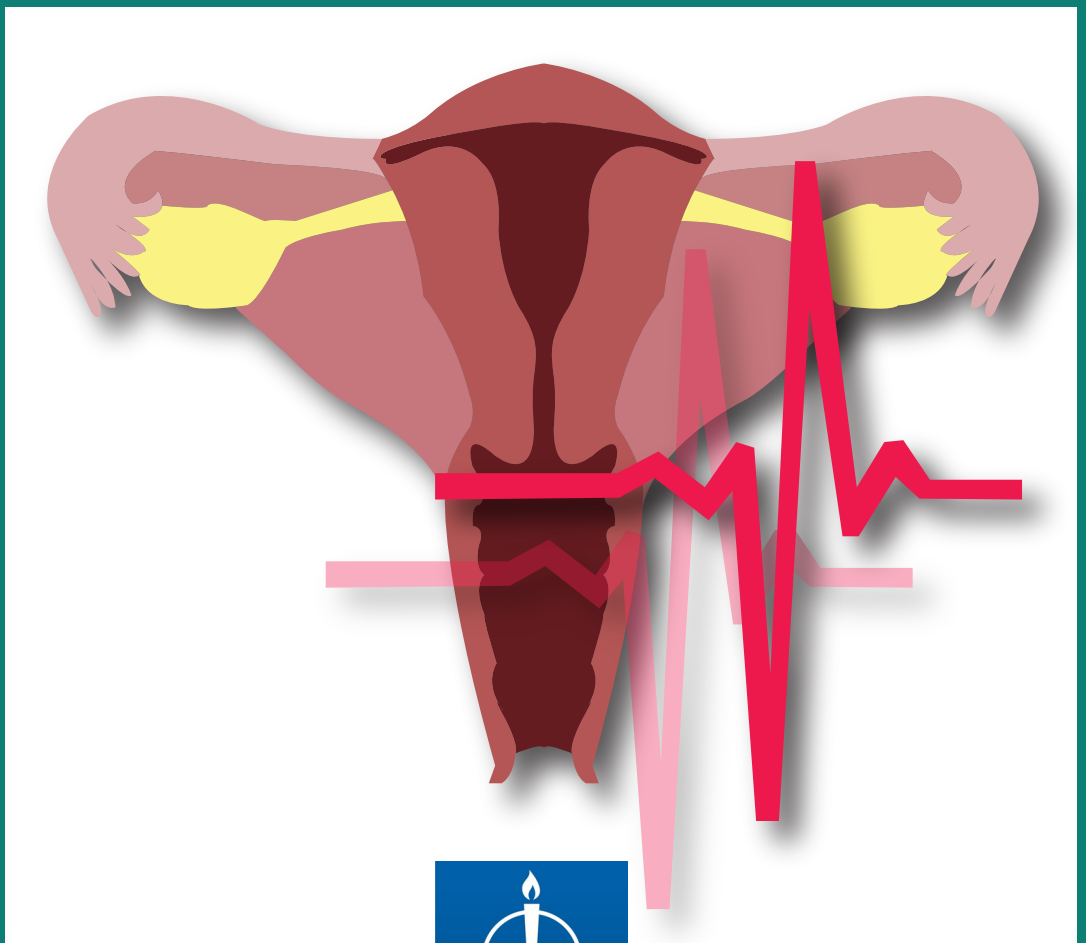
CURRENT APPROACHES IN GYNECOLOGY AND GYNECO-ONCOLOGY

EDITOR
Assist. Prof. Dr. Mehmet YILMAZ



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PREFACE

Research on human is exceeding total researches on other species. Over the last decade several developments were obtained on diseases, medical technology, research topics and treatment approaches to improve patients conditions. Diagnosis has important implications for patient care. An accurate and timely diagnosis provide a patient opportunity for a positive health outcome. Accurate diagnosis requires holistic approach and updated knowledge on current progresses in the study area to provide optimum solution. To add a milestone on that way, we searched international high quality articles published in English language including different experimental methods, sample sizes, sample sources, and research perspectives on various studies on evidence based obstetrics and gynecology system to improve women's health. Reader may find infos on the evaluation, critical assessment, update of current status, insights, opinions, approaches, trends, progresses, characteristics, developmental paths, presentations of future perspectives on important clinical strategies and protocols.

Given summaries of literature reviews, case reports and research outputs may help healthcare professionals on detecting diseases, etiology, pathogenesis, genetics, diagnosis, management, therapy, therapeutic roles, surgery, potential hazards, applications, safety, practice patterns, treatments, problems, technical possibilities, optimization of a practice, prognostic factors for survival, future directions and controversies.

Assist Prof. Dr. Mehmet YILMAZ

CHAPTER 1

ECTOPIC PREGNANCY: A REVIEW OF SYSTEMATIC REVIEWS AND META-ANALYSIS

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INTRODUCTION

Ectopic pregnancy is a major health problem but main risk factors of ectopic pregnancy are different for countries. Ectopic pregnancy or extrauterine pregnancy invariably result in abortion or rupture. It is directly related to tubal infection. Systemic methotrexate and dilatation and curettage were not recommended as first-line approaches for cesarean scar ectopic pregnancy, due to their association with high complication and hysterectomy rates. Chronic ectopic pregnancy is a variant of ectopic pregnancy with absent or low serum human chorionic gonadotropin levels, resistance to methotrexate. Ectopic pregnancy incidence increases fastly with assisted-reproductive technology. Improved diagnostic tools and the treatment options over the years significantly reduced the mortality from Ectopic pregnancies complication.

Here in this review, reader may find a review of systematic reviews and meta-analysis published after 2012 on ectopic pregnancy.

Ectopic pregnancy is a major health problem for child-bearing aged women. Ectopic pregnancy is the pregnancy occurring outside the uterine cavity covering 1,2–1,4% of all reported pregnancies. Identified maternal risk factors are pelvic inflammatory disease, smoking, *Chlamydia trachomatis* infection, tubal surgery, endometriosis and induced conception cycle. The diagnosis measure of ectopic pregnancy are serum human chorionic gonadotropin, progesterone measurement, urinary hCGRP/i-hCG, computed tomography, vascular endothelial growth factor, transvaginal ultrasound scan, disintegrin and

metalloprotease-12 and hysterosalpingography. A treatment option is surgical treatment by laparoscopy or laparotomy. Treatment is generally systemic or via local route, or by expectant treatment (Rana et al., 2013).

Ectopic pregnancy is related directly to tubal infection, and so prevention of gonorrhea and chlamydia must be the watchword to lower its risk and incidence. With correct determination of very low human chorionic gonadotropin concentrations and sonography, >85% of patients get diagnosed prior to tubal rupture, which led to medical therapy and laparoscopic surgery with tubal preservation and potential future fertility. Early intervention decreases morbidity, but still ectopic pregnancy represents for 4-10% of pregnancy-related deaths and leads to a high incidence of ectopic site gestations in subsequent pregnancies (Marion & Meeks, 2012).

Main risk factors of ectopic pregnancy are different in countries related to cultural and social characteristics (Parashi et al., 2014).

1. Systematic Reviews and Meta-Analysis

1.1. Occurrence and variants

Chronic ectopic pregnancy is a variant of ectopic pregnancy with absent or low serum human chorionic gonadotropin levels, resistance to methotrexate, and an adnexal mass with fibrosis, necrosis, and blood clots due to repeated and gradual fallopian tube wall disintegration. This may complicate ectopic pregnancy and is difficult to diagnose. Systematic review of the literature of chronic ectopic pregnancy which was conducted by Tempfer et al., (2019) revealed that serum human

chorionic gonadotropin was negative in 40/124 cases (32%) with reported levels of serum human chorionic gonadotropin. The most common presenting symptom was abdominal pain (284/399; 71%), followed by irregular vaginal bleeding (219/399; 55%), and fever (20/399; 5%). Asymptomatic women number were 73/399 (18%). An adnexal mass was seen in 144/298 (48%) cases with perioperative ultrasound examination and with a mean largest diameter of 6,8 cm. Data on treatment modalities and outcomes were available for 297 women. Of these, 89% underwent surgery as first-line therapy. Laparoscopy was implemented in most cases. Methotrexate was the first-line therapy in a minority of cases. Complete resolution was achieved by first-line therapy in 287/297 (97%) cases. Adverse events were reported in 218 patients with chronic ectopic pregnancy. Among those, adverse events $\geq$ grade 3 were seen in 186/218 (85%) cases. There was no case of treatment-related mortality. Chronic ectopic pregnancy is a variant of ectopic pregnancy with low or absent trophoblast activity. A prolonged clinical course is typical and surgery is the mainstay of treatment.

Ectopic pregnancy incidence increases fastly with assisted-reproductive technology, occurring in approximately 1–2% of patients undergoing in-vitro fertilization. Abdominal ectopic pregnancy is a rare form of ectopic pregnancy due to potentially high maternal morbidity. Yoder et al., (2016) performed a systematic literature search and study on case reports of abdominal or heterotopic abdominal ectopic pregnancies after in-vitro fertilization. Infertility causes included tubal factor (46%), male factor (14%), endometriosis (14%), pelvic adhesive disease (7%),

structural/Diethylstilbestrol exposure (7%), and unexplained infertility (14%). A history of ectopic pregnancy was identified in 39% of cases. A history of tubal surgery was identified in 50% of cases, 32% cases having had bilateral salpingectomy. Transfer of two embryos or more (79%) and fresh embryo transfer (71%) were reported in the majority of cases. Heterotopic abdominal pregnancy occurred in 46% of cases while 54% were abdominal ectopic pregnancies. The systematic review was revealed several trends in reported cases of abdominal ectopic pregnancy after in-vitro fertilization including tubal factor infertility, history of tubal ectopic and tubal surgery, higher number of embryos transferred, and fresh embryo transfers.

Chlamydia trachomatis has an important role on the occurrence of ectopic pregnancy. Xia et al., (2020) conducted a meta-analysis on the association between *Chlamydia trachomatis* infections with ectopic pregnancy. 25 studies including 11.960 patients were assessed. Analysis showed a clear association between ectopic pregnancy and prior *Chlamydia trachomatis* infections. *Chlamydia trachomatis* infections increased the risk of ectopic pregnancy occurrence.

An ectopic pregnancy after hysterectomy is a rare but is potentially life-threatening. Women with this condition might not be appropriately investigated, resulting in delays in diagnosis and treatment. Case reports or case series published reviewed by Shao et al., (2018) and revealed that abdominal pain was the predominant symptom. Implantation in a remaining fallopian tube was common. Most patients were managed surgically. A high index of suspicion and a low threshold

for implementing a β-hCG (β subunit of human chorionic gonadotrophin) pregnancy test is recommended in all women presenting with clinical symptoms of ectopic pregnancy, regardless of the hysterectomy status. This could lead to earlier diagnosis and fewer complications.

The ovarian ectopic pregnancy is a very serious and rarest type of extra-uterine pregnancy, in which, implantation of the gestational sac happens in the ovum. Rarity, accompanied morbidity, risk of complications, and even death makes early diagnosis and treatment crucial. The diagnosis is hard, relies on preoperative findings, have poor clinical symptomatology and a difficult ultrasound diagnosis. Its management of choice remains surgical therapy despite the progress in medical treatments with fertility preservation. Patients' symptomatology, radiological and lab findings, addition to her obstetric history and desire for future procreation must also be taken into consideration (Varshney et al., 2021).

