancy loss stems from a variety of factors, but it all starts with establishing who matches diagnostic criteria for recurrent pregnancy loss, which varies and changes frequently. Even though they do not satisfy the criteria for recurrent pregnancy loss, many patients seek obstetrical assistance after losses, and even those who exactly meet the criteria frequently present a dilemma as to the etiology of their disease (Pritchard et al., 2016).

Independent of a positive family history of venous thromboembolism, women with significant thrombophilia have a high absolute risk of pregnancy-related venous thromboembolism. Regardless of a family history of venous thromboembolism, these women should be considered for regular prenatal thromboprophylaxis (Gerhardt et al., 2016).

Ocular vascular occlusion is generally the result of the physiologic thrombophilia of pregnancy superimposed on previously undiagnosed familial or acquired thrombophilia associated with spontaneous abortion, eclampsia, or maternal thrombosis, and is first recognized during or shortly after birth. Ocular vascular occlusion during pregnancy may be a sign of inherited or acquired thrombophilia, which increases the mother's and pregnancy's thrombotic risk and is linked to spontaneous abortion and eclampsia. Ocular vascular occlusion during pregnancy should trigger an early thrombophilia examination and thromboprophylaxis to prevent harmful maternal and fetal-placental thrombotic events, especially when combined with prior unfavorable pregnancy outcomes (Kurtz et al., 2016).

Doppler ultrasound of the uterine radial artery resistance index (URa-RI) may detect alterations in the uteroplacental circulation and be linked to adverse outcomes in early pregnancy. Thrombophilia is linked to recurrent pregnancy losses, and anticoagulation with low molecular weight heparin improves pregnancy outcomes in women with RPL and thrombophilia. Increased URa-RI at 8 weeks gestation was related with spontaneous abortion in women with recurrent pregnancy losses and hereditary thrombophilia, regardless of other risk factors, while they were on anticoagulation medication (Bao et al., 2019).

Thyroid autoimmunity has been linked to a number of systemic autoimmune diseases, including hereditary thrombophilia and

antiphospholipid syndrome. These disorders must be studied simultaneously in an iodine-deficient nation (Pauleț et al., 2020).

Despite advances in identifying a number of primary causes of fetal miscarriage, some women continue to lose their pregnancies for unknown reasons. It was thought that a hidden genetic influence of coexisting hereditary thrombophilia played a role. Females who carry the D allele of the ACE I/D gene polymorphism are more likely to have multiple pregnancies. In order to provide correct management and genetic counseling to high-risk couples, screening for hereditary thrombophilia in females who are planning to conceive and have a history of recurrent pregnancy losses of unknown cause is very important (Issa et al., 2021).

4. Management & Therapeutic Implications

Pregnancy is a prothrombotic physiological state. The most common cause of direct maternal mortality is venous thromboembolism. Thrombotic processes and thrombophilia are linked to negative pregnancy outcomes like miscarriage and pre-eclampsia. Antithrombotic therapies, including low-molecular-weight heparin, have been studied in women who have had a prior pregnancy outcome, although the results have been mixed. This could be due to the research groups' and disease processes' heterogeneity, resulting in insufficient stratification to guide antithrombotic therapies. Furthermore, the gestational age at which low-molecular-weight heparin treatment is started may be significant. Due to a lack of other effective treatments and its perceived safety in pregnancy, low-molecular-weight heparin is frequently administered in an attempt to prevent these problems, despite scant evidence of efficacy. To better understand disease processes, identify potential biomarkers, and so establish more homogeneous groups for focused treatment, further research is required (Ormesher et al., 2016).

Inherited (hereditary) thrombophilia is a genetic disorder that affects coagulation, being responsible for more than 60% of idiopathic (spontaneous or unprovoked) thromboembolic events. Inherited thrombophilia raises the risk of thromboembolic disease during pregnancy, and it may be linked to a variety of problems, including preeclampsia, recurrent miscarriage, intrauterine growth restriction, early placental detachment, and preterm. Because of the various natural changes in the coagulation system in pregnant women, interpreting a positive thrombophilia test might be problematic. After a thrombotic event or during a pregnancy complication, genetic

identification of thrombophilia is critical not only to ascertain the etiology but also to determine the length of anticoagulant treatment and risk stratification for preventive treatment. In young women with a personal history of venous thromboembolism, first-degree relatives with a history of high-risk thrombophilia, or a personal history of second-trimester miscarriage, screening for hereditary thrombophilia is suggested. History of venous thromboembolism, type and related risk of hereditary thrombophilia, and existence of additional risk factors all influence the decision to offer thromboprophylaxis with anticoagulant medication in pregnant women with inherited thrombophilia. For prophylaxis in pregnancy, low-molecular-weight heparins are chosen, with doses varying based on thrombophilia type, personal history, and associated risk factors. The link between two procoagulant disorders, hereditary thrombophilia and pregnancy, has significant implications for both the mother and the fetus (Trasca et al., 2019).

Recurrent pregnancy loss is characterized as the loss of two or more pregnancies and is generally complex, with aneuploidy and anatomic or physiological problems accounting for the majority of miscarriages. Inherited or acquired thrombophilias, on the other hand, have been linked to recurrent pregnancy loss, however the evidence is mixed. While inherited thrombophilias, such as factor V Leiden and prothrombin gene mutation, are more common in women who have recurrent pregnancy loss than in the general population, a conclusive causative link has yet to be proven. Recent research has suggested that systemic inflammation, as measured by high-sensitivity C-reactive protein, may have a role in infertility. Antithrombotic treatment and antiplatelet medications have been suggested as possible methods for preventing recurrent pregnancy loss based on limited prospective trial results. Because of the complex nature of recurrent pregnancy loss and infertility, these women may be referred to obstetricians and gynecologists, endocrinologists, hematologists, or vascular medicine specialists. This, along with gaps in the data, frequently results in widely disparate diagnostic and therapeutic recommendations, particularly in the area of thrombophilia testing and therapy (Grandone & Piazza, 2021).

Patients with hereditary thrombophilia who were treated with LMWH and low-dose aspirin had greater live-birth rates and fewer miscarriages than those with unexplained recurrent pregnancy loss. Despite thrombophilia

prevention, recurrent pregnancy loss individuals with genetic thrombophilia have an increased risk of preeclampsia (Karada et al., 2017).

The biology of recurrent pregnancy loss and recurrent implantation failure (RPL-RIF) is complicated, with multiple etiologies, with faulty thrombosis being one of the most important and common reasons. Several thrombophilia-related genes and variants linked to RPL-RIF have been widely documented (Udumudi & Lava, 2022). Antithrombin III deficiency, protein C deficiency, Leiden mutation, familial hyperhomocysteinemia, and mutations of additional clotting factors are among the most common thrombophilia gene variants. Hyperaggregation is also linked to various types of thrombophilia. Heparin and its derivatives are now thought to be the safest and most effective medicines for thrombosis prevention and treatment. Due to their low sensitivity, established methods (activated partial thromboplastin time, thrombin time, prothrombin time) and markers of intravascular coagulation activation (soluble fibrin-monomer complexes, D-dimer) cannot be used to assess the efficacy of heparins. The thrombodynamics test, which can detect even minor coagulation problems, is one of the novel tests for qualitative and quantitative evaluation of the plasma coagulation system (Galaiko et al., 2017).

Women who are heterozygous for FVL G1691A or PGA G20210A, or who have a protein C or protein S deficiency, with or without a family history of venous thromboembolism, should follow the instructions. The American Society of Hematology (ASH) guidelines advise against using thromboprophylaxis in these women, although the Royal College of Obstetricians and Gynecologists (RCOG) guidelines advocate it, especially if there are other risk factors for VTE present, such as a high body mass index (Arachchillage, 2020).

All guidelines urge thromboprophylaxis to avoid venous thromboembolism during pregnancy for women who are homozygous for FVL G1691A or have compound heterozygosity for thrombophilic abnormalities, regardless of a family history of venous thromboembolism. However, the ASH guidelines advocate against using antepartum antithrombotic therapy to prevent a first venous thromboembolism in women who are homozygous for PGA G20210A but have no family history of venous thromboembolism, although other guidelines recommend it. We propose antithrombotic prophylaxis during pregnancy for women who have an AT deficit, regardless of whether they have a family history of venous

thromboembolism, but the ASH guidelines suggest that this method be used solely in women who have a family history of venous thromboembolism. Although there is a risk of venous thromboembolism in all three trimesters, the risk appears to be highest in the third. Furthermore, because the postpartum period is substantially shorter than the antepartum period, the daily risk of venous thromboembolism after birth is higher than before (Kourlaba et al., 2016).

Literatures

- Alecsandru, D., Klimczak, A. M., Velasco, J. A. G., Pirtea, P., & Franasiak, J. M. (2021). Immunologic causes and thrombophilia in recurrent pregnancy loss. *Fertility and Sterility*, 115(3), 561-566.
- Arachchillage, D. R. (2020). New paradigms for anticoagulation in pregnant women with inherited thrombophilia. *Clinical Advances in Hematology & Oncology: H&O*, 18(10), 632-635.
- Arachchillage, D. R., & Makris, M. (2019). Inherited thrombophilia and pregnancy complications: should we test?. In *Seminars in thrombosis and hemostasis* (Vol. 45, No. 01, pp. 050-060). Thieme Medical Publishers.
- Arachchillage, D. R., & Makris, M. (2019). Inherited thrombophilia and pregnancy complications: should we test?. In *Seminars in thrombosis and hemostasis* (Vol. 45, No. 01, pp. 050-060). Thieme Medical Publishers.
- Bao, S. H., Chigirin, N., Hoch, V., Ahmed, H., Frempong, S. T., Zhang, M., ... & Kwak-Kim, J. (2019). Uterine radial artery resistance index predicts reproductive outcome in women with recurrent pregnancy losses and thrombophilia. *BioMed research international*, 2019.
- Barut, M. U., Bozkurt, M., Kahraman, M., Yıldırım, E., Imirzalioglu, N., Kubar, A., ... & Çoksüer, H. (2018). Thrombophilia and recurrent pregnancy loss: the enigma continues. *Medical science monitor: international medical journal of experimental and clinical research*, 24, 4288.
- Conti, E., Zezza, L., Ralli, E., Comito, C., Sada, L., Passerini, J., ... & Volpe, M. (2014). Pulmonary embolism in pregnancy. *Journal of thrombosis and thrombolysis*, 37(3), 251-270.
- Croles, F. N., Nasserinejad, K., Duvekot, J. J., Kruip, M. J., Meijer, K., & Leebeek, F. W. (2017). Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis. *Bmj*, 359.
- Galaiko, M. V., Rybina, O. V., Litvinenko, M. S., Klimov, Y., Al'tshuler, B., & Gubkin, A. V. (2017). Thrombophilia and Pregnancy. *Clinical Oncohematology*, 10(3), 409-22.
- Gerhardt, A., Scharf, R. E., Greer, I. A., & Zotz, R. B. (2016). Hereditary risk factors for thrombophilia and probability of venous thromboembolism during pregnancy and the puerperium. *Blood, The Journal of the American Society of Hematology*, 128(19), 2343-2349.
- Grandone, E., & Piazza, G. (2021). Thrombophilia, inflammation, and recurrent pregnancy loss: a case-based review. In *Seminars in reproductive medicine*. Thieme Medical Publishers, Inc..
- Ikejiri, M., Wada, H., Yamada, N., Nakamura, M., Fujimoto, N., Nakatani, K., ... & Ito, M. (2017). High prevalence of congenital thrombophilia in patients with pregnancy-related or idiopathic venous thromboembolism/pulmonary embolism. *International journal of hematology*, 105(3), 272-279.
- Issa, N. M., El-Neily, D. A. M., El Tawab, S. S., & El-Attar, L. M. (2021). The prevalence of specific gene polymorphisms related to thrombophilia in Egyptian women with recurrent pregnancy loss. *Journal of Human Reproductive Sciences*, 14(1), 73.

- Karadağ, C., Yoldemir, T., Karadağ, S. D., İnan, C., Dolgun, Z. N., & Aslanova, L. (2017). Obstetric outcomes of recurrent pregnancy loss patients diagnosed with inherited thrombophilia. *Irish Journal of Medical Science (1971-)*, 186(3), 707-713.
- Kourlaba, G., Relakis, J., Kontodimas, S., Holm, M. V., & Maniadas, N. (2016). A systematic review and meta-analysis of the epidemiology and burden of venous thromboembolism among pregnant women. *International Journal of Gynecology & Obstetrics*, 132(1), 4-10.
- Kurtz, W. S., Glueck, C. J., Hutchins, R. K., Sisk, R. A., & Wang, P. (2016). Retinal artery and vein thrombotic occlusion during pregnancy: markers for familial thrombophilia and adverse pregnancy outcomes. *Clinical Ophthalmology (Auckland, NZ)*, 10, 935.
- Middeldorp, S. (2016). Inherited thrombophilia: a double-edged sword. *Hematology 2014, the American Society of Hematology Education Program Book*, 2016(1), 1-9.
- Middeldorp, S., Naue, C., & Köhler, C. (2022). Thrombophilia, Thrombosis and Thromboprophylaxis in Pregnancy: For What and in Whom?. *Hämostaseologie*, 42(01), 054-064.
- Montagnana, M., Lippi, G., & Danese, E. (2017). An overview of thrombophilia and associated laboratory testing. *Hemostasis and Thrombosis*, 113-135.
- Ormesher, L., Simcox, L., Tower, C., & Greer, I. A. (2016). Management of inherited thrombophilia in pregnancy. *Women's Health*, 12(4), 433-441.
- Pauleț, F. P., Țurcan, N., Gherghiceanu, F., Bohîlțea, R. E., Nemescu, D., & Cirstoiu, M. M. (2020). Prognosis of autoimmune thyroid disease associated with hereditary thrombophilia during pregnancy. *Experimental and Therapeutic Medicine*, 20(3), 2429-2433.
- Piazza, G., & Grandone, E. (2021). Thrombophilia, Antithrombotic Therapy, and Recurrent Pregnancy Loss: A Call for Pragmatism in the Face of Unknowns. In *Seminars in reproductive medicine (Vol. 39, No. 05/06, pp. 167-169)*. Thieme Medical Publishers, Inc..
- Pritchard, A. M., Hendrix, P. W., & Paidas, M. J. (2016). Hereditary thrombophilia and recurrent pregnancy loss. *Clinical obstetrics and gynecology*, 59(3), 487-497.
- Rai, R., & Regan, L. (2006). Recurrent miscarriage. *The Lancet*, 368(9535), 601-611.
- Skeith, L., Carrier, M., Kaaja, R., Martinelli, I., Petroff, D., Schleichner, E., ... & Rodger, M. A. (2016). A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. *Blood, The Journal of the American Society of Hematology*, 127(13), 1650-1655.
- Stevens, S. M., Woller, S. C., Bauer, K. A., Kasthuri, R., Cushman, M., Streiff, M., ... & Douketis, J. D. (2016). Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. *Journal of thrombosis and thrombolysis*, 41(1), 154-164.
- Trasca, L. F., Patrascu, N., Bruja, R., Munteanu, O., Cirstoiu, M., & Vinereanu, D. (2019). Therapeutic implications of inherited thrombophilia in pregnancy. *American Journal of Therapeutics*, 26(3), e364-e374

- Udumudi, A., & Lava, C. (2022). Genetic markers for inherited thrombophilia related pregnancy loss and implantation failure in Indian population—implications for diagnosis and clinical management. *The Journal of Maternal-Fetal & Neonatal Medicine*, 1-9.
- Voicu, D. I., Munteanu, O., Gherghiceanu, F., Arsene, L. V., Bohiltea, R. E., Gradinaru, D. M., & Cirstoiu, M. M. (2020). Maternal inherited thrombophilia and pregnancy outcomes. *Experimental and Therapeutic Medicine*, 20(3), 2411-2414.

CHAPTER 23

POSTOPERATIVE AND POSTPARTUM HEMORRHAGE

Dr Melike Pündük YILMAZ¹

¹ Duzce Provincial Health Directorate, Midwifery, Düzce, Türkiye.
ORCID: <https://orcid.org/0000-0001-5942-8026>
E- MAİL: melikepunduk@gmail.com

Overview:

Postpartum hemorrhage (PPH) is an obstetric emergency case. PPH occurring in the first 24 hours after birth is called primary or early PPH, while PPH occurring 24 hours to 12 weeks after birth is called secondary, late or delayed PPH. Many criteria are used for the diagnosis of PPH worldwide.

Diagnosis and Incidence:

PPH is defined by the volume of blood loss, and the estimated blood loss is defined as ≥ 500 mL after vaginal delivery or ≥ 1000 mL after cesarean section. The incidence of PPH has been reported to be 1 to 3 percent of births using estimated blood loss (Sheldon et al, 2014; Reale et al, 2020). Symptoms related to blood loss are given in table 1.

Table 1: Symptoms of Postpartum Hemorrhage and Blood Loss (Bonnar, 2000)

Blood loss, % (mL)	Systolic blood pressure, mmHg	Signs and Symptoms
10 to 15 (500 to 1000)	normal and ≥ 90	Lightheadedness, palpitations, no or mild increase in heart rate
15 to 25 (1000 to 1500)	80 to 90	Sweating, tachycardia (100 to 120 beats/minute), weakness, tachypnea (respiratory rate of 20 to 24)
25 to 35 (1500 to 2000)	70 to 80	Restlessness, pallor, confusion, tachycardia (120 to 140 beats/minute), oliguria, cool and clammy skin
35 to 45 (2000 to 3000)	50 to 70	Lethargy, anuria, air hunger, tachycardia (>140 beats/minute), collapse

Etiology:

The most common causes of PPH are atony (the most common cause), trauma and acquired or congenital coagulation defects. Atony is responsible for at least 80 percent of PPH cases in the United States (Sheldon et al, 2014). The diagnosis of atony is generally made when the uterus does not

become firm after routine management of the third stage of labor. Atony is described in another chapter. Bleeding from trauma may be due to lacerations (including uterine rupture) or surgical incisions. Cervical and vaginal lacerations may develop after normal delivery and are recognized by lower genital tract examination. In cesarean delivery, bleeding from the uterine incision is usually caused by lateral extension of the incision.