Jayaram et al., (2018) systematically reviewed reported cases and case series of caesarean scar ectopic pregnancy managed expectantly without any intervention to see the outcomes of pregnancy to guide clinicians and patients in treatment choices. Total 56 cases of caesarean scar pregnancy from 11 reports were analysed. Live births were in 73% of cases (1/3 of them were born before 34 weeks). Hysterectomy rate were 70%. In 12/44 (27%) of cases, pregnancies were lost due to complications before 24 weeks. 67% of the caesarean scar pregnancies with no foetal cardiac activities resolved on expectant management and

the remaining required intervention for bleeding. Caution should be exercised when choosing expectant management in cases of viable caesarean scar pregnancies, and if chosen, the patient should be counselled adequately for possible outcomes including loss of pregnancy and hysterectomy. As a result, expectant management was found acceptable in caesarean scar pregnancies with no foetal cardiac activity.

1.2. Relation with other diseases

Inflammatory bowel disease, irritable bowel syndrome, and celiac disease more commonly affect women of reproductive age. Talavera et al., (2021) studied the association between ectopic pregnancy in women with inflammatory bowel disease, IBS, and celiac disease. They included five population-based cohort studies. The odds of ectopic pregnancy significantly increased in Crohn's disease, but not ulcerative colitis as compared to inflammatory bowel disease-free controls. The odds of ectopic pregnancy significantly increased in IBS as compared to women without irritable bowel syndrome. No significant difference was observed for odds of ectopic pregnancy in women with and without celiac disease. Possible evidence of associations between ectopic pregnancy and Crohn's disease as well as irritable bowel syndrome were observed; however, not with ulcerative colitis and celiac disease. Pregnant women with chronic inflammatory bowel pathologies may warrant cautious monitoring.

1.3. Diagnosis and treatment

Improved diagnostic tools and the treatment options over the years significantly reduced the mortality from ectopic pregnancies complication. Tsakiridis et al., (2020) conducted a study to review and compare the recommendations from published guidelines of "Royal College of Physicians of Ireland", "Royal College of Obstetricians and Gynaecologists", "Society of Obstetricians and Gynaecologists of Canada", "National Institute for Health and Care Excellence" and "American College of Obstetricians and Gynecologists". All guidelines pointed out the crucial role of sonography in the prompt diagnosis of ectopic pregnancies and describe similar sonographic findings. There was a consensus on the indications and contraindications to the use of methotrexate, the post-treatment surveillance, and the criteria of expectant management. Surgical approaches were not well established. "Royal College of Physicians of Ireland", "Royal College of Obstetricians and Gynaecologists", "National Institute for Health and Care Excellence" and "American College of Obstetricians and Gynecologists" agree that a laparoscopy is preferred to laparotomy for hemodynamically stable patients. The latter was considered a better option only in emergency conditions. However, there was controversy in the recommended methotrexate protocols and the evaluation of β-human chorionic gonadotrophin and progesterone levels.

Creatine phosphokinase is an intracellular enzyme found in higher levels in the brain, myocardium, soft muscle and skeletal muscle, as well as the fallopian tube. Ghorbani et al., (2020) reviewed the role of

serum creatine phosphokinase in early diagnosis of tubal ectopic pregnancy. Most studies approved the usage of creatine phosphokinase measurements in ectopic pregnancy diagnosis. The main variable in majority of the studies was the mean total creatine phosphokinase level. But, there was limited info about the efficacy of measuring creatine phosphokinase levels in ectopic pregnancy diagnosis. Review showed positive results regarding the use of creatine phosphokinase in ectopic pregnancy diagnosis. Results highlighted the potential benefits of creatine phosphokinase as a marker for early diagnosis of ectopic pregnancy.

Hamza et al., (2016) reviewed articles on early pregnancy loss and ectopic pregnancy. Results revealed that β-hCG (β subunit of human chorionic gonadotrophin) discriminatory zone may be extended in clinically stable cases without evidence of bleeding. A possible cut-off is 4300 mIU/ml, which corresponds to when a sonographer should detect an intrauterine pregnancy. Embryonic demise approved when transvaginal ultrasound finding showed no heartbeat in an embryo of more than 7 mm CRL, no embryo in a gestational sac with a mean sac diameter of more than 25 mm, or no appearance of an embryo within 7–10 days after the primary examination. These were considered definitive signs of embryonic demise. Suggestive signs of embryonic demise requires closer monitoring of the pregnancy.

Kanat-Pektas et al., (2016) analyzed studies describing women with cesarean scar ectopic pregnancy to determine efficacy and safety of different primary treatment management applications of cesarean scar

ectopic pregnancy. Systemic methotrexate, dilatation and curettage, uterine artery embolization, hysterotomy, and hysteroscopy were the most frequent first-line approaches. The success rates of systemic methotrexate, uterine artery embolization, hysteroscopy, dilatation and curettage, and hysterotomy were 9%, 18%, 39%, 62%, and 92%, respectively. The hysterectomy rates were 4%, 1%, 0%, 7%, and 2% in cesarean scar ectopic pregnancy cases that were treated by systemic methotrexate, uterine artery embolization, hysteroscopy, dilatation and curettage, and hysterotomy, respectively. The ability to achieve a subsequent term pregnancy is related to successful systemic methotrexate treatment or hysterotomy. Future term pregnancy was significantly more frequent in the hysterotomy group. Hysteroscopy and laparoscopic hysterotomy are safe and efficient surgical procedures that can be adopted as primary treatment modalities for cesarean scar ectopic pregnancy. Uterine artery embolization should be reserved for cases with significant bleeding and/or a high suspicion index for arteriovenous malformation. Systemic methotrexate and dilatation and curettage were not recommended as first-line approaches for cesarean scar ectopic pregnancy, due to their association with high complication and hysterectomy rates.

Extrauterine pregnancy (or ectopic pregnancy) always result with abortion or rupture. Cases with provisional diagnosis of ectopic pregnancy were analysed in a study of Kathpalia et al., (2018). Eighty cases were incorporated in the study. Management was relied on standard practice. All cases include urine pregnancy test, routine blood investigations and transvaginal ultrasound. Serial βhCG measurements

were applied in cases when diagnosis was not clear. There was single case of suspected interstitial pregnancy approved on laparoscopy. Total 27 cases were managed medically, and nine were managed expectantly. 46 cases were managed surgically either by laparoscopy or by laparotomy. Salpingectomy was implemented in 37 cases, and salpingostomy in seven cases either laparoscopically or by laparotomy. Researchers concluded that, ectopic pregnancy can be managed by laparotomy, operative laparoscopy, and medically and occasionally by observation alone. Management must be customized to the clinical condition and needs of future fertility of the patient.

Effectiveness and safety of different methotrexate dosages for the treatment of unruptured tubal ectopic pregnancy was determined by a systematic review and meta-analysis using six studies by Yang et al., (2017). Overall success rate of multiple-dose was similar to single-dose protocol. The difference between double-dose protocol and single-dose protocol groups was not significant. The incidence of side-effects of single-dose regimen was similar with double-dose regimen. However, side-effects were more frequent in multiple-dose. This meta-analysis indicated that the incidence of side-effects of multiple-dose protocol was significantly higher than single-dose protocol, and the success rates between them were similar. Double-dose was an efficient and safe regimen alternative to the single-dose.

Magnetic resonance imaging has superior soft tissue resolution and is a valuable alternative to diagnose ectopic pregnancy when transvaginal ultrasound results are inconclusive. Although an extrauterine

gestational sac is the most specific finding, there are other key magnetic resonance imaging findings that can aid in diagnosing ectopic pregnancy. As availability of magnetic resonance imaging access in the emergency department setting increases, its utility in women with a positive pregnancy test has also increased. Gopireddy et al., (2021) conducted a review and determined that specific magnetic resonance imaging findings that are diagnostic of ectopic pregnancy include absence of intrauterine pregnancy, adnexal mass separate from the ovary, and hemoperitoneum. In addition, intrauterine ectopic locations, especially intramural, cornual, and cervical pregnancies, can be diagnosed with increased accuracy with the help of magnetic resonance imaging. Magnetic resonance imaging is also useful in excluding potential mimics of ectopic pregnancy, including adnexal cysts, ovarian neoplasms, and fibroids. In summary, providing an accurate diagnosis and determining the precise location of an ectopic pregnancy, which is supported by the use of magnetic resonance imaging, is imperative for guiding a patient's treatment to prevent a potentially fatal outcome.

Gilbert et al., (2020) determined in their review that direct methotrexate injection into the gestational sac for nontubal ectopic pregnancy is safe and effective. The failure rate of 7% is considerably lower than what was previously reported for a failure of systemic methotrexate in similar cases (25%). Resolution of serum human chorionic gonadotropin after treatment can be quite prolonged even in uncomplicated cases.

1.4. Fertility outcomes

Ozcan et al., (2021) evaluated the fertility outcomes of salpingectomy compared to salpingostomy among patients treated for tubal ectopic pregnancies. Salpingectomy was clearly advantageous over salpingostomy. Trials consisting mainly of patients classified as low risk show no difference in outcomes between salpingectomy and salpingostomy. However, in cohort studies inclusive of all patients, the likelihood of a subsequent spontaneous intrauterine pregnancy is decreased in patients treated with salpingectomy, and salpingostomies may be especially underused in women with risk factors for tubal disease.

Salpingectomy is routinely implemented in ectopic pregnancy but the effect of surgery on ovarian reserve and ovarian response in ectopic pregnancy patients is uncertain. Luo et al., (2019) conducted a meta-analysis and determined that the amount of gonadotropin was significantly higher in the post-salpingectomy group compared to pre-salpingectomy group. There was no significant difference in the left parameters of the ovarian response including the duration of gonadotropin stimulation, the estrogen level on the human chorionic gonadotropin triggering day and the number of retrieved oocytes between two groups.

2. CONCLUSIONS

Systemic methotrexate and dilatation and curettage were not recommended as first-line approaches for cesarean scar ectopic pregnancy, due to their association with high complication and

hysterectomy rates. Chronic ectopic pregnancy is a variant of ectopic pregnancy with absent or low serum human chorionic gonadotropin levels, resistance to methotrexate. Ectopic pregnancy incidence increases fastly with assisted-reproductive technology. Improved diagnostic tools and the treatment options over the years significantly reduced the mortality from Ectopic pregnancies complication.

It is of paramount importance to build consistent international protocols, so as to help clinicians all over the world diagnose ectopic pregnancies in the most timely and accurate way and subsequently treat them effectively as a nonurgent medical condition, with the intention to lower the mortality and morbidity rate.

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CHAPTER 2

SPONTANEOUS PREGNANCY LOSS: A REVIEW OF SYSTEMATIC REVIEWS AND META-ANALYSIS

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INTRODUCTION

Human reproduction is remarkably inefficient due to low rate of live births. Pregnancy is a very specific and complex period. Woman's age is the first risk factor for pregnancy due to increase in the average age of pregnancy in last decades. Trauma in pregnancy is a major contributor to maternal and fetal morbidity and mortality. Pregnant women have an increased severity of infections with some organisms. Antidepressant usage, maternal smoking, alcohol consumption, benzodiazepine use, low iron uptake and many other reasons increase risk of spontaneous abortion.

Here in this review, reader may find a review of systematic reviews and meta-analysis published after 2012 on spontaneous abortion.

Today, 88% of pregnancies has a physiological course with basic care, while in 12% of cases is a high-risk pregnancy requiring additional and specific assistance. The approach used for supervision of all pregnant women is considering them as having a normal pregnancy until evidence to contrary. Pregnancy is decided at at risk when medical conditions may affect maternal or fetal health. Woman's age is the first risk factor for pregnancy due to increase in the average age of pregnancy in last decades. Also diet is important at pregnancy and diabetes or autoimmune diseases frequently lead to pregnancy failure. Complications occur for hypertension during pregnancy, and infectious diseases, too. Fears and anxieties typical risk pregnancy and prevent the couples happiness during gestation. Effective communication, control

and early detection are required to plan the best treatment strategies and to minimize the risks for mother and fetal (Coco et al., 2014).