Risk Factors:

There are many interrelated risk factors. Some of those are retained placenta, lacerations, instrumental delivery, large for gestational age newborn, hypertensive disorders, induction of labor, prolonged first or second stage of labor, abnormal placentation and placental abruption (Sheiner et al, 2005; Mhyre et al, 2013). Other risk factors are previous PPH, high parity, chorioamnionitis, uterine inversion, leiomyoma, uterine enlargement (eg, multiple gestation, polyhydramnios, macrosomia) and bleeding diathesis (Bateman et al, 2010).

Management:

Observational estimates are misleading, especially if bleeding is heavy. For this reason, the important thing is to measure blood loss. In this way, early intervention can prevent possible complications. Maternal death, need for blood transfusion, postpartum hysterectomy, Sheehan syndrome and abdominal compartment syndrome are possible consequences of postpartum hemorrhage. While the risk of recurrence is partly dependent on the underlying cause, the overall risk of recurrence in subsequent pregnancy reaches 18 percent (Oberge et al, 2014; Ruiters et al, 2019). Other causes of postpartum hemorrhage, except for uterine atony, which is described in another section, are discussed below.

1- Puerperal uterine inversion

Uterine inversion is turning the uterus partially or completely inside out. It is a rare complication (about 1 in 3500 to 20000 deliveries) of vaginal or cesarean delivery (Coad et al, 2017; Witteveen et al, 2013). If not recognized and treated, uterine inversion can lead to severe hemorrhage and shock. Although the pathogenesis is not fully understood, excessive cord traction and Credé maneuver are blamed (Lipitz and Frenkel, 1988). There

are other possible underlying causes as well. Some of risk factors are rapid or prolonged labor and delivery, macrosomia, short umbilical cord, nulliparity, use of uterine relaxants, retained placenta, uterine anomalies (Coad et al, 2017; Witteveen et al, 2013; Adesiyun, 2007). On vaginal examination, the inverted fundus fills the vagina and the uterine fundus is not palpable on abdominal examination. The most common disorder in differential diagnosis is a prolapsed fibroid. In order to reposition the uterine fundus, uterotonic drugs should be discontinued and a manual attempt should be made to return it to its normal position. Uterine relaxants can be used as a supplement. If this procedure is unsuccessful, laparotomy should be initiated. Huntington procedure or Haultain procedure is applied in laparotomy. Meanwhile, the placenta should not be removed before the uterus returns to its normal position, because its removal beforehand increases blood loss (Witteveen et al, 2013; You and Zahn, 2006). A uterotonic agent is administered after uterine replacement to induce myometrial contraction, maintain uterine involution, and prevent reinversion.

2- Perineal lacerations

Vaginal and perineal trauma commonly occurs with vaginal delivery. Approximately 70 percent of patients who give birth require surgical repair (Rogers et al, 2014; Vale de Castro Monteiro et al, 2016). Examination of the distal perineum, vagina and anorectum should be performed after vaginal delivery to determine the extent of the vaginal tear. Injuries are divided into four by classification (Sultan, 1999; ACOG, 2016). In first-degree lacerations, the perineal muscles remain intact. In second-degree lacerations, the anal sphincter muscles remain intact, while the perineal muscles are not intact. Third-degree lacerations affect the internal and/or external sphincter, while fourth-degree lacerations affect the anal mucosa (Table 2).

Table 2: Classification of Obstetric Lacerations (ACOG)

First degree
Injury to perineal skin only
Second degree
Injury to perineum involving perineal muscles but not involving anal sphincter
Third degree
Injury to perineum involving anal sphincter complex
3a: Less than 50% of external anal sphincter thickness torn
3b: More than 50% external anal sphincter thickness torn
3c: Both external anal sphincter and internal anal sphincter torn
Fourth degree
Injury to perineum involving anal sphincter complex (external anal sphincter and internal anal sphincter) and anal epithelium

Antibiotics may not be routinely administered prior to repair of first- and second-degree obstetric lacerations but a single dose of antibiotics should be given before repair of third- or fourth-degree obstetric lacerations. Complications from third- and fourth-degree laceration and repair include infection and symptoms of pelvic floor dysfunction such as incontinence and prolapse.

3- Female lower genital tract trauma

Lacerations of the cervix, vagina or vulva commonly occur during childbirth. Obstetric risk factors associated with lower genital tract trauma include nulliparity, large baby, precipitous birth, operative delivery, and episiotomy. Non-obstetric vulvar hematomas are most common with blunt trauma, whereas most vaginal injuries occur as a result of penetrating

trauma. Vulvar hematomas are managed conservatively if possible. Deep or large vaginal lacerations may be repaired in one or more layers.

4- Obstetric anal sphincter injury

It is a complication that occurs during vaginal delivery. Also called third and fourth degree perineal lacerations, these injuries involve the anal sphincter complex and, in more severe cases, the anal mucosa. While the risk is 5.7 percent in the first delivery, the overall risk is 6.3 percent (Jha and Parker, 2016). The risk factors are vaginal delivery, obstetric factors (primiparity, large birth weight, and vaginal birth after cesarean delivery), operative vaginal delivery, episiotomy, fetal macrosomia, shoulder dystocia, prolonged second stage, fetal occiput posterior presentation, and increasing maternal age (Fenner et al, 2003; Pergialiotis et al, 2020). Factors that appear to reduce the incidence of obstetric anal sphincter injury are episiotomy avoidance, perineal massage, and maternal delivery position, but they do not eliminate the risk. Obstetric anal sphincter injury increases the risk of loss of bowel control. For this reason, a decision should be made for future delivery. However, there is insufficient data to make recommendations regarding the mode of delivery in the next pregnancy for these women (Webb et al, 2017). However, it should be noted that women with two previous obstetric anal sphincter injury have an approximately 10-fold increased risk of sphincter injury in the next delivery (Edwards et al, 2006). If it is diagnosed following vaginal delivery, surgical repair is the mainstay of treatment.

5- Puerperal hematomas

Puerperal hematomas occur in 1:300 to 1:500 births and are rarely a potentially life-threatening delivery complication (Zahn and Yeomans, 1990; Villella et al, 2001). Most puerperal hematomas are associated with operative delivery or episiotomy. The risk factors are nulliparity, fetal macrosomia, preeclampsia, prolonged second stage of labor and operative vaginal delivery (Guerriero et al, 2004; Ridway, 1995). The most common locations for puerperal hematomas are the vulva, vaginal-paravaginal area and retroperitoneum. Most vulvar hematomas arise during episiotomy or from injuries to branches of the pudendal artery (Zahn and Yeomans, 1990; Guerriero et al, 2004). Small, nonexpanding vulvar hematomas will often resolve with conservative management. However, if the hematoma enlarges

or the hematocrit decreases on physical examination or imaging studies, immediate surgical intervention is required. While vaginal-paravaginal hematomas are usually associated with forceps delivery, they are mainly caused by injuries to the descending branches of the uterine artery (Zahn and Yeomans, 1990; Ridway, 1995). The approach to vaginal hematomas is similar to vulvar hematomas. As with vulvar hematomas, vaginal hematomas larger than approximately 4 cm may need to be drained (Benrubi et al, 1987; Zahn et al, 1996). Retroperitoneal hematomas typically result from injury to branches of the hypogastric artery. The patient with retroperitoneal hematoma usually requires surgical treatment, but since it is a confined space, conservative treatment may be sufficient. After opening the retroperitoneal space, hemostasis can be achieved by identifying and ligating the ruptured blood vessel or ligating the hypogastric artery. Although small hematomas may be asymptomatic, most hematomas are associated with pain and mass effects, however, hemodynamic instability may be a manifestation of ongoing bleeding. Venous bleeding almost always occurs in hemodynamically stable patients; arterial hemorrhages often cause hemodynamic instability. Diagnostic evaluation is used to evaluate the growth of the hematoma and to evaluate retroperitoneal bleeding that cannot be detected on physical examination. Although ultrasound is used first, computed tomography is more useful in retroperitoneal hemorrhages.

6- Uterine rupture

The term rupture is defined as the complete disruption of all uterine layers, including the serosa, while dehiscence is a condition in which the serosa is intact. The overall incidence of uterine rupture in patients who have had a previous cesarean delivery is approximately 0.3 percent. However, uterine rupture is far more common among women who undergo a trial of labor after cesarean than in those who undergo planned repeat cesarean delivery (Guise et al, 2010). Factors that increase the risk of rupture are previous uterine rupture, previous fundal, high or low vertical hysterotomy and use of induction in women who have had a previous cesarean delivery. Although there is no fetal heart rate pattern specific to rupture in the clinic, it is the most common sudden and prolonged fetal bradycardia. In addition, there may be findings such as abdominal pain, vaginal bleeding, loss of uterine tone, elevation of the prominent fetal part, and hemodynamic instability. Definitive diagnosis is based on identification of complete

disruption of all uterine layers during imaging or laparotomy. Between 14 and 33 percent of patients with uterine rupture have undergone hysterectomy. The perinatal mortality rate from rupture ranges from 5 to 26 percent (NIHCDC, 2010; Al- Zirgi et al, 2018). While delivery at 36-37 weeks is recommended for those with a history of rupture in a previous pregnancy, delivery at 37-38 weeks is recommended for dehiscence (ACOG, 2019) .

In addition, there is unscarred uterine rupture and is rare (Gibbins et al, 2015). Its etiology includes motor vehicle accident and obstetric maneuvers such as fundal compression. The some of risk factors are uterine anomaly, dystocia, macrosomia, multiple gestation and abnormal placentation (Gibbins et al, 2015; Khabbaz et al, 2001). Clinical findings are similar to scarred uterine rupture. It is difficult to diagnose because it is unexpected and rare, but it is not critical to place a preoperative diagnose because urgent delivery is required due to disturbances in fetal heartbeat. Uterine rupture includes a wide spectrum of perinatal complications, from prolonged intrauterine hypoxia to death (Chauhan et al, 2003; Phelan et al, 2007). The decision for hysterectomy or defect repair is based on a combination of factors, such as the patient's desire for a future pregnancy and the extent of uterine damage from the rupture. If the defect is repaired, a reasonable approach is a two- or three-layer closure with an absorbable suture, similar to repair of any hysterotomy.

7- Placental abruption

Placental abruption is the partial or complete detachment of the placenta before delivery in pregnancies over 20 weeks. Main symptoms are vaginal bleeding, abdominal pain, uterine tenderness, and a nonreassuring fetal heart rate pattern. It is an important cause of both maternal morbidity and neonatal morbidity and mortality. Its incidence at birth is between 3 and 10 per 1000 (Maeland et al, 2021; Lueth et al, 2021). The most important risk factor is the history of ablation, and other major risk factors are listed in Table 3 (Ruiter et al, 2015; Ananth et al, 2001) (Table 3).

Table 3: Major Risk Factors for Placental Abruption (Ananth and Kinzler, 2022)

Risk factor	Singleton gestations		Twin gestations	
	Strength	RR/OR	Strength	RR/OR
Acute etiology				
Abdominal trauma/accidents	+++			
Cocaine or other drug abuse	+++	5.0 to 10.0		
Polyhydramnios	++	2.0 to 3.0	++	1.7
Obstetric/medical risk factors				
Chronic hypertension	++	1.8 to 5.1		
Preeclampsia/pregnancy-induced hypertension	++	0.4 to 4.5		
Eclampsia	+++	3.0 to 5.5	++	1.6 to 2.0
Premature rupture of membranes	++	1.8 to 5.1	++	1.5 to 2.5
Chorioamnionitis	++	2.0 to 2.5	++	1.7
Previous ischemic placental disease				
Preeclampsia	++	1.5		
Fetal growth restriction/small for gestational age infant	++	1.4		
Previous abruption	++++	8.0 to 12.0		
Sociodemographic/behavioral				
Maternal age	+	1.1 to 1.3	+	1.1 to 1.4
Parity	+	1.1 to 1.6	+	1.1 to 1.7
Smoking during pregnancy	++	1.4 to 2.5	++	1.7

OR: odds ratio; RR: relative risk.

Patients present with vaginal bleeding, mild to moderate abdominal and/or back pain, and uterine contractions. Diagnosis is made clinically. In patients with classical symptoms, fetal heart rate abnormalities support the diagnosis. Vaginal bleeding may not be at all in some patients, while it may be life-threatening in others.

Retroplacental hematoma is the classic ultrasound finding, but is absent in many patients. As a supportive imaging modality for diagnosis, the sensitivity of ultrasound findings for the diagnosis of abruption is only 25 to 60 percent (Glantz and Purnell, 2002; Shinde et al, 2016).

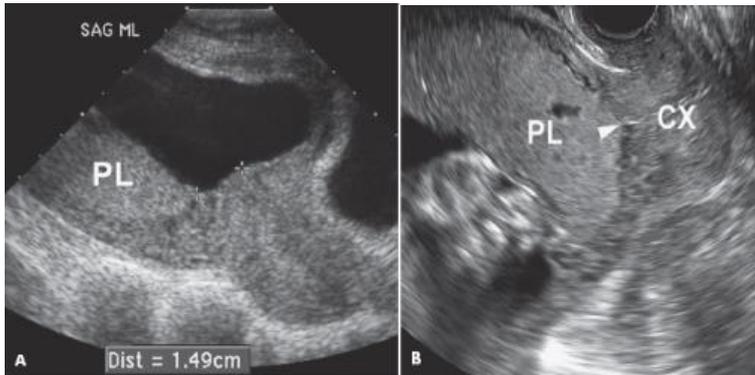
Maternal outcomes are associated with excessive blood loss. Some of these include hypovolemic shock, renal failure, adult respiratory distress syndrome, multiple organ failure, peripartum hysterectomy, and rarely death (Oyelese and Ananth, 2006; Tikkanen, 2011). Neonatal consequences are increased perinatal morbidity and mortality related to hypoxemia, asphyxia, low birth weight and preterm birth (Ananth et al, 1999; Lueth et al, 2021). In an unstable mother with a living fetus, a cesarean section is the best option if delivery is not imminent, but if the fetus is dead, a vaginal delivery can be attempted, although a cesarean section is usually preferred because placental separation is greater than 50 percent. In these patients, care should be taken in terms of Couvelaire uterus, and treatment of atony and postpartum hemorrhage should be performed aggressively. The response to treatment may be lower than other causes of atony, and these patients are at high risk for postpartum hysterectomy. Differential diagnoses include labor, placenta previa, uterine rupture, and subchorionic hematoma.

8- Placenta previa

Placenta previa is a condition in which the placenta partially or wholly blocks the cervix, so interfering with normal delivery of a baby. The characteristic symptom of placenta previa is painless vaginal bleeding. The major risk factors for placenta previa are multiple gestation, history of placenta previa and history of cesarean delivery (Ananth et al, 1999; Klar and Michels, 2014). Other risk factors are multiparity, smoking, advanced maternal age and history of uterine surgery. Placenta previa should be suspected in every woman presenting with vaginal bleeding above the 20th gestational week. The diagnosis of placenta previa is preferably made using transvaginal ultrasound. It is divided into two as complete and low-lying placenta previa. While it is defined as complete placenta previa that

completely covers the placental os, those that are closer than 20 mm to the cervical os are called low lying placenta previa (Figure 1- Figure 2). For the low-lying placenta, it is adjacent to the internal os but does not cover it.

Figure 1: Low-lying Placenta- A **Figure 2:** Complete Placenta Previa- B



When placenta previa is diagnosed, the possibility of placenta previa-accreta spectrum should be considered. This is particularly important if the placenta extends over the area of the previous hysterotomy and is therefore most common in anterior placenta previa (Silver et al, 2006). The frequency of malpresentation, vasa previa, fetal growth restriction and congenital anomalies has increased. Placenta previa recurs in 4 to 8 percent of subsequent pregnancies (Lavery, 1990; Roberts et al, 2012). Maternal morbidity from placenta previa is mainly associated with antepartum and postpartum hemorrhage (Crane et al, 2000). Neonatal morbidity and mortality are associated with preterm birth (Salihu et al, 2003). Planned cesarean birth of patients with stable placenta previa should be accomplished at 36+0 to 37+6 weeks and interruption of the placenta should be avoided as this increases the risk of fetal bleeding.

9- Placenta accreta spectrum

Placenta accreta spectrum (PAS) is a general term used to describe abnormal trophoblast invasion into the myometrium, and sometimes to or beyond the serosa. It has three subtypes: placenta accreta, increta, and percreta. In placenta accreta placental villi attach to the myometrium. Placenta increta, on the other hand, placental villi invades myometrium. The

placental villus extends to the serosa in the placenta percreta. The incidence rates are accreta, increta, and percreta, respectively (Jauniaux et al, 2019). The most important risk factor is a placenta previa after a prior cesarean delivery. The frequency of PAS is much lower in women who delivered by cesarean section in the absence of placenta previa (Silver et al, 2006). Other risk factors are previous uterine surgery, multiparity, manual abruption of the placenta, maternal age greater than 35 years, history of pelvic irradiation and postpartum endometritis (Kohn et al, 2018; Miller et al, 2021). It is usually suspected on ultrasound examination in the asymptomatic patient and clinical manifestation is life-threatening bleeding during removal of the placenta. Placental lacunae and disruption of the interface between the bladder wall-uterine serosa are the most reliable sonographic diagnostic findings. Magnetic resonance imaging is helpful when the diagnosis is unclear and for the extent of placental invasion. For patients who are stable, have no bleeding or are not at risk of preterm delivery, delivery is planned between 34 and 36 weeks. Peripartum hysterectomy may be necessary to prevent or control postpartum hemorrhage. It is the safest approach. In rare cases, uterine preservation may be attempted if a future childbearing is desired.

10- Secondary (late) postpartum hemorrhage

A- Overview:

It is defined as any important uterine bleeding occurring between 24 hours and 12 weeks postpartum (CPBO, 2017; Dossou, 2015). It most commonly occurs between one and two weeks after birth (Dossou, 2015). All patients present with vaginal bleeding.

B- Etiology and Risk Factors:

The most common reasons of secondary PPH are retained placenta and infection (Dossou, 2015). Inherited or acquired bleeding diatheses, arteriovenous malformations and choriocarcinoma are rare reasons (Aziz et al, 2004; Zubor et al, 2014).