Human reproduction is remarkably inefficient because, approximately 70% of human conceptions do not finalise with live birth. Spontaneous fetal aneuploidy is a frequent cause for spontaneous loss, especially for the first trimester of pregnancy. Although losses owing to de novo fetal aneuploidy occur at similar frequencies among women with sporadic and recurrent losses, some couples with recurrent pregnancy loss have additional associated genetic factors and some have nongenetic etiologies. Genetic testing of couples experienced two or more losses may help to define underlying etiology (Hyde & Schust, 2015).

Reasons and assessments

Trauma in pregnancy is a major contributor to maternal and fetal morbidity and mortality. Maternal injury or death, shock, intrauterine fetal demise, internal hemorrhage, abruptio placentae, direct fetal injury, and uterine rupture are potential complications. The leading causes of obstetric trauma are falls, motor vehicle accidents, gunshots, assaults and ensuing injuries are classified as blunt abdominal trauma, pelvic fractures, or penetrating trauma. Many of the assessment and management actions of obstetric trauma are unique to pregnancy, although initial evaluation and resuscitation should always be maternally directed. After establishing maternal stability, vigilant evaluation of fetal well-being becomes warranted. Continuous fetal heart monitoring, computed tomography, ultrasonography, exploratory

laparotomy or open peritoneal lavage may be indicated for obstetric trauma (Mirza et al., 2010).

Pregnant women have an increased severity of infections with some organisms, including influenza virus, herpes simplex virus, hepatitis E virus and malaria parasites (Kourtis et al., 2014).

Human parvovirus B19 infection is widespread. Nearly 30–50% of pregnant women are nonimmune. Vertical transmission following maternal infection during pregnancy is common. Fetal infection may be associated with a normal outcome. Diagnosis is generally via serology and polymerase chain reactions. Surveillance needs sequential ultrasound and Doppler screening for fetal anaemia, heart failure and hydrops signs. Immunoglobulins, antiviral and vaccination are not available yet, but intrauterine transfusion in some cases can be life saving (Lamont et al., 2011).

Any unexpected or unanticipated medical or obstetric condition associated with pregnancy with an actual or potential hazard to the health of mother or fetus is considered a high-risk pregnancy. Complicated pregnancies may require changes in lifestyle, medication regimens, technical support and hospitalization (Holness, 2018).

Pregnancy is a very specific and complex period in a woman's life. Changes are not only observed on the biological or physiological plane but also in mother's psychological and social functioning. Changes in psychological functioning may start from the beginning until the end of pregnancy, including postpartum period. At pregnancy, visible changes occur in the appearance of body, in femininity, sexuality, affections.

Mother experiences psychological am-bivalence, emotional disturbances, mood changes (from exhaustion to exaltation) and mixed anxiety-depressive disorder (Bjelica et al., 2018). A part of women get pregnant with active psychiatric symptoms or disorders, with or without psychotropic medication. Untreated depression and stress at pregnancy may have negative effects for birth outcome and child development. Also antenatal exposure to antidepressant medications may have adverse effects on birth outcome and child development. Antidepressant usage at pregnancy makes a small increase risk of miscarriage, congenital cardiac malformations, preterm birth, persistent pulmonary hypertension of the newborn, and transient neonatal symptoms in up to one-third of neonates. In addition, there is a possible increased risk of delayed motor development in children (Pearlstein, 2015). The use of antidepressants, especially paroxetine, venlafaxine or the combined use of different classes of antidepressants, during pregnancy was associated with an increased risk of spontaneous abortion (Nakhai-Pour et al., 2010).

Maternal smoking during pregnancy is a significant threat to the fetus (Vardavas et al., 2010). Smoking during pregnancy increases the risk for fetal growth restriction, preterm delivery, and infant death. In 2002, 5-8% of preterm deliveries, 13-19% of term infants with growth restriction, 5-7% of preterm-related deaths, and 23-34% of deaths from sudden infant death syndrome were attributable to prenatal smoking in the United States (Tong et al., 2013).

Many pregnant women consume alcohol instead of clinical recommendations and public health warnings on the risks associated with alcohol consumption at pregnancy. Prepregnants' alcohol consumption frequency and quantity were found associated with abuse or violence during pregnancy. Care providers should assess these factors for better detection of alcohol-exposed pregnancies (Skagerstrom et al., 2011).

Incidence of acute kidney injury related to pregnancy has declined during last 30 years, but is still an important cause of maternal and fetal morbidity and mortality. Pregnancy-related causes of acute kidney injury such as preeclampsia, acute fatty liver of pregnancy, HELLP (Hemolysis, Elevated Liver function tests, Low Platelets) syndrome, and the thrombotic microangiopathies (thrombotic thrombocytopenic purpura, atypical hemolytic-uremic syndrome) exhibit overlapping features and often present as diagnostic dilemmas. Differentiating among these conditions may be impossible or difficult. In difficult and rare cases, a renal biopsy can be required for diagnosis, but the risks and benefits are needed to be balanced. Usage of eculizumab to treat atypical hemolytic-uremic syndrome has demonstrated its efficacy. Non–pregnancy related causes such as volume depletion and pyelonephritis require early and aggressive resuscitative as well as antibiotic measures respectively (Jim et al., 2017).

Benzodiazepine use in early pregnancy is associated with spontaneous abortion (Sheehy et al., 2019).

Iron requirements increases during pregnancy for maternal erythropoietic expansion and fetal growth and development. To meet dietary iron requirement, absorption increases and iron stores get mobilized. It is believed that the iron-regulation hormone hepcidin controls the concentration of ferroportin, which is the only exporter of iron into the extracellular fluid and blood plasma. In healthy pregnancy, hepcidin increases in the first trimester compared to nonpregnant women, but then decreases during the second trimester. The second trimester hepcidin level decrease despite stable serum iron concentration suggest the active suppression of hepcidin, presumably to enhance iron availability as iron demand increases. During the first trimester, in women with spontaneous abortion, concentrations of hepcidin, serum iron, and ferritin were all increases compared to healthy pregnancy. Maternal hepcidin is regulated by signals related to the progression of pregnancy, and that pregnancy loss is associated with profound changes in maternal iron metabolism. These results reveal the existence of fetoplacental signals that modulate maternal iron homeostasis (Guo et al., 2019).

Systematic Reviews and Meta-Analysis on Spontaneous Abortion

Placenta accreta, characterized by complete or partial absence of the decidua basalis and imperfect development of the fibrinoid layer (Nitabuch layer), can be a life-threatening complication during pregnancy. It may complicate a first-trimester abortion rarely, and can be difficult to recognize. Wang et al., (2019) reviewed 19 articles and 23 case reports and determined that the risk factors for the development

of abnormal placentation are previous cesarean section (87%), previous history of uterine curettage (43%), and previous history of surgical evacuation of a retained placenta (4%). Most patients clinically presented intermittent or irregular vaginal bleeding, persistent bleeding, and profuse or massive bleeding. The onset of symptoms were during the intra- or immediate postoperative period. Some patients showed delayed symptoms 1 week to 2 years postoperatively. Conservative management was attempted as the primary rescue, including transcatheter arterial chemoembolization with dactinomycin, uterine artery embolization, and laparoscopic hysterotomy with placental tissue removal. But, many reports suggested abdominal or laparoscopic hysterectomy as the definitive treatment for first-trimester postabortal placenta accreta. High index of clinical suspicion with anticipation of placenta accreta in early pregnancy is required for timely diagnosis, for better opportunities to promptly manage this emergent condition and to improve outcomes.

Infections

Toxoplasma gondii is an intracellular pathogen which can lead to abortion in infected pregnant women. This parasite is important during pregnancy since it can pass placental barrier and infect the embryo. Passing placental barrier and infecting the fetus result with abortion, fetal death or severe congenital defects (hydrocephaly and chorioretinitis). Nayeri et al., (2020) analysed and reviewed eight cross-sectional studies including 1.275 women who had abortion in present pregnancy and 40 cross-sectional studies including 9.122 women who

had a history of abortion. Prevalence of anti-*T. gondii* IgG antibody in women who had abortion in present pregnancy and women who had a history of abortion were 33% (17-49%) and 43% (27-60%), respectively. As a results of the study, it was determined that *T. gondii* infection could be a potential risk factor for abortion.

To estimate the impact of human papillomavirus infection on spontaneous abortion, spontaneous preterm birth, pregnancy rate of females undergoing assisted reproductive technologies, and spontaneous abortion of assisted reproductive technologies pregnancy, Xiong et al., (2018) analysed and reviewed 18 studies. Eight studies revealed no significant association between human papillomavirus infection and spontaneous abortion. But, subgroup analysis showed while high-risk-human papillomavirus infection had no significant effect, the indiscriminate genotype human papillomavirus infection increased the ratio of spontaneous abortion. The results showed that indiscriminate human papillomavirus genotype infection can increase the risk of spontaneous abortion and high-risk-human papillomavirus infection was a risk factor for spontaneous preterm birth. However, there was not enough evidence to indicate the association between human papillomavirus infection and pregnancy rate of assisted reproductive technologies, and spontaneous abortion of assisted reproductive technologies pregnancy. Different genotypes of human papillomavirus infection may play a discrepant role in adverse pregnancy outcomes.

To assess whether the peri-conceptional or pregnancy exposure of human papillomavirus vaccination would increase the risk of spontaneous abortion Tan et al., (2019) investigated the association between exposure of human papillomavirus vaccines (2vHPV, 4vHPV or 9vHPV) during peri-conceptional period or pregnancy and spontaneous abortion before 28 gestational weeks. Analyses determined that 2vHPV vaccination was not increasing the risk of spontaneous abortion regardless of exposure period during 90 days before last menstrual period or pregnancy. But, 2vHPV vaccination during Pre-45 days to last menstrual period increased the risk of spontaneous abortion. No support was found on the association between 4vHPV vaccination and spontaneous abortion regardless of exposure period during 45 days before last menstrual period or pregnancy and 45 days before last menstrual period. Additionally, 9vHPV during within 30 days of conception also increased the risk.

Pregnant women are considered the most important risk group for influenza vaccination. McMillan et al.,(2015) systematically reviewed studies on the safety of influenza vaccination during pregnancy on fetal development. Investigates were on 1st trimester immunisation for congenital malformation outcomes. Results did not relate maternal influenza vaccination with increased risk of fetal death, spontaneous abortion, or congenital malformations.

Untreated sexually transmitted or urinary tract infections are associated with significant morbidity during pregnancy, including preterm birth, low birth weight and spontaneous abortion. Approximately 1/4 of

women get an antibiotic at pregnancy, accounting for nearly 80% of medications in pregnant women. Antibiotic exposure during pregnancy was associated with both short-term (congenital abnormality) and long-term effects (gut microbiome changes, atopic dermatitis and asthma) in the newborn. Instead, it is estimated that only 10% of medications have sufficient data related to safe and effective use in pregnancy. Antibiotics such as vancomycin, beta-lactams, nitrofurantoin, clindamycin, metronidazole, and fosfomycin are generally considered effective and safe in pregnancy. Fluoroquinolones and tetracyclines are generally avoided in pregnancy (Bookstaver et al., 2015). Although antibiotics are widely used during pregnancy, evidence regarding their fetal safety remains limited. Use of azithromycin, clarithromycin, metronidazole, sulfonamides, tetracyclines and quinolones were associated with an increased risk of spontaneous abortion (Muanda et al., 2017).

Salmonella infections are frequent but generally not severe. But, during pregnancy it can result with life-threatening infection and foetal loss. So, a greater alertness to food-borne infections is recommended for pregnant women. In diarrhoea cases in pregnant women, stool culture for Salmonella and an early medical treatment may avoid serious complications. Cases reported in literature argue that bacteraemia due to non-typhoid *Salmonella* species is more severe at pregnancy (Delcourt et al., 2019).