C- Diagnosis

Physical examination and a complete history are required for diagnosis. Birth history, presence of fever, risk factors for a bleeding

diathesis, and drug use are questioned. With the examination, the bleeding focus is tried to be clarified. Examination with ultrasound, complete blood count, coagulation tests, measurement of human chorionic gonadotropin values are helpful for diagnosis. Ultrasound examination of the uterus can identify the cause of bleeding and helps to exclude certain factors in the differential diagnosis.

D- Treatment

The approach in treatment is primarily to determine the etiology and accordingly to choose the medical or surgical treatment option. Methylergonovine, carboprost tromethamine and oxytocin are used in medical treatment. Surgical procedures (dilation and curettage, aspiration curettage) are probably the best approach when a significant amount of tissue is present in the uterine cavity. Surgical procedures are often effective when medical treatment fails, even if retained tissue cannot be identified sonographically (Hoveyda and Mackenzie, 2001; King et al, 1989). The major complications of curettage are uterine perforation and intrauterine adhesions. Performing curettage with ultrasound guidance reduces uterine perforation rates (Mulic- Lutvica and Axelsson, 2006). If there is fever, pelvic tenderness and foul-smelling discharge, which are signs of endometritis during the examination, antibiotic use is necessary. For other rare causes, the necessary treatment is planned according to the diagnosis.

REFERENCES

- Adesiyun, A.G. (2007). Septic postpartum uterine inversion. *Singapore Med J* 48:943.
- Aiken, C.E., Aiken, A.R., Prentice, A. (2015). Influence of the duration of the second stage of labor on the likelihood of obstetric anal sphincter injury. *Birth* 42:86.
- Al-Zirqi, I., Daltveit, A.K., Vangen, S. (2018). Infant outcome after complete uterine rupture. *Am J Obstet Gynecol* 219:109.e1.
- Al-Zirqi, I., Vangen, S. (2020). Prelabour uterine rupture: characteristics and outcomes. *BJOG* 127:1637.
- American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 205: Vaginal Birth After Cesarean Delivery. *Obstet Gynecol* 2019; 133:e110.
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 165: Prevention and Management of Obstetric Lacerations at Vaginal Delivery. *Obstet Gynecol*. 2016 Jul;128(1):e1-e15. doi: 10.1097/AOG.0000000000001523. PMID: 27333357.
- American College of Obstetricians and Gynecologists (ACOG). Available at: <https://www.acog.org/media/Departments/Patient-Safety-and-Quality-Improvement/2014reVITALizeObstetricDataDefinitionsV10.pdf?dmc=1&ts=20190103T1910133780> (Accessed on May 3, 2022).
- Ananth, C.V., Berkowitz, G.S., Savitz, D.A., Lapinski, R.H. (1999). Placental abruption and adverse perinatal outcomes. *JAMA* 282:1646.
- Ananth, C.V., Demissie, K., Smulian, J.C., Vintzileos, A.M. (2003). Placenta previa in singleton and twin births in the United States, 1989 through 1998: a comparison of risk factor profiles and associated conditions. *Am J Obstet Gynecol* 188:275.
- Ananth, C.V., Kinzler, W.L. (2022). Placental abruption: Pathophysiology, clinical features, diagnosis, and consequences. UpToDate. https://www.uptodate.com/contents/placental-abruption-pathophysiology-clinical-features-diagnosis-and-consequences?search=Placental%20abruption:%20Pathophysiology,%20clinical%20features,%20diagnosis,%20and%20consequences&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
- Ananth, C.V., Smulian, J.C., Demissie, K., et al. (2001). Placental abruption among singleton and twin births in the United States: risk factor profiles. *Am J Epidemiol* 153:771.
- Aziz, N., Lenzi, T.A., Jeffrey, R.B. Jr, Lyell, D.J. (2004). Postpartum uterine arteriovenous fistula. *Obstet Gynecol* 103:1076.
- Baskett, T.F. (2002). Acute uterine inversion: a review of 40 cases. *J Obstet Gynaecol Can* 24:953.

- Bateman, B.T., Berman, M.F., Riley, L.E., Leffert, L.R. (2010). The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesth Analg* 110:1368.
- Benrubi, G., Neuman, C., Nuss, R.C., Thompson, R.J. (1987). Vulvar and vaginal hematomas: a retrospective study of conservative versus operative management. *South Med J* 80:991.
- Bonnar, J. (2000). Massive obstetric haemorrhage. *Baillieres Best Pract Res Clin Obstet Gynaecol* 14:1.
- Chauhan, S.P., Martin, J.N. Jr, Henrichs, C.E., et al. (2003). Maternal and perinatal complications with uterine rupture in 142,075 patients who attempted vaginal birth after cesarean delivery: A review of the literature. *Am J Obstet Gynecol* 189:408.
- Coad, S.L., Dahlgren, L.S., Hutcheon, J.A. (2017). Risks and consequences of puerperal uterine inversion in the United States, 2004 through 2013. *Am J Obstet Gynecol* 217:377.e1.
- Committee on Practice Bulletins-Obstetrics (CPBO). (2017). Practice Bulletin No. 183: Postpartum Hemorrhage. *Obstet Gynecol* 130:e168.
- Crane, J.M., Van den Hof, M.C., Dodds, L., et al. (2000). Maternal complications with placenta previa. *Am J Perinatol* 17:101.
- Dossou, M., Debost-Legrand, A., Déchelotte, P., et al. (2015). Severe secondary postpartum hemorrhage: a historical cohort. *Birth* 42:149.
- Edwards, H., Grotegut, C., Harmanli, O.H., et al. (2006). Is severe perineal damage increased in women with prior anal sphincter injury? *J Matern Fetal Neonatal Med* 19:723.
- Fenner, D.E., Genberg, B., Brahma, P., et al. (2003). Fecal and urinary incontinence after vaginal delivery with anal sphincter disruption in an obstetrics unit in the United States. *Am J Obstet Gynecol* 189:1543.
- Ford, J.B., Roberts, C.L., Bell, J.C., et al. (2007). Postpartum haemorrhage occurrence and recurrence: a population-based study. *Med J Aust* 187:391.
- Gibbins, K.J., Weber, T., Holmgren, C.M., et al. (2015). Maternal and fetal morbidity associated with uterine rupture of the unscarred uterus. *Am J Obstet Gynecol* 213:382.e1.
- Glantz, C., Purnell, L. (2002). Clinical utility of sonography in the diagnosis and treatment of placental abruption. *J Ultrasound Med* 2002; 21:837.
- Guerriero, S., Ajossa, S., Bargellini, R., et al. (2004). Puerperal vulvovaginal hematoma: sonographic findings with MRI correlation. *J Clin Ultrasound* 32:415.
- Guise, J.M., Eden, K., Emeis, C., et al. (2010). Vaginal birth after cesarean: new insights. *Evid Rep Technol Assess (Full Rep)* :1.
- Hoveyda, F., MacKenzie, I.Z. (2001). Secondary postpartum haemorrhage: incidence, morbidity and current management. *BJOG* 108:927.
- Jaffe, M.H., Schoen, W.C., Silver, T.M., et al. (1981). Sonography of abruptio placentae. *AJR Am J Roentgenol* 137:1049.
- Jauniaux, E., Bunce, C., Grønbeck, L., Langhoff-Roos, J. (2019). Prevalence and main outcomes of placenta accreta spectrum: a systematic review and meta-analysis. *Am J Obstet Gynecol* 221:208.

- Jha, S., Parker, V. (2016). Risk factors for recurrent obstetric anal sphincter injury (rOASI): a systematic review and meta-analysis. *Int Urogynecol J* 27:849.
- King, P.A., Duthie, S.J., Dong, Z.G., Ma, H.K. (1989). Secondary postpartum haemorrhage. *Aust N Z J Obstet Gynaecol* 29:394.
- Khabbaz, A.Y., Usta, I.M., El-Hajj, M.I., et al. (2001). Rupture of an unscarred uterus with misoprostol induction: case report and review of the literature. *J Matern Fetal Med* 10:141.
- Klar, M., Michels, K.B. (2014). Cesarean section and placental disorders in subsequent pregnancies--a meta-analysis. *J Perinat Med* 42:571.
- Kohn, J.R., Shamshirsaz, A.A., Popek, E., et al. (2018). Pregnancy after endometrial ablation: a systematic review. *BJOG* 125:43.
- Kojima, T., Takami, M., Shindo, R., et al. (2021). Perinatal outcomes of recurrent placental abruption. *J Matern Fetal Neonatal Med* 34:2192.
- Lavery, J.P. (1990). Placenta previa. *Clin Obstet Gynecol* 33:414.
- Lipitz, S., Frenkel, Y. (1988). Puerperal inversion of the uterus. *Eur J Obstet Gynecol Reprod Biol* 27:271.
- Lueth, A., Blue, N., Silver, R.M., et al. (2021). Prospective evaluation of placental abruption in nulliparous women. *J Matern Fetal Neonatal Med* 1.
- Maeland, K.S., Morken, N.H., Schytt, E., et al. (2021). Placental abruption in immigrant women in Norway: A population-based study. *Acta Obstet Gynecol Scand* 100:658.
- Meister, M.R., Cahill, A.G., Conner, S.N., et al. (2016). Predicting obstetric anal sphincter injuries in a modern obstetric population. *Am J Obstet Gynecol* 215:310.e1.
- Mhyre, J.M., Shilkrut, A., Kuklina, E.V., et al. (2013). Massive blood transfusion during hospitalization for delivery in New York State, 1998-2007. *Obstet Gynecol* 122:1288.
- Miller, H.E., Leonard, S.A., Fox, K.A., et al. (2021). Placenta Accreta Spectrum Among Women With Twin Gestations. *Obstet Gynecol* 137:132.
- Mulic-Lutvica, A., Axelsson, O. (2006). Ultrasound finding of an echogenic mass in women with secondary postpartum hemorrhage is associated with retained placental tissue. *Ultrasound Obstet Gynecol* 28:312.
- Nageotte, M.P. (2014). Always be vigilant for placenta accreta. *Am J Obstet Gynecol* 211:87.
- National Institutes of Health Consensus Development Conference Panel (NIHCDC). (2010). National Institutes of Health Consensus Development conference statement: vaginal birth after cesarean: new insights March 8-10, 2010. *Obstet Gynecol* 115:1279.
- Oberg, A.S., Hernandez-Diaz, S., Palmsten, K., et al. (2014). Patterns of recurrence of postpartum hemorrhage in a large population-based cohort. *Am J Obstet Gynecol* 210:229.e1.
- Oyelese, Y., Ananth, C.V. (2006). Placental abruption. *Obstet Gynecol* 108:1005.
- Pergialiotis, V., Bellos, I., Fanaki, M., et al. (2020). Risk factors for severe perineal trauma during childbirth: An updated meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 247:94.

- Phelan, J.P., Korst, L.M., Martin, G.I. (2007). Causation--fetal brain injury and uterine rupture. *Clin Perinatol* 34:409.
- Propst, A.M., Thorp, J.M., Jr. (1998). Traumatic vulvar hematomas: conservative versus surgical management. *South Med J* 91:144.
- Reale, S.C., Easter, S.R., Xu, X., et al. (2020). Trends in Postpartum Hemorrhage in the United States From 2010 to 2014. *Anesth Analg* 130:e119.
- Ridgway, L.E. (1995). Puerperal emergency. Vaginal and vulvar hematomas. *Obstet Gynecol Clin North Am* 22:275.
- Roberts, C.L., Algert, C.S., Warrendorf, J., et al. (2012). Trends and recurrence of placenta praevia: a population-based study. *Aust N Z J Obstet Gynaecol* 52:483.
- Rogers, R.G., Leeman, L.M., Borders, N., et al. (2014). Contribution of the second stage of labour to pelvic floor dysfunction: a prospective cohort comparison of nulliparous women. *BJOG* 121:1145.
- Ruiter, L., Kazemier, B.M., Mol, B.W.J., Pajkrt, E. (2019). Incidence and recurrence rate of postpartum hemorrhage and manual removal of the placenta: A longitudinal linked national cohort study in The Netherlands. *Eur J Obstet Gynecol Reprod Biol* 238:114.
- Ruiter, L., Ravelli, A.C., de Graaf, I.M., et al. (2015). Incidence and recurrence rate of placental abruption: a longitudinal linked national cohort study in the Netherlands. *Am J Obstet Gynecol* 213:573.e1.
- Saleem, Z., Rydhström, H. (2004). Vaginal hematoma during parturition: a population-based study. *Acta Obstet Gynecol Scand* 2004; 83:560.
- Salihi HM, Li Q, Rouse DJ, Alexander GR. Placenta previa: neonatal death after live births in the United States. *Am J Obstet Gynecol* 2003; 188:1305.
- Sheiner E, Sarid L, Levy A, et al. Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study. *J Matern Fetal Neonatal Med* 2005; 18:149.
- Sheldon, W.R., Blum, J., Vogel, J.P., et al. (2014). Postpartum haemorrhage management, risks, and maternal outcomes: findings from the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG* 121 Suppl 1:5.
- Shinde, G.R., Vaswani, B.P., Patange, R.P., et al. (2016). Diagnostic Performance of Ultrasonography for Detection of Abruption and Its Clinical Correlation and Maternal and Foetal Outcome. *J Clin Diagn Res* 10:QC04.
- Sholl, J.S. (1987). Abruptio placentae: clinical management in nonacute cases. *Am J Obstet Gynecol* 156:40.
- Silver, R.M., Landon, M.B., Rouse, D.J., et al. (2006). Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol* 107:1226.
- Sultan, A.H. (1999). Obstetric perineal injury and anal incontinence (editorial). *Clin Risk* 5:193.
- Witteveen, T., van Stralen, G., Zwart, J., van Roosmalen, J. (2013). Puerperal uterine inversion in the Netherlands: a nationwide cohort study. *Acta Obstet Gynecol Scand* 92:334.

- You, W.B., Zahn, C.M. (2006). Postpartum hemorrhage: abnormally adherent placenta, uterine inversion, and puerperal hematomas. *Clin Obstet Gynecol* 49:184.
- Zubor, P., Kajo, K., Dokus, K., et al. (2014). Recurrent secondary postpartum hemorrhages due to placental site vessel subinvolution and local uterine tissue coagulopathy. *BMC Pregnancy Childbirth* 14:80.

CHAPTER 24

UTERINE ATONY AND ASSOCIATED HEMORRHAGES

Dr. Melike Pündük YILMAZ¹

¹ Duzce Provincial Health Directorate, Midwifery, Düzce, Türkiye.
ORCID: <https://orcid.org/0000-0001-5942-8026>
E- MAIL: melikepunduk@gmail.com

1- Overview:

Atony is the most common cause of postpartum hemorrhage. Atony is responsible for at least 80 percent of postpartum hemorrhage cases in the United States (Reale et al, 2020). The diagnosis of atony is usually made after the third stage of labor, when the uterus does not become firm. While blood loss may be much greater than observed with diffuse atony, it usually responds to administration of uterotonic drugs. In focal localized atony, the lower uterine segment and lower uterine segment are usually atonic and difficult to detect on abdominal examination.

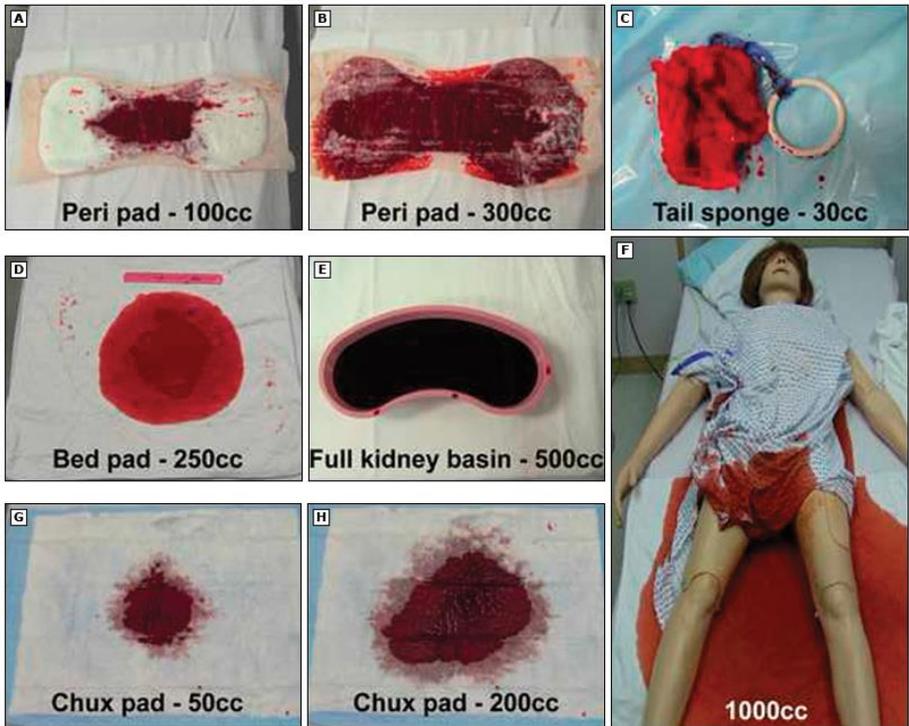
2- Risk Factors:

In many women, the development of uterine atony is partially predictable from the course of labor. However, in one study, no risk factor was found in half of the women who developed atony after cesarean section (Rouse, 2006). Some risk factors for atonia are primiparity, high parity, large for gestational age newborn, polyhydramnios, multiple gestation, induction and augmentation of labor, hypertonic or hypotonic uterine activity and a history of atony (Driessen, 2011).

3- Assessment:

Primarily, vital signs such as blood pressure, heart rate, respiratory rate and urine output should be evaluated. Signs of tachypnea, tachycardia, hypotension, low oxygen saturation and hypovolemia are seen in excessive bleeding. As a general rule, a progressive increase in heart rate and a decrease in blood pressure in any obstetric patient indicates ongoing bleeding. The patient should be examined to determine the bleeding focus. Uterine tone should be evaluated quickly. However, it should be kept in mind that significant bleeding may occur from a poorly contracted and enlarged lower segment despite adequate upper segment contraction (Figure 1).