Hormonal

Polycystic ovary syndrome is a complex endocrinopathy. The risk of spontaneous abortion in patients with polycystic ovary syndrome

undergoing assisted reproductive treatment is higher than that in patients without polycystic ovary syndrome. Sun et al., (2020) was performed a systematic review and meta-analysis study to assess the impact of relevant risk factors on spontaneous abortion in patients with polycystic ovary syndrome. High body mass index and insulin resistance were associated with increased risk of spontaneous abortion in polycystic ovary syndrome patients undergoing assisted reproductive treatment. Embryonic chromosomal aberrations, older age and hyperandrogenism were not associated with high spontaneous abortion rate in patients with polycystic ovary syndrome. Subgroup analysis of body mass index revealed that there was no statistically significant difference in the effect between overweight and obesity on spontaneous abortion in polycystic ovary syndrome patients undergoing assisted reproductive treatment. As a conclusion, high body mass index and insulin resistance were two risk factors for an increased risk of spontaneous abortion in polycystic ovary syndrome patients undergoing assisted reproductive treatment. Losing weight and mitigating insulin resistance may decrease the spontaneous abortion rate for these patients.

Although oral contraceptives are widely used by women of childbearing age. Tang et al., (2020) systemically reviewed these complications in women who used oral contraceptives before pregnancy compared to control group. The risk of preterm birth was slightly higher in the exposed group. But, there was a lower risk for spontaneous abortion compared with the control group. No significant difference was found in the incidence of low birth weight.

Genetics

A high sperm DNA fragmentation index influences human reproduction and is observed in infertile men. However, the influence of DNA fragmentation index on unexplained recurrent spontaneous abortion remains controversial. Findings of Yifu et al., (2020) support an association between sperm DNA fragmentation index and recurrent pregnancy loss. Previous studies revealed that DNA fragmentation index negatively impacts unexplained recurrent spontaneous abortion.

Antiphospholipid syndrome is an autoimmune disease related to arterial or venous thrombosis, recurrent fetal abortion or thrombocytopenia. Yu & He, (2021) reviewed relevant trials to determine the effects of heparin and aspirin treatment on recurrent spontaneous abortion in women with antiphospholipid syndrome. Studies revealed that aspirin and heparin significantly improved live birth ratio compared to treatments of intravenous immunoglobulin, aspirin alone or aspirin combined with prednisone. Also, aspirin and heparin sharply increased the birth weight compared to placebo and improved vaginal delivery relative to intravenous immunoglobulin. Gestational age at birth was significantly higher in the aspirin and heparin group compared to placebo group. Incidence of intrauterine growth restriction was lower in the aspirin and heparin group compared to the placebo group. Heparin and aspirin reduced the incidence of miscarriage compared to aspirin group and the placebo group. The incidence of pre eclampsia was lower in the heparin and aspirin group than the placebo group.

Drugs

Pregnant women and their fetuses are orphan populations for efficacy and safety of drugs. Physiological, absorption, distribution, metabolism and excretion modifications during pregnancy can significantly affect pharmacokinetics of drug and may necessitate dose adjustment (Ke et al., 2014). Selective serotonin reuptake inhibitors are frequent prefered antidepressants at pregnancy. Nikfar et al., (2012) meta-analysed pregnancy outcomes following usage of selective serotonin reuptake inhibitors (paroxetine, fluoxetine, citalopram, sertraline, escitalopram and fluvoxamine). Results revelaed that selective serotonin reuptake inhibitors increase the risk of spontaneous abortion and major malformations during pregnancy while they don't increase the risk of cardiovascular malformations.

Nonaspirin nonsteroidal anti-inflammatory drugs are one of the most commonly used medications during pregnancy. Nakhai-Pour et al., (2011) reviewed association between spontaneous abortion and types and dosages of nonaspirin nonsteroidal anti-inflammatory drugs in a cohort of pregnant women. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy was significantly associated with the risk of spontaneous abortion. Especially, usage of diclofenac, celecoxib, naproxen, ibuprofen and rofecoxib alone and combinations were all associated with increased risk of spontaneous abortion. No dose–response effect was seen. These drugs should be used with caution during pregnancy.

Tumors

Uterine leiomyomas are benign smooth muscle tumors of the uterus. Sundermann et al., (2017) systematically reviewed studies on spontaneous abortion among pregnant women of typical reproductive potential with and without uterine leiomyomas. Leiomyoma presence was not associated with increased risk of spontaneous abortion in an analysis of more than 20.000 pregnant women.

CONCLUSIONS

Woman's age is the first risk factor for pregnancy due to increase in the average age of pregnancy in last decades. Trauma in pregnancy is a major contributor to maternal and fetal morbidity and mortality. Pregnant women have an increased severity of infections with some organisms. Antidepressant usage, maternal smoking, alcohol consumption, benzodiazepine use, low iron uptake and many other reasons increase risk of spontaneous abortion.

During pregnancy, maternal physiology undergoes continual adaptation. These, often interlinked, changes affect all the body systems and are effected by the hormonal influences of the placenta and mechanical adaptations required to accommodate the growing fetus. These expected physiological changes can lead to decompensation in parturients with pre-existing co-morbidities or unmasking of pre-pregnancy disease.

The ideal dose and medication interval of misoprostol needs to be further researched. Further and more comprehensive investigations to

determine the effect of *T. gondii* infection on abortion to prevent and control toxoplasmosis are required.

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CHAPTER 3

RARE BENIGN TUMORS OF OVARY: A REVIEW

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1. INTRODUCTION

Ovarian tumours are source of major gynaecological problems in women. They significantly vary in their histological types. Leydig cell tumor, Sertoli cell tumor, Sertoli–Leydig cell tumor, Ovarian Thecoma, Luteoma, Teratoma, Struma ovarii, and Corpus luteum cyst are rare ovarian tumors. Ultrasonography, Computed Tomography and Magnetic Resonance Imaging are currently used to evaluate ovarian tumors. Ovarian tumours are usually surgically removed due to presumed risk of complications.

This review is aimed to provide information extracted from articles published mostly during the last decade on the rare benign ovarian tumors.

Ovarian tumours are a major cause of gynaecological problems in women and present significant variation in their histological types. Relative frequency of these lesions are different for countries (Ashraf et al., 2012). Tumours are a main type of lesion of the ovary. With exception of these neoplasms, the ovary appears remarkably resistant to disease. There are diversified types of ovarian tumours, both benign and malignant. Approximately 80% of these benign and occur mostly in young women aged between 20-45 years. Malignant tumours are more frequent in women agedbetween 40-65 (Mall et al., 2014).

Ultrasonography, Computed Tomography and Magnetic Resonance Imaging are currently used to evaluate ovarian tumors. Ultrasonography is the first-line imaging investigation for adnexal

masses. Color Doppler Ultrasonography helps to identify vascularized components within the mass. Computed Tomography is frequentlyperformed in preoperative evaluation of a suspected ovarian malignancy, but patients get exposed to radiation. When Ultrasonography findings are nondiagnostic or equivocal, Magnetic Resonance Imaging can be a valuable instrument also to give surgical planning information. Magnetic Resonance Imaging is well known to provide accurate information about hemorrhage, fat, and collagen (Valentini et al., 2012).

Ovarian tumours are usually surgically removed due to presumed risk of complications (Froyman et al., 2019). All ovarian tumors are fall into groups of epithelial tumors, mesenchymal tumors, mixed epithelial and mesenchymal tumors, sex cord-stromal tumors, mixed sex cord-stromal tumors, germ cell tumors, monodermal teratoma and somatic-type tumors arising from a dermoid cyst, germ cell-sex cord-stromal tumors, miscellaneous tumors, mesothelial tumors, soft tissue tumors, tumor-like lesion, lymphoid and myeloid tumors, secondary tumors (Kurman et al., 2014).

Leydig cell tumor, Sertoli cell tumor, Sertoli–Leydig cell tumor, Ovarian Thecoma, Luteoma, Teratoma, Struma ovarii, and Corpus luteum cyst are rare ovarian tumors.

2. Leydig cell tumor

Androgen-secreting ovarian tumors include Leydig cell tumors. They are extremely rare; less than 0,1% of all ovarian tumors. Majority

Leydig cell tumors (95%) are unilateral; but, radiological localization of themcan be challenging (Shwana et al., 2021).Small sizesof Leydig cell tumors make diagnose by routine imaging procedures difficult. Presence of both adrenal and ovarian tumors in a female with androgen excess is a condition which is diagnostically very challenging (Durgia et al., 2021).

Leydig cell tumors usually occur in postmenopausal women. Its diagnosis must be considered in all postmenopausal women with hyperandrogenism. Bilateral adnexectomy by laparoscopy is recommended as a diagnostic test and definitive treatment (Sanz et al., 2007).

3. Sertoli cell tumor

According to the WHO Classification, pure Sertoli cell tumor is a rare sex cord tumor and a subtype of Sertoli-Leydig cell tumors. Sertoli cell tumor lack a Leydig cell component and does not contain immature neoplastic stroma of the Sertoli-Leydig cell category neoplasms. These tumors occur in women at reproductive age but can also visible in children. The ages of patients range between 2-79 years. Abdominal pain, swelling and menstrual abnormalities are frequent at patients at reproductive aged and postmenopausal women. Sertoli cell tumorsoccasionally occur in patients who have Peutz-Jeghers syndrome. These tumors are hormone functional (estrogenic, androgenic or both) in 40-60% of cases and usually yellow to brownish, solid or contain several cystic zones. Microscopically they always show a tubular growth, but may also be in different growth patterns which

complicate correct diagnosis. EMA, inhibin, chromogranine, CD99 and calretinin including immunohistochemical panel is often helpful for the diagnosis. Many of Sertoli cell tumors are Stage I, unilateral, cytologically bland, and clinically benign, occasional are at higher stages. Approximately 11% of Stage I tumors have histologic features may denote an adverse outcome (Zizi-Sermpetzoglou et al., 2010).

The main neoplasms in the differential diagnosis for primary ovarian tumors with a tubule-rich pattern are pure Sertoli cell tumor, endometrioid tumors (including borderline tumor, well-differentiated carcinoma, and the sertoliform variant of endometrioid carcinoma), and carcinoid tumor. Traditional immunohistochemical markers such as pan-cytokeratin (pan-CK), low molecular weight cytokeratin (CK8/18), epithelial membrane antigen (EMA), inhibin, calretinin, CD99, chromogranin, and synaptophysin can have diagnostic limitations. Alternative markers such as cytokeratin 7 (CK7), estrogen receptor (ER), progesterone receptor (PR), CD10, and CD56 have better diagnostic utility compared to traditional markers for this differential diagnosis. When traditional immunohistochemical markers are problematic for the differential diagnosis of ovarian Sertoli cell tumor versus endometrioid tumors versus carcinoid tumor, adding CK7, ER, and/or PR to a panel of markers can be helpful. Endometrioid tumors more frequently express CK7, ER, and PR and show a greater extent of immunostaining in contrast to Sertoli cell tumor and carcinoid tumor. CD10 is not helpful in the differential diagnosis (Zhao et al., 2007).

4. Sertoli–Leydig cell tumor

Sertoli-Leydig cell tumors belong to the group of sex-cord stromal tumors of the ovary. They represent less than 0,5% of all ovarian neoplasms. The majority of these tumors are benign, and almost all are localised unilaterally (Lantzsch et al., 2001). Ovarian Sertoli-Leydig cell tumors are the most frequent virilising tumors in reproductive aged women (Persechini et al., 2011). Sertoli-Leydig cell tumors generally present in the second or third decade of life and have androgen excess features (amenorrhoea, deepening of the voice, hirsutism and clitoral enlargement) (Gui et al., 2012).

The WHO (World Health Organization) Classification includes three histologic types of Sertoli-Leydig cell tumors (well-differentiated, moderate-differentiated and poor-differentiated) (de Kock et al., 2017). More than 95% of these tumors are unilateral, FIGO Stage 1, and either moderately or poorly differentiated. Probably the pathogenesis is through mutation in the DICER1 gene (Gui et al., 2012).

5. Ovarian Thecoma (theca cell tumors) (theca lutein cyst)

Ovarian thecoma-fibroma groups are rare sex cord-stromal neoplasms. Most of them are benign. The fibromas are composed in variable proportion of spindle cells asin collagen form, while thecomas source from stromal cells which resemble the perifollicular thecal cells, and occasionally there are histologic features of both fibroma and thecoma, giving rise to the term fibrothecoma. Typical sonography of Ovarian thecoma-fibroma groups have adnexal hypoechoic masses

with clear borders and acoustic attenuation as well as minimal Doppler flow signals. These features make ultrasound imaging atool to improve diagnostic accuracy (Chen et al., 2016).

Ovarian thecoma occurs generally in postmenopausal and perimenopausal women. Increased serum cancer antigen (CA)125 levels in postmenopausal women with solid adnexal masses, pleural effusion and ascites are highly suggestive for malignant ovarian tumors. But, surgery and histological confirmation of the preoperative diagnosis are mandatory. Because a small part of patients with these findings have a benign conditionknown as Meigs' syndrome. This condition disappears after the removal of the pelvic tumor (Ting et al., 2016).

Atrophy or compression of the cortical areafindings are significant for diagnosis of Thecoma tumoral growth because thecoma tumor is considered to be originatedfrom ovarian medulla (Nocito et al., 2008).

6. Luteoma

Luteoma of pregnancy is a rareovarian mass that develops during pregnancy and regresses after delivery. These masses are generally discovered incidentally at cesarean delivery or tubal ligation. Some patients develop hirsutism or virilization during late pregnancy with/without fetal masculinization as a result of circulating androgens (Tannus et al., 2009). Luteoma tumor occurs in the ovaries at pregnancy. Pregnancy-associated tumors are rare. So, pregnancy luteomas must always be considered at pregnancy. They are often symptomatic (Tan et al., 2008). Stromal luteomas are frequently present

with hyperoestrogenic symptoms when Leydig cell tumors are mostly present with hyper-androgenism. Steroid cell tumors are classified into three groups, according to the origin of the cells that generate the tumor: stromal luteomas; Leydig cell tumors; and steroid cell tumors not otherwise specified. Stromal luteomas 20-25% and Leydig cell tumorsconstitute 20-25% of all steroid cell tumors(Numanoglu et al., 2015).

Luteoma must be considered in the differential diagnosis of ovarian masses in ovarian ectopic pregnancies that diagnosis of this entity may avoid unnecessary radical surgery (Pillai & Chitra, 2021).

7. Teratoma

Mature cystic teratomas represent 10–20% of all ovarian neoplasms. Mature teratomas are frequently benign. They may be asymptomatic or present with acute abdomen due to infection or rupture (Khanna et al., 2012). By age, patients of ovarian teratoma have different clinical manifestations (Kim et al., 2011). There are few studies on clinical pathology of malignant transformation arising in ovarian mature cystic teratoma. 80% of mature cystic teratomas are diagnosed during the reproductive age.Malignant transformation is probably related to long-term presence of nonremoved mature cystic teratoma in the abdomen. Regular ovary examination through pelvic ultrasonogram during reproductive age is helpful for prevention and early detection of its malignant transformation (Rim et al., 2006).Ovarian teratoma is the most common ovarian neoplasm at children. Oophorectomy is the

standard treatment but can impair fertility (Chabaud-Williamson et al., 2011).

Ovarian mature cystic teratomas are the most common adnexal massfor premenopausal women. Gynecologists face many challenges for deciding the best surgical management. There is lack of consensus and variation in surgical practices. Laparoscopic approach is generally considered as gold standard for the management. Oophorectomy is the standard operation (except for younger women with a single small cyst). Chemical peritonitis risk after content spillage is very rare and can be overcome with thorough peritoneal lavage using warmed fluid (Sinha & Ewies, 2016).

Association of anti-N-methyl-D-aspartate receptor encephalitis and ovarian teratoma is a serious and potentially fatal pathology which occurs in young women and is under-recognized. This association is relatively unknown or not reported in many countries and among gynecologists. Heightened recognition of behavioral changes, diagnosis through transvaginal ultrasound and subsequent tumor removal in addition to diagnostic confirmation through the presence of anti-N-methyl-D-aspartate receptor antibodies must be emphasized (Acien et al., 2014).

8. Struma ovarii

Struma ovarii is the most common monodermal ovarian teratoma and consists mainly of thyroid tissue. Only 5% of Struma ovarii patients have features of hyperthyroidism. The pathophysiology of

hyperthyroidism in struma ovarii is not clear. The struma ovarii is always needed to be considered when a pelvic mass is associated with features of hyperthyroidism (Guida et al., 2005). Diagnosis of struma ovarii may be masked and delayed for several years by Graves' disease. Pleural effusion, ascites and increased CA-125 may result from a benign struma ovarii (Anastasilakis et al., 2013). Many cases are asymptomatic. Diagnosis is easy with the help of investigations like thyroid profile, pelvic ultrasonogram and radioiodide scan. Though struma ovarii has a good prognosis, extensive sampling should be done with caution to rule out a nidus of malignancy (Kannusamy & Subramanyam, 2013). Struma ovarii is an uncommon ovarian teratoma comprised predominantly of mature thyroid tissue. The combination of pseudo-Meigs' syndrome, and elevation of CA 125 to the struma ovarii is a rare condition that can mimic ovarian malignancy (Jin et al., 2015).

9. Corpus luteum cyst

Corpus luteum cyst is a functional cyst formed during the second phase of ovarian cycle. Its natural history typically includes regression in the absence of pregnancy or regression after the first trimester of pregnancy and maturation of placenta. It has a very vascular structure and occasionally a subject of rupture. Blood loss is usually self-limited, but rarely can lead to massive hematoperitoneum and even death. Due to variable clinical presentation and sonographic appearance, misdiagnosis potential is high (Vidakovic et al., 2013).Corpus luteum cysts are functional, and many of them completely disappear

spontaneously. As a thinwalled vascular structure, these cysts are predisposed toward rupture (Takeda et al., 2007).

Rupture of a corpus luteum cyst in an undescended ovary should be included in the differential diagnosis of acute abdomen in adolescents (Suh et al., 2016).Ruptured corpus luteum cyst is a common finding in women of the reproductive age group, but hemoperitoneum in a case of reputured corpus luteum cyst in women on anticoagulants is an uncommon finding. Thus, management in such cases can be done by dose adjustment of anticoagulants (Agarwal et al., 2017).The application of enhanced computed tomography in patients with hemorrhage corpus luteum cyst is of great value. It can provide accurate data reference for clinical treatment and is worthy of promoting its clinical application (Gao et al., 2020).

10. CONCLUSIONS

Ovarian tumours are source of major gynaecological problems in women. They significantly vary in their histological types. Leydig cell tumor, Sertoli cell tumor, Sertoli–Leydig cell tumor, Ovarian Thecoma, Luteoma, Teratoma, Struma ovarii, and Corpus luteum cyst are rare ovarian tumors. Ultrasonography, Computed Tomography and Magnetic Resonance Imaging are currently used to evaluate ovarian tumors. Ovarian tumours are usually surgically removed due to presumed risk of complications.

Radiological localization of the Leydig cell tumors can be challenging and its diagnosis must be considered in all postmenopausal women with

hyperandrogenism. Sertoli cell tumor can also visible in children and occasionally occur in patients who have Peutz-Jeghers syndrome. Ovarian Sertoli-Leydig cell tumors are the most frequent virilising tumors in reproductive aged women. Ovarian thecoma occurs generally in postmenopausal and perimenopausal women. Some Luteoma patients develop hirsutism or virilization during late pregnancy with/without fetal masculinization as a result of circulating androgens. Ovarian teratoma is the most common ovarian neoplasm at children. Oophorectomy is the standard treatment but can impair fertility. Struma ovarii diagnosis is easy with the help of investigations like thyroid profile, pelvic ultrasonogram and radioiodide scan. For Corpus luteum cyst, due to variable clinical presentation and sonographic appearance, misdiagnosis potential is high.

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CHAPTER 4

COMMON BENIGN TUMORS OF OVARY: A REVIEW

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1. INTRODUCTION

There is a wide spectrum of ovarian lesions exhibiting varied clinical manifestation and histomorphology. “Ovarian endometriosis”, “Ovarian serous cystadenoma”, “Ovarian mucinous cystadenoma”, “Brenner tumor”, “Sex cord tumor with annular tubules”, “Ovarian fibroma” and “Follicular cyst of ovary” are the most common ovarian tumors. Due to their atypical presentation, these benign ovarian tumors are frequently misdiagnosed as cancers which result with radical surgery. This review is aimed to provide information extracted from articles published mostly during the last decade on the common benign ovarian tumors.

Female genital tract is a common site for tumors in females (Ramesh et al., 2013). Ovarian tumors exhibit a wide spectrum variation in behaviour and structure. There are many types of ovarian tumors, all they fall into benign, borderline, or atypical proliferative and malignant categories. Benign ovarian tumors can occur at any time in life and represent approximately 90% of all ovarian tumors (Myroshnychenko et al., 2020). Wide spectrum of ovarian lesions result with varied clinical manifestation and histomorphology. Due to their rarity and atypical presentation, they are frequently misdiagnosed as cancers and result with radical surgery (Lalwani et al., 2012). The importance of benign ovarian tumors as precursors or risk markers for ovarian cancer is not well understood. Benign ovarian tumors can be associated with long-term increased risk for mucinous ovarian cancer (Guleria et al., 2020).

Ovarian neoplasms can be divided into three major groups by origin cell type as epithelial, stromal and germ cell (Sujatha & Babu, 2009). Surface epithelial tumors account approximately 90% of ovarian tumors, of which serous tumors represent 46%. Sex-cord stromal tumors constitute 8% of ovarian tumors, fibroma is the most common, comprising 70% of this category. Combination of different types of tumors can occur in ovary where Mucinous cystadenoma and Brenner tumor are the most frequent (Jayalakshmy et al., 2012).

Transvaginal pelvic ultrasound is the first-line imaging for presumed benign ovarian tumors in adult women (Brun et al., 2014). Surgical management of ovarian tumors at pregnant is similar to non-pregnant women. Procedures are resection of the tumor (enucleation), removal of an ovary or ovaries (oophorectomy), or surgical excision of the fallopian tube and ovary (salpingo-oophorectomy). Options are open surgery (laparotomy) or keyhole surgery (laparoscopy) techniques for this procedure. Benefits of laparoscopic surgery are short hospital stays, early return to normal life and reduced post-operative pains (Bunyavejchevin & Phupong, 2013).

“Ovarian endometriosis”, “Ovarian serous cystadenoma”, “Ovarian mucinous cystadenoma”, “Brenner tumor”, “Sex cord tumor with annular tubules”, “Ovarian fibroma” and “Follicular cyst of ovary” are the most common ovarian tumors.

2. Ovarian endometriosis

Endometriosis is a common gynecological disorder characterized by the presence of ectopic endometrial glands and stroma. Although it is a benign condition, malignant transformation of endometriosis is possible. Endometriosis is likely to be associated with benign epithelial type histology than germ cell tumors (Apostol et al., 2015). Papillary projections and mural nodules may be observable in benign ovarian endometriosis and malignant transformation of ovarian endometriosis (endometriosis-associated ovarian cancer). This is a challenging diagnostic situation for clinicians. The “Height” and ““Height-Width ratio” of the mural nodules in the cyst may be a diagnostic factor for differentiating “benign ovarian endometriosis with mural nodules” from “endometriosis-associated ovarian cancer” (Tanase et al., 2018).

Endometriotic cyst formation and associated alterations in structural tissues in normal ovarian cortex may cause reduction in ovarian reserves (Kitajima et al., 2011).

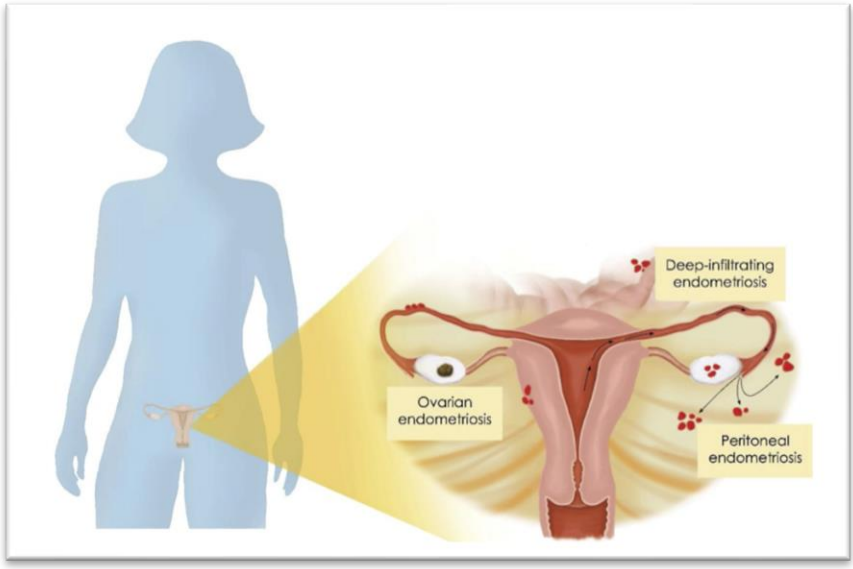

Fig. 1. Three different types of endometriosis: ovarian, peritoneal, and deep-infiltrating endometriosis, with different etiologies and pathogenesis (Rizner & Penning, 2020).

3. Ovarian serous cystadenoma

Ovarian serous cystadenomas arise from ovarium surface epithelium. According to the amount of the fibrous tissue, they are classified into cystadenoma, adenofibroma, cystadenofibroma, papillary cystadenofibroma, papillary cystadenoma, and papillary adenofibroma. Serous cystadenomas are usually oval, between 3–10 cm in diameter, contain a glistening surface and from clear to yellowish cystic fluid. They have a single microscopical layer of simple cuboidal non-ciliated epithelium or ciliated simple columnar. Simple papillary projections may be observable, stroma has fibroblasts at different degrees (Abu Sulb et al., 2016). Ovarian serous cystadenomas are common lesions which can be precursors of serous borderline tumors and can progress into low-grade serous carcinomas (Cheng et al., 2004).

4. Ovarian mucinous cystadenoma

Mucinous cystadenoma is a benign cystic ovarian tumor of the ovarium surface epithelium. It presents usually with vague, unspecific abdominal symptoms. If detected late, they may grow to a significant size with huge abdominal distention presenting various compression symptoms. Mucinous cystadenomas most commonly occur in the 3rd to 6th decades of life but rarely can occur in extreme ages (Akhras et al., 2019).

Ovarian mucinous cystadenoma are classified into three categories (benign, borderline malignancy, malignancy) based on histopathologic evaluations (Iwasaki et al., 2010). About 80% of mucinous tumors are benign, 10% are border-line and 10% are malignant. Due to mucinous fluid content, its rupture leads to mucinous deposits on the peritoneum. They can be in huge sizes (Kamel, 2010).

Benign mucinous cystadenomas represent 15% of all ovarian neoplasms and up to 80% of all mucinous tumors. Laparoscopy is an accepted method fort he management of ovarian cysts with expanding role due to ability to safely and effectively manage large benign adnexal masses greater than 10 cm (Mittal et al., 2008).

5. Brenner tumor

Brenner tumors of the ovary are uncommon and mostly benign. As a common agreement, Brenner tumors are derived from ovary surface epithelium or pelvic mesothelium through transitional cell metaplasia. It is necessary to categorise them as benign, borderline or malignant as

biological behaviour and surgery choice differs for these three categories (Tsikouras et al., 2016).

Brenner tumor signs are not generally much specific where pelvic pain or heaviness, metrorrhagia and menstrual irregularity may be observed. Brenner tumor can exceptionally induce Demons-Meigs's syndrome which associates one or more benign tumors of female reproductive tract with pleural and peritoneal effusions. This may indicate a rich but disturbing clinical condition. Prognosis and regression of symptomatology are nevertheless excellent following surgical resection of tumor (Coveliers et al., 2018).

When mucinous and Brenner tumors are combined, there is a shared clonal relationship between these two different tumor components, some pure mucinous tumors may develop from Brenner tumor, Brenner tumor component becomes compressed and obliterated by an expanding mucinous neoplasm (Wang et al., 2015).

6. Sex cord tumor with annular tubules

Sex cord tumors with annular tubules are a rare subtype of sex cord stromal tumor of the ovary. Management with follow-up evaluations is difficult due to rarity of these tumors (Nosov et al., 2009). “Sex cord tumor with annular tubules” are generally cured at time of diagnosis by surgical resection with an oophorectomy. They have a 100% (disease related) 5-year survival. 1/3 of these tumors are associated with Peutz-Jeghers syndrome (Jaegle et al., 2018). Other associated rare neoplasms are adenoma malignum of cervix, dysgerminoma, Turners syndrome,

endometrial carcinoma, gonadoblastoma and endometriosis of fallopian tube (Singh et al., 2014).

The predominant component of "sex cord tumor with annular tubules" has intermediate morphologic features between Sertoli cell tumors and granulosa cell tumors. Unilateral salpingo-oophorectomy is a feasible treatment for primary "sex cord tumor with annular tubules" cases with intact capsules and without Peutz–Jeghers syndrome. Complete tumor resection is suggested for recurrent cases. Long-term follow-up is highly recommended. Instead of high risk of recurrence, "sex cord tumor with annular tubules" prognosis is relatively favorable (Qian et al., 2015).

7. Ovarian fibroma

Ovarian fibroma tumor is in the group of sex cord-stromal cell tumors (Maccio et al., 2014). Ovarian fibromas and adenofibromas are benign tumours composed of spindle-like stromal cells (pure fibroma) or a mixture of fibroblast and epithelial components (adenofibroma). 40% of benign serous ovarian tumours are likely primary fibromas due to the neoplastic alterations restricted to the stromal compartment of these tumours (Hunter et al., 2020).

Ovarian fibroma is the most widespread benign solid tumor of the ovary and is frequently difficult to diagnose pre-operatively. Ovarian fibroma is often difficult to diagnose pre-operatively and usually misdiagnosed as uterine myoma due to solid nature of the mass on examination, and ultrasonic similarities between the two anomalies (Najmi et al., 2014).

Ovarian fibromas generally exhibit low signal intensity on T2-weighted images, which reflects their abundant fibrocollagenous stroma. But mass of larger tumors mainly demonstrates higher signal intensity on T2-weighted images, which reflects varied degenerative changes, such as cystic degeneration, hemorrhagic infarction, edematous change, or necrosis caused by torsion and myxomatous change (Kitajima et al., 2008). DCE MRI can distinguish ovarian fibromas from uterine leiomyomas and should be used if sonography fails to show the origin of a pelvic mass (Thomassin-Naggara et al., 2007).

8. Follicular cyst of ovary

Cystic abdominal tumors are extremely common and are diagnosed more frequently and earlier due to the use of ultrasonography as a primary modality for a pelvic examination. Benign cystic ovarian mass is a very common incidentally detected mass lesion in the reproductive age group female. Imaging modalities including ultrasonography and magnetic resonance imaging play a pivotal role in the differential diagnosis of cystic ovarian mass lesions. Imaging modality collaboration with the histopathological findings may lead to accurate diagnosis of cystic ovarian mass. Ultrasonography and magnetic resonance imaging play a vital role to narrow differential diagnosis, which can be further confirmed on histopathological investigations (Sharma et al., 2020).

Cystic abdominal lesions are very common in adolescent girls. Early diagnosis of ovarian tumours in adolescents is important. Since most of these tumours are benign, surgical treatment should be conservative to

minimise the risk of subsequent infertility (Rajput et al., 2014). Small follicular cysts are common to found in the ovaries of prepubertal girls, but they are not clinically important in most cases. These cysts are usually self-limiting and resolve spontaneously. But, they cysts can enlarge and continue producing estrogen which result in signs of sexual precocity (Chae & Rheu, 2013).

Large solitary follicular cysts of the ovaries have been found in association with pregnancy and puerperium and are presumably related to hCG stimulation. They have also been encountered in nonpregnant patients secondary to treatment with clomiphene citrate or gonadotrophin stimulation (Mohan et al., 2006).

9. Conclusions

Female genital tract is a common site for tumors in females. Due to their rarity and atypical presentation, these benign ovarian tumors are frequently misdiagnosed as cancers which result with radical surgery. Benign ovarian tumors can be associated with long-term increased risk for mucinous ovarian cancer.

Papillary projections and mural nodules may be observable in benign ovarian endometriosis and malignant transformation of ovarian endometriosis. Serous cystadenomas are usually oval, between 3–10 cm in diameter, contain a glistening surface and from clear to yellowish cystic fluid, simple papillary projections may be observable, stroma has fibroblasts at different degrees. About 80% of mucinous tumors are benign and can be in huge sizes. Brenner tumor can exceptionally

induce Demons-Meigs's syndrome which associates one or more benign tumors of female reproductive tract with pleural and peritoneal effusions. Sex cord tumor with annular tubules" are associated with Peutz-Jeghers syndrome, adenoma malignum of cervix, dysgerminoma, Turners syndrome, endometrial carcinoma, gonadoblastoma and endometriosis of fallopian tube. Ovarian fibroma is the most widespread benign solid tumor of the ovary and is frequently difficult to diagnose pre-operatively. Cystic abdominal lesions are very common in adolescent girls and early diagnosis of ovarian tumours in adolescents is important.

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CHAPTER 5

CANCER OF THE VAGINA: A REVIEW

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1. INTRODUCTION

Vaginal cancer is a rare disease and comprise approximately 2-3% of all gynecologic cancers. Most of the reported vaginal cancers are squamous cell carcinomas. Major risk factor for vaginal cancer is a persistent Human papillomavirus infection. and chronic mechanic irritation of the vagina. There are many factors effecting the treatment choice such as type of cancer, stage of cancer, potential side effects, patient preference and overall health. Surgery is generally used only for small stage I or II vaginal cancers and for cancers which were not cured by radiation treatment. Advanced cancers are generally treated with radiation therapy with simultaneous administration of combined chemotherapy.

This review is aiming to provide data on the epidemiology, pathogenesis, diagnosis, detection, staging, management strategies and treatment of vaginal cancer with the help of case articles and reviews published after 2012.

Primary vaginal cancer is a rare disease (Mannle et al., 2021). Vaginal cancer is comprising approximately 2-3% of all gynecologic cancers (Rajaram et al., 2015). This cancer type has very little documentation. When spread from primary other cancers or vulva is ruled out, vaginal cancer is designated as primary in origin. Most of the reported vaginal cancers are squamous cell carcinomas. Major risk factors are Human papillomavirus and age. Frequent symptoms are abnormal vaginal bleeding. Pathological confirmation is required for the diagnosis (Shrivastava et al., 2015). An international guideline on primary vaginal

cancer is absent to support and guide clinical decision makings. Historical results reveal poor outcomes with chemotherapy for stage IVB vaginal squamous cell carcinoma (Ansari et al., 2021).

Primary vaginal cancer should be carefully assigned as spread from cervix, vulva, and other metastatic tumors to vagina can occur. Although vaginal cancer traditionally occurs in older postmenopausal women, high-risk human papillomavirus-induced cancer incidence is increasing in young women. Squamous cell carcinoma is the most common histopathologic type followed by adenocarcinoma (Rajaram et al., 2015).

2. Causes

Major risk factor for vaginal cancer is a persistent Human papillomavirus infection. Also chronic mechanic irritation of the vagina is a suspected contributer for the vaginal cancer development. Mannle et al., (2021) studied possible associations between genital prolapse and vaginal cancer incidence by conducting a systematic article search on this association. Also searched on "Centre for Gynaecological Oncology of the Ortenau Clinic Offenburg" case analysis and determined that the most frequent histological subtype was squamous cell carcinoma (90%). Median age for genital prolapse-associated vaginal carcinoma patients was 75 years (73 ± 12 years). Prolapse-associated vaginal cancers had FIGO stage IV more often than cases of vaginal cancer in general. FIGO stage I was reported as most frequent (39%). FIGO stage IV was the second most frequent stage in prolapse-associated cases (25%). Disease-free survival for the prolapse-

associated cases FIGO stages I and II was far better; but prognosis at the advanced stages is much worse. As a conclusion, researchers informed that in addition to Human papillomavirus infection, patients with genital prolapsed and patients with ongoing systemic corticosteroid therapy or other immunocompromising medications, are in risk groups and should regularly examined.

The microbiome of human is an microorganism aggregation forming a mutualistic complex with the host. Symbiotic microbiome ecosystem has crucial roles in physiological functions of hosts. Disruption of this relationship may cause cancer. Xu et al., (2020) investigated compositional factors, environmental factors, beneficial co-existence and associations between vaginal microbiomes and ovarian carcinoma. They reviewed latest researches and determined that some microbiome presence may facilitate the Human papillomavirus infection, but reverse was also found possible that Human papillomavirus infection harbors a salubrious environment for microbial needs. Only a small percentage of women with persistent Human papillomavirus infection subsequently acquire clinically significant diseases. These microbiotas may play roles in Human papillomavirus persistent infection.

Human papillomavirus, p16, and p53 have been investigated as prognostic markers in various HPV-related cancers. For vaginal cancer, the evidence remains sparse. Rasmussen et al., (2021) conducted a systematic review of published studies on the prognostic significance of Human papillomavirus and immunohistochemical expression of p16 and p53 among women with vaginal cancer. Included total 12 studies

which were reported survivals after histologically verified vaginal cancers tested for HPV, p16, and/or p53. Vast majority of vaginal cancer cases were squamous cell carcinomas (84–100%). Seven studies reported survival after vaginal cancer according to HPV status and majority of these studies found a tendency towards improved survival for women with Human papillomavirus-positive vaginal cancer. Three out of four studies reporting survival according to p16 status found an improved survival among women with p16-positive vaginal cancer. For p53, only 1/6 studies reported an association between p53 expression and survival. As a conclusion, researchers suggested that Human papillomavirus-positive and p16-positive vaginal cancer patients have an improved prognosis compared to HPV-negative or p16-negative vaginal cancer patients. They reached no conclusion for p53.

3. Staging

FIGO (The Federation Internationale de Gynecologie et d'Obstetrique) staging of vaginal cancer (2009) follows cervical cancer rules. It needs routine clinical investigative modalities for staging. FIGO encourages advanced imaging modalities usage (Computed tomography, magnetic resonance imaging, and positron emission tomography) to guide therapy. But imaging findings can not be used to change or reassign the stage. “TNM staging of the American Joint Committee on Cancer”, and examination of the resected specimen of pelvic and inguinal lymph nodes may be used for staging (Rajaram et al., 2015).

4. Treatment

There are many prognostic factors effecting the treatment choice. Lymph node metastasis is an important prognostic factor where others are histology, size and age. In a new SEER analysis of approximately 2.000 patients, five year disease specific survival was found 84%, 75% and 57% for stage 1, stage II and advanced tumors, respectively (Shrivastava et al., 2015).

Surgery or radiation therapy are common to treat early carcinomas. Advanced cancers are generally treated with radiation therapy with simultaneous administration of combined chemotherapy. Though early stage vaginal cancers have better outcome treated with surgery or radiotherapy or surgery followed by radiotherapy. Radiotherapy alone is preferred mode of treatment in vaginal cancers (Shrivastava et al., 2015).

5. Surgical treatment

Surgery is generally used only for small stage I or II vaginal cancers and for cancers which were not cured by radiation treatment. The extent of the surgery depends on the size, location, and stage of the cancer. Wang et al., (2014) reported a case of a 3rd-degree uterine prolapse complicated by an isolated primary vaginal cancer and its surgical treatment. The cervix was normal, but a large exogenous hard lesion developed on the nearby prolapsed vaginal wall was observed. Lesion biopsy revealed squamous carcinoma. The patient was asymptomatic without recurrence for last four years follow-up after surgical + radiotherapy treatment. They concluded that the surgical treatment ±

radiotherapy is the optimum treatment for uterine prolapse with early-stage vaginal squamous cell carcinoma, although the majority of vaginal malignancies are treated with radiotherapy. Performing a biopsy prior to surgery in prolapse-induced ulceration is also recommended.

Types of surgery used for vaginal cancer are: 1) Local excision (surgeon takes out the cancer along with a nearby edge or rim of normal tissue). 2) Vaginectomy (vaginectomy is partial or whole removing of the vagina). 3) Trachelectomy (removing only the cervix and leaving the rest of uterus behind). 4) Hysterectomy (uterus and cervix must be removed, as well as all or part of the vagina).

Prameela et al., (2016) retrospectively analyzed prognostic factors and relevance in the outcomes of primary vaginal cancer. Medical records of primary vaginal cancers cases were between 2004-2012, from a tertiary care center in southern India. Total number of cases was 32 with median age of 64 years at presentation. Squamous histology accounted for 85%, with the rest being adenocarcinoma. Surgery was offered for five patient (16%), and concurrent chemotherapy for 14 patient (44%). Three patients recieved only surgery. All others received radiotherapy. 20 patients received external beam radiation and vaginal brachytherapy (for seven, only external beam radiation and for two, adjuvant radiation). Median follow-up was 55 months. 12 patients were alive at last follow-up (38%), while 14 were dead (44%; 8 from disease and 6 from other reasons). Six patients were lost to follow-up (19%). 20 patients were disease free. Median overall survival was 86 months,

disease-free survival was 90 months, and disease-specific survival was 97 months. When well and moderately differentiated tumors were taken together, the 5-year overall survival, disease-free survival, and disease-specific survival rates were, 57%, 64%, and 82%. For poorly differentiated tumors, median overall survival, disease-free survival, and disease-specific survival were, 21, 15, and 21 months, with statistically significant advantage for better grade tumors, for disease-specific survival. Better 5-year overall survival, disease-free survival, and disease-specific survival rates were observed for stage I + II group, with 55%, 80%, and 79%, compared with advanced stage where the same were 55%, 38% and 69%. Grade and stage of tumor had statistically significant predictive value over the outcomes, while tumor size showed a significant trend. Patients treated with combination of external beam radiation and vaginal brachytherapy fared well. Study concluded that grade of differentiation was a significant predictor of poor survival as was stage of disease. Combination of vaginal brachytherapy and external beam radiotherapy provided a good disease-free survival.

6. Radiotherapy / Chemotherapy / Chemoradiation / Brachytherapy

Treatment options and recommendations depend on several factors, such as type of cancer, stage of cancer, potential side effects, patient preference and overall health. Patients data from the “National Cancer Data Base” diagnosed with vaginal cancer between 1998-2011 who received definitive radiation therapy were analysed by Rajagopalan et

al., (2014). Of the 13.689 patients identified, 8.222 (60%) received radiation therapy. Of these, 3.932 (48%) received concurrent chemoradiotherapy and its use increased from 21% to 59% during 1998–2011. Study revealed that younger age, larger tumor size, later year of diagnosis, higher facility volume, squamous histology and higher stage are independently associated with concurrent chemoradiotherapy usage. Median overall survival was longer with concurrent chemoradiotherapy compared to radiation alone (56 vs. 41 months). Younger age, higher facility volume, squamous histology, lower comorbidity score, concurrent chemoradiotherapy, brachytherapy utilization and lower stage are independently prognostic of improved survival.

Joseph et al., (2020) reviewed the treatment outcomes in primary vaginal cancer patients who underwent definitive treatment at their institution. Total 43 patients with histologically proven primary vaginal cancer were identified, who were treated between 2005-2015. All patients were treated with definitive radiotherapy ± concurrent chemotherapy. Radiotherapy was delivered in combination with external beam radiotherapy and brachytherapy with a minimum dose of 60 Gy. Four patients were FIGO stage I, 13 patients were stage II, 23 patients were stage III and three patients were stage IVA. The median age was 60 years (range 42–76). The median follow-up was 29 months (range 3-70 months). The different variables looked into like the histology, lower third of vagina involvement and prior hysterectomy did not show any difference in survival. Addition of concurrent chemotherapy was the only factor for the trend towards better survival.

Even in the subset of patients with prior hysterectomy, patients received definitive treatment + concurrent chemo-radiotherapy showed a better two-year progression-free survival than sole radiotherapy received patients (57% vs 11%). As a conclusion, combination of external beam radiation therapy and brachytherapy with concurrent chemotherapy was found a reasonable option in the management of primary vaginal cancer. Further optimization of the dose and techniques of radiotherapy are warranted.

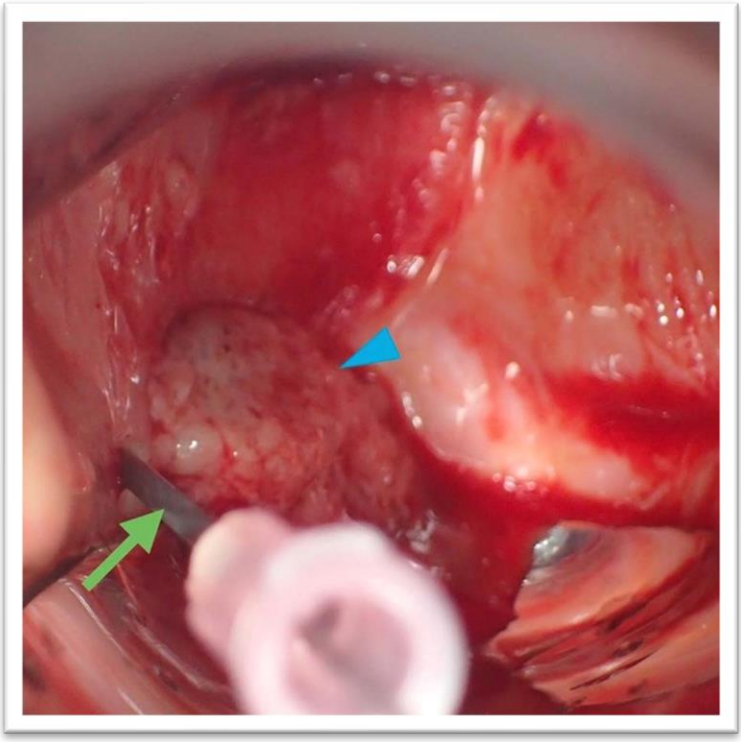

Fig. 1. Insertion of marker in a vaginal cancer patient with. 18-gauge injection needle (arrow); vaginal tumor (arrow head) (Sekii et al., 2019).

Vaginal cancer results with poor outcomes. Adequate radiation dose is essential to ensure curative management. Concurrent chemotherapy should be considered for vaginal cancer patients (Miyamoto & Viswanathan, 2013). Early stage of the disease, small tumor size, previous hysterectomy, high pre-treatment/treatment hemoglobin levels, and patient age correlates with a better clinical outcome. A brachytherapy boost should be delivered, especially in patients with late-stage disease. The addition of concurrent weekly cisplatin should be considered in most patients, and transfusion should be used to maintain high hemoglobin levels (Guerri et al., 2019). Utilization rates of brachytherapy in vaginal cancer are decreasing in the United States. Use of brachytherapy in vaginal cancer imparts a benefit in disease specific and overall survival. Larger tumors experienced the greatest benefit from brachytherapy (Orton et al., 2016).

A panel of members of the American Brachytherapy Society reviewed the literature, added their clinical experience, and formulated recommendations for interstitial brachytherapy usage in patients with vaginal cancer or recurrent endometrial cancer in the vagina and Beriwal et al., (2012) presented the results of this study. They determined that patients with bulky disease (approximately >0,5 cm thick) should be considered for treatment with interstitial brachytherapy. Three-dimensional treatment planning was recommended with computed tomography scan and/or magnetic resonance imaging. The treatment plan should reduce the dose to critical organs (rectum, urethra, bladder and sigmoid colon).

7. Cancer mimicking infections

Malakoplakia is a rare chronic inflammatory disease that develops in the urogenital system. Although its clinical presentation can vary from asymptomatic to urgent depend on location, mass effect, and other factors, its appearance can be mistaken for malignancy. However, the histological identification of von Hansemann histiocytes and Michaelis-Gutmann bodies confirm the diagnosis of malakoplakia. (Patel et al., 2021).

8. CONCLUSIONS

Major risk factor for vaginal cancer is a persistent Human papillomavirus infection. and chronic mechanic irritation of the vagina. There are many factors effecting the treatment choice such as type of cancer, stage of cancer, potential side effects, patient preference and overall health. Surgery is generally used only for small stage I or II vaginal cancers and for cancers which were not cured by radiation treatment. Advanced cancers are generally treated with radiation therapy with simultaneous administration of combined chemotherapy.

Preventive strategies include safe sex and HPV vaccination. Primary vaginal cancer is rare. Without history of cervix cancer or vulva cancer in past or absence of cervical squamous cell carcinoma or vulvar carcinoma within five years are generally considered as primary vaginal cancer.

Further investigations are needed to improve treatment and develop new interventions for women's health. Investigation of unique microbiome signatures in different cancers may provide insights for prognosis, prevention and development of treatments.

Use of concurrent chemoradiotherapy for patients with vaginal cancer has increased and is associated with a significant improvement in survival. Concurrent chemoradiotherapy should be integrated into treatment guidelines for vaginal cancer.

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CHAPTER 6

CANCER OF THE VULVA: A REVIEW

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INTRODUCTION

Vulvar cancer is a rare disease with peak incidence at ages of 70-79 years. But number of young patients with vulvar cancer is sharply increasing. 85-90% of vulvar cancers are squamous origined. Melanoma is the second most common cancer affecting vulva. Awareness on the possibility of metastatic conditions in relation to the vulva is important for accurate diagnosis and treatment.

Vulvar malignancy diagnosis is dependent on biopsy and pathologic evaluation. Overall survival varies by diagnosis. Early stage vulvar cancer can be treated and cured by surgical excision. Advanced level disease requires treatment either with mutilating surgery or a combination of chemotherapy and radiotherapy. For locally advanced vulval cancer, there is no consensus for the management. Complication incidence is high in vulvar cancer. Surgical resection is the gold standard treatment but radical vulval resections are in association with significant morbidity. Alternative forms of treatment such as chemoradiation and targeted therapies minimise psychosexual morbidity of radical surgery.

This review is aiming to provide data on the epidemiology, pathogenesis, diagnosis, early detection, staging, management strategies and treatment of vulvar cancer with the help of case articles and reviews published after 2011.

Vulvar cancer is a rare disease, representing 4-5% of all malignant neoplasms of the female genital tract and less than 1% of cancers of women. The incidence is betwen 1-3,6 cases per 100.000 women,

increases with age, with peak incidence at ages of 70-79 years. But number of young patients with vulvar cancer is sharply increased due to relation with human papillomavirus infection. The risk for developing vulvar cancer is related to behavioral, reproductive, hormonal and genetic aspects. Factors increasing risk are other genital cancers, vulvar chronic inflammatory diseases, smoking, genital warts and vulvar intraepithelial neoplasia. Based on epidemiological evidence, there are two etiologic pathways for vulvar cancer:

1) Older patients related (during the seventh or eighth decades of life), associated with mutations in TP53 and non-neoplastic epithelial disorders (such as chronic inflammation or vulvar lichen), shows precursor lesions of differentiated vulvar intraepithelial neoplasia.

2) Mostly young patients related, accounting for approximately 43-60% of squamous carcinoma of the vulva, associated with human papillomavirus infection, common precursor lesion of vulvar intraepithelial neoplasia.

85-90% of vulvar cancers are squamous origined (squamous cell carcinoma); but, when embryological origin of the vulva considered (the three germ layers), different histologic types may compose neoplasms affective in the region (Anschau & Gonçalves, 2016). Cancer of the vulva accounted for 0.3% of all new cancers in the United States in 2019, with approximately six thousands newly diagnosed cases (Michalski et al., 2021).

1. Types

Cancer entities of the vulva include vulvar intraepithelial neoplasms, squamous cell carcinoma, malignant melanoma, basal cell carcinoma, neuroendocrine tumors, and adenocarcinomas. “Vulvar intraepithelial neoplasms” represent premalignant precursors to “squamous cell carcinoma” of the vulva. There are many histopathologic subtypes of “squamous cell carcinoma” and treatments depend on primary tumor and lymph node involvement characteristics. Melanoma is the second most common cancer affecting vulva, and staging is based on tumor, node, and metastatic spread (Michalski et al., 2021).

Squamous cell carcinoma is the most frequently occurring subtype of vulvar cancer and is a disease of older post-menopausal women. It occurs with a background of lichen sclerosus and other epithelial conditions of the vulvar skin which may be associated with well-differentiated vulvar intra-epithelial neoplasia. Human papillomavirus infections increase vulvar squamous carcinomas in younger women, resulting from human papillomavirus-associated high-grade vulvar squamous intra-epithelial lesions (Rogers, 2022).

Two cases of metastatic lung cancer involving the vulva were presented by McAlinden et al., (2011). Metastasis from primary lung cancer is a rare cause of a vulval tumour which may require specific immunohistochemical stains to determine if vulval tumour is primary or secondary. Awareness on the possibility of metastatic conditions in relation to the vulva is important for accurate diagnosis and treatment.

2. Diagnosis

Vulvar malignancy diagnosis is dependent on biopsy and pathologic evaluation. Overall survival varies by diagnosis. Treatment of vulvar malignancies depends on histopathologic diagnosis and ranges from wide local excision with or without lymph node biopsy or dissection to radiation therapy with chemotherapy or immunotherapy (Michalski et al., 2021).

Meads et al., (2014) conducted a study was to determine the accuracy of sentinel lymph node biopsy with technetium 99 and/or blue dye-enhanced lymphoscintigraphy for vulval cancer. Studies with at least 75% of women with FIGO stage IB or II vulval cancer evaluating sentinel lymph node biopsy with technetium 99, blue dye or both with reference standard of inguinofemoral lymphadenectomy or clinical follow-up were included. Total 29 studies (1.779 women) were included; most of them evaluated technetium 99 combined with blue dye. Of these, 24 studies reported results for sentinel lymph node followed by inguinofemoral lymphadenectomy, and five reported clinical follow-up only for sentinel lymph node negatives. Mean sentinel lymph node detection rates were 94%, 69% and 98% for technetium 99, for blue dye or for both, respectively. Sentinel lymph node biopsy had pooled sensitivity of 95% with negative predictive value of 98% in studies using technetium 99/blue dye, ultrastaging and immunohistochemistry with inguinofemoral lymphadenectomy as reference. Pooled sensitivity for sentinel lymph node with clinical follow-up for sentinel lymph node negatives was 91% (85–95%) with

negative predictive value 96%. Patients undergoing sentinel lymph node biopsy experienced less morbidity compared to undergoing inguinofemoral lymphadenectomy. As a conclusion, sentinel lymph node biopsy using technetium 99, blue dye and ultrastaging with immunohistochemistry was found highly accurate when restricted to carefully selected patients, within a rigorous protocol, with close follow-up and where sufficient numbers for learning curve optimisation exist. Patients must make an informed choice between the slightly higher groin recurrence rates of sentinel lymph node biopsy vs the greater morbidity of inguinofemoral lymphadenectomy.

3. Surgical management of vulvar cancer

Early stage vulvar cancer can be treated and cured by surgical excision. Nearly 30% of women present advanced level disease and requires treatment either with mutilating surgery or a combination of chemotherapy and radiotherapy. This is an effective treatment but has side effects. New less morbid approaches to treatment includes drugs targeting various steps of the biological pathway from pre-cancer to cancer. Here the aim is preventing the growth of vulvar cancers (Rogers, 2022).

For locally advanced vulval cancer, there is no consensus for the management. Evidence for surgery, chemotherapy, or radiotherapy is inadequate and biased. Survival appears most favourable with surgery or chemoradiation ± surgery. As a result of absence of randomised trials, many questions, different treatment options and their efficacy are unanswered (O'Donnell et al., 2017).

Wills & Obermair, (2013) reviewed articles published between 1965 and August 2012 to identify the complications associated with contemporary surgical treatment for vulva cancer and discussed preventative strategies. They assessed complications resulting from surgery to the vulva or groins of vulva cancer patients. Most studies advocated for change in surgical technique to reduce complications associated with inguino-femoral lymphadenectomy and surgery to the vulva, with varying success. The most effective means of preventing complications is by omitting systematic lymph node dissection. This was safely achieved by sentinel lymph node biopsy. Saphenous vein sparing, VTE prophylaxis, the use of flaps and grafts, and preoperative counseling are additional ways to decrease morbidity. As a conclusion, instead of technical advances, complications following surgical treatment for vulva cancer was high.

O'Donnell et al., (2017) conducted a retrospective study on locally advanced vulva cancer patients treated with anovulvectomy, reported oncological outcomes and morbidity. Also they performed a systematic literature review (between 1946–2015) for all treatment options. Total 57/70 patients (81%) were treated in the primary setting with anovulvectomy and 13 patients underwent anovulvectomy for recurrent disease. The median overall survival was 69 months (1–336) with disease specific survival of 159 months (1–336). Following anovulvectomy for primary disease, time to progression and overall survival were significantly higher in node negative disease (10 vs. 96 months; 19 vs. 121 months). Post-surgical complications were observed in 36 (51%), the majority of which were Grade I/II infections. There

was one peri-operative death. Review showed that chemotherapy, radiotherapy or combination are alternative treatments to surgery. It was unclear if survival or morbidity was better in any one group. However, results for chemoradiation are encouraging enough to warrant further investigation. As a conclusion, evidence was inadequate to identify an optimal treatment for locally advanced vulva cancer. But, there was sufficient evidence to support a trial of anovulvectomy versus chemoradiation. Neoadjuvant chemotherapy or radiotherapy alone may be best reserved for the palliative setting or metastatic disease.

Complication incidence is high in vulvar cancer. For reduction of complications, extensive lymph node dissection can be avoided. The mainstay of treatment