Figure 1: Visual Aid for Estimating Intrapartum Blood Loss (Zuckerwise at al, 2014)



Visual aid. Pocket card with images of measured volumes of artificial blood.

4- Treatment:

Uterine massage and the use of uterotonic drugs are very important for the treatment of atony. Fundal massage stimulates the contraction of the atonic uterus. In bimanual uterine massage, which manually compresses the corpus between the clinician's two hands, one hand is made into a fist and placed vaginally on the anterior fornix, while the other massages the abdominal region while pressing the fundus firmly against the vaginal hand. Massage should be continued until the uterus becomes firm and bleeding decreases. If the uterus is well contracted but bleeding continues unabated, other possible bleeding areas should be investigated.

4.1- Medical treatment:

While oxytocin is routinely started to reduce postpartum hemorrhage, the dose of oxytocin may be increased if bleeding is greater than normal. A dose of 40 units of oxytocin should be administered intravenously or 10 units intramuscularly at a rate sufficient to control uterine atony. Although higher doses of oxytocin intravenously have been used for a short time to treat atony, lower doses have been just as effective. Also, caution is required as rapid infusion of high-dose oxytocin can cause significant hypotension and cardiovascular collapse.

If bleeding continues after administration of oxytocin, administer carboprost tromethamine or methylergonovine. Carboprost tromethamine can be administered in up to eight doses, while methylergonovine can be repeated every two to four hours as needed.

Misoprostol is most useful for reducing blood loss in settings where methylergonovine and carboprost tromethamine are unavailable or contraindicated (e.g. hypertension, asthma). The optimal dose and route of administration of misoprostol is unclear (Hofmeyr et al, 2005; Lokugamage et al, 2001). Sublingual administration is probably the most appropriate route of administration for postpartum hemorrhage, as there is no first-pass effect through the liver compared to oral administration. Rectal administration takes longer to reach peak concentration than oral or sublingual administration, which is disadvantageous in the bleeding patient, but may be advantageous in unconscious patients as it has a longer duration of action. Vaginal administration is not recommended because absorption of the drug is impaired due to bleeding (Tang et al, 2002; Tang et al, 2007).

Dinoprostone is an alternative prostaglandin to misoprostol. It can be given again at two-hour intervals. It can be used in women with hypertension or asthma (ACOG, 2009).

Carbetocin, a long-acting analogue of oxytocin, is used to prevent uterine atony and bleeding. It appears to be as effective as oxytocin (Su et al, 2020). Its toxicity spectrum is similar to oxytocin. Its effectiveness in treating rather than preventing uterine atony is not well documented.

Because uterine atony is the most common cause of postpartum hemorrhage, uterotonic therapy is used for atony until it becomes clear that medications are ineffective. The important thing is not the order of the drugs, but the rapid initiation of uterotonic treatment and the rapid evaluation of its effect. Within half an hour, drug therapy (e.g. oxytocin, tranexamic acid and

a prostaglandin or methylergonovine) should be successful. If unsuccessful, invasive intervention is required.

4.2- Surgical treatment:

While medical treatment is the first approach in patients with atony who had a vaginal delivery or whose cesarean delivery was completed; laparotomy is usually the last resort when less invasive interventions fail. In patient evaluation, surgically midline laparotomy is the best after vaginal delivery, while an existing incision can be enlarged laterally if necessary in patients after cesarean section.

Ligation of the uterine-ovarian arteries and uterine arteries can reduce uterine bleeding. Although bleeding cannot be fully controlled in uterine atony, it may reduce blood loss while other interventions are attempted. This procedure does not harm the uterus and reproductive function (Doumouchsis et al, 2014).

Although it cannot fully control the bleeding, another method that saves time for other interventions is to place a clamp on the utero-ovarian ligament together with the fallopian tube. However, unlike the other method, this method may adversely affect future pregnancies.

Another surgical technique is hypogastric artery ligation. Bilateral ligation of the internal iliac arteries reduces the pulse pressure of blood flowing to the uterus (Evans and McShane, 1985). However, uterine compression sutures and uterine artery ligation are frequently used instead of this procedure, due to the difficulty of the technique.

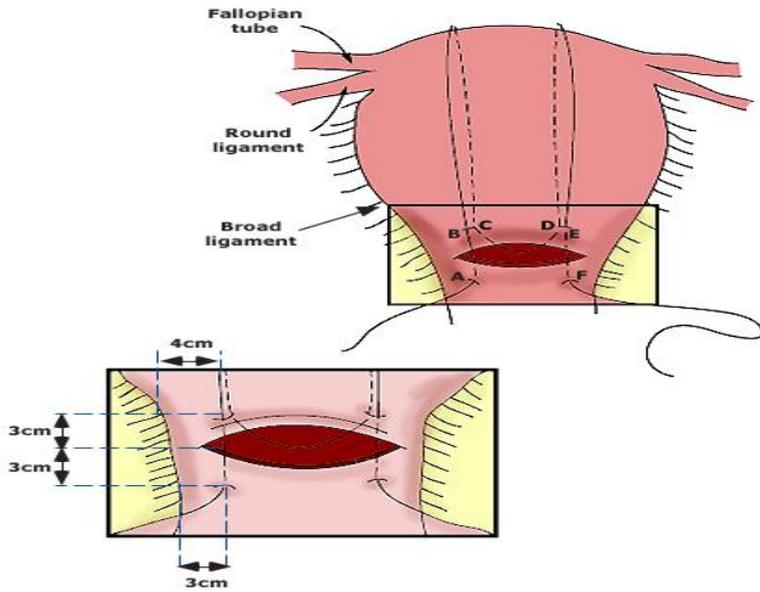
Uterine tamponade is effective in many patients with atony or lower segment bleeding. Intrauterine balloon catheter or intrauterine package can be used for tamponade. Many types of balloon catheters have been used for intrauterine tamponade. In a meta-analysis involving more than 4700 patients, the highest success in the use of uterine tamponade was achieved in uterine atony. This is followed by the spectrum of placenta previa and placenta accreta (Suarez et al, 2020). The balloon stabilizes the patient by reducing the blood flow to the uterus and gives time to take other measures. Various types of packaging can also be used for intrauterine tamponade. Examples of these are plain gauze or laparotomy sponges, hemostatic gauze and compressed mini-sponges. The advantages of balloon tamponade are ease of insertion, reduce the risk of retained foreign body and monitoring of intrauterine bleeding. The advantage of gauze packaging is that it is usually

cheap. The disadvantage is that the risk of foreign body remains and the ongoing bleeding cannot be evaluated clearly. Intrauterine tamponade with balloon or gauze is an effective method to control uterine bleeding due to atony. In uterine atony, uterine balloons can be inserted from the abdomen before closure of the hysterotomy after cesarean section or vaginally after vaginal delivery. In cases of uterine atony, it may be necessary to inflate the uterine balloon with more than 500 mL of fluid to effectively stop bleeding (Kaya et al, 2014). Complications include uterine perforation, separation of the hysterotomy repair during insertion of a balloon or pack, and cervical trauma due to improper inflation of the balloon (Kaya et al, 2014; Spencer and Saad, 2021). The uterine balloon should remain in the uterus for not more than 24 hours, if bleeding has decreased, it can be removed before 24 hours (CTS, 2020; Bakri, 2020). If the bleeding has decreased, the balloon or tampon is removed 2 to 12 hours after insertion. Broad-spectrum antibiotic prophylaxis can be used after uterine balloon or package application to reduce the risk of endometritis (Wong et al, 2021). Keeping a tamponade longer than 12 hours has been associated with an increased risk of endometritis.

External compression sutures such as B-Lynch or Hayman sutures can be used if balloon tamponade or medical therapy fails (Nelson and O'Brien, 2007; Diemert et al, 2012).

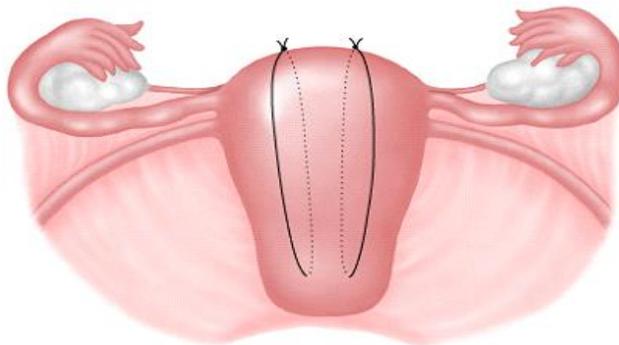
The B-Lynch suture envelops and compresses the uterus, similar to the result achieved with manual uterine compression (B-Lynch et al, 1997) (Figure 2). The most common technique, B-Lynch, has been quite successful in controlling uterine bleeding from atony when other methods have failed (B-Lynch et al, 1997; Smith and Baskett, 2003). Complications such as uterine necrosis, erosion, and pyometra have rarely been observed, also presumed to have no adverse effects on future pregnancies (Doumouchtsis et al, 2014; Pechtor et al, 2010; Gizzo et al, 2013).

Figure 2: B-Lynch Suture (B-Lynch et al, 1997)



Hayman is the placement of two to four vertical compression sutures from the anterior wall of the uterus posteriorly (Figure 3). It is a good choice for the surgical treatment of atony after vaginal delivery (Hayman et al, 2002; Nanda and Singhal, 2011).

Figure 3: Hayman Stitch (Hayman et al, 2002)



Pereira stitch and Cho stitch which different modifications of the B-lynch suture have been used for the uterus in small case series in the surgical treatment of atony (Pereira et al, 2005; Alouini et al, 2011) (Figure 4) (Figure 5).

Figure 4: Pereira Stitch (Pereira et al, 2005)

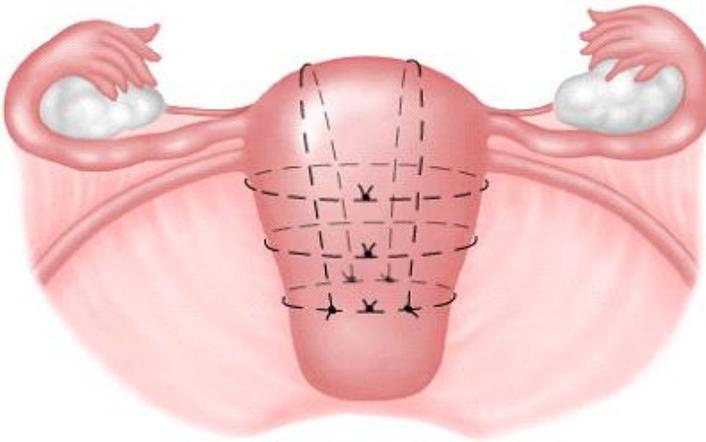
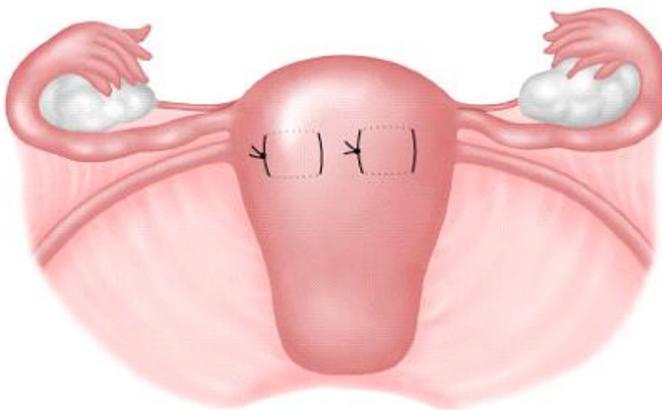


Figure 5: Cho Stitch (Cho et al, 2000)



Hysterectomy is the last treatment for postpartum hemorrhage. Uterine atony can usually be controlled with the medical and surgical treatments described above, but if it cannot be controlled, there is no option other than hysterectomy.

REFERENCES

- ACOG. (2009). Committee on Practice Bulletins Obstetrics. ACOG Practice Bulletin No. 107: Induction of labor. *Obstet Gynecol* 2009; 114:386.
- Allam, M.S., B-Lynch, C. (2005). The B-Lynch and other uterine compression suture techniques. *Int J Gynaecol Obstet* 89:236.
- Alouini, S., Coly, S., Mégier, P., et al. (2011). Multiple square sutures for postpartum hemorrhage: results and hysteroscopic assessment. *Am J Obstet Gynecol* 205:335.e1.
- Bakri. (2020). Postpartum Balloon with Rapid Installation Components. https://www.cookmedical.com/data/resources/RH-D54670-EN-F_M3_1585061971661.pdf.
- B-Lynch, C., Coker, A., Lawal, A.H., et al. (1997). The B-Lynch surgical technique for the control of massive postpartum haemorrhage: an alternative to hysterectomy? Five cases reported. *Br J Obstet Gynaecol* 104:372.
- Cho, J.H., Jun, H.S., Lee, C.N. (2000). Hemostatic suturing technique for uterine bleeding during cesarean delivery. *Obstet Gynecol* 96:129.
- Complete Tamponade System (CTS) for Use. (2020). <https://clinicalinnovations.com/wp-content/uploads/2020/06/ebb-Instructions-for-Use-050-0834-REV-D>.
- Doumouchtsis, S.K., Nikolopoulos, K., Talaulikar, V., et al. (2014). Menstrual and fertility outcomes following the surgical management of postpartum haemorrhage: a systematic review. *BJOG* 121:382.
- Diemert, A., Ortmeier, G., Hollwitz, B., et al. (2012). The combination of intrauterine balloon tamponade and the B-Lynch procedure for the treatment of severe postpartum hemorrhage. *Am J Obstet Gynecol* 206:65.e1.
- Evans, S., McShane, P. (1985). The efficacy of internal iliac artery ligation in obstetric hemorrhage. *Surg Gynecol Obstet* 160:250.
- Ferguson, J.E., Bourgeois, F.J., Underwood, P.B. (2000). B-Lynch suture for postpartum hemorrhage. *Obstet Gynecol* 95:1020.
- Ghezzi, F., Cromi, A., Uccella, S., et al. (2007). The Hayman technique: a simple method to treat postpartum haemorrhage. *BJOG* 114:362.
- Gizzo, S., Saccardi, C., Patrelli, T.S., et al. (2013). Fertility rate and subsequent pregnancy outcomes after conservative surgical techniques in postpartum hemorrhage: 15 years of literature. *Fertil Steril* 99:2097.
- Hayman, R.G., Arulkumaran, S., Steer, P.J. (2002). Uterine compression sutures: surgical management of postpartum hemorrhage. *Obstet Gynecol* 99:502.
- Hofmeyr, G.J., Walraven, G., Gülmezoglu, A.M., et al. (2005). Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG* 112:547.
- Kaya, B., Tuten, A., Daglar, K., et al. (2014). Balloon tamponade for the management of postpartum uterine hemorrhage. *J Perinat Med* 42:745.
- Lokugamage, A.U., Sullivan, K.R., Niculescu, I., et al. (2001). A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstet Gynecol Scand* 80:835.

- Nanda, S., Singhal, S.R. (2011). Hayman uterine compression stitch for arresting atonic postpartum hemorrhage: 5 years experience. *Taiwan J Obstet Gynecol* 50:179.
- Nelson, W.L., O'Brien J.M. (2007). The uterine sandwich for persistent uterine atony: combining the B-Lynch compression suture and an intrauterine Bakri balloon. *Am J Obstet Gynecol* 196:e9.
- O'Brien, P., El-Refaey, H, (1998). Gordon A, et al. Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. *Obstet Gynecol* 92:212.
- Pechtor, K., Richards, B., Paterson, H. (2010). Antenatal catastrophic uterine rupture at 32 weeks of gestation after previous B-Lynch suture. *BJOG* 117:889.
- Pereira, A., Nunes, F., Pedroso, S., et al. (2005). Compressive uterine sutures to treat postpartum bleeding secondary to uterine atony. *Obstet Gynecol* 106:569.
- Price, N., Whitelaw, N., B-Lynch, C. (2006). Application of the B-Lynch brace suture with associated intrauterine balloon catheter for massive haemorrhage due to placenta accreta following a second-trimester miscarriage. *J Obstet Gynaecol* 26:267.
- Reale, S.C., Easter, S.R., Xu, X., et al. (2020). Trends in Postpartum Hemorrhage in the United States From 2010 to 2014. *Anesth Analg* 130:e119.
- Sentilhes, L., Gromez, A., Razzouk, K., et al. (2008). B-Lynch suture for massive persistent postpartum hemorrhage following stepwise uterine devascularization. *Acta Obstet Gynecol Scand* 87:1020.
- Smith, K.L., Baskett, T.F. (2003). Uterine compression sutures as an alternative to hysterectomy for severe postpartum hemorrhage. *J Obstet Gynaecol Can* 25:197.
- Spencer, N.R., Saad, A. (2021). Perforation with Bakri balloon into broad ligament during management of postpartum hemorrhage. *Am J Obstet Gynecol* 224:227.
- Su, L.L., Chong, Y.S., Samuel, M. (2007). Oxytocin agonists for preventing postpartum haemorrhage. *Cochrane Database Syst Rev* CD005457.
- Suarez, S., Conde-Agudelo, A, (2020). Borovac-Pinheiro A, et al. Uterine balloon tamponade for the treatment of postpartum hemorrhage: a systematic review and meta-analysis. *Am J Obstet Gynecol* 222:293.e1.
- Tang, O.S., Gemzell-Danielsson, K., Ho, P.C. (2007). Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. *Int J Gynaecol Obstet* 99 Suppl 2:S160.
- Tang, O.S., Schweer, H., Seyberth, H.W., et al. (2002). Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod* 17:332.
- Wong, M.S., Dellapiana, G., Greene, N., Gregory, K.D. (2019). Antibiotics during Intrauterine Balloon Tamponade Is Associated with a Reduction in Endometritis. *Am J Perinatol* 36:1211.
- Zuckerwise, L.C., Pettker, C.M., Illuzzi, J., et al. (2014). Use of a novel visual aid to improve estimation of obstetric blood loss. *Obstet Gynecol* 123:982. DOI: 10.1097/AOG.000000000000233.



IKSAD
Publishing House



ISBN: 978-625-8377-65-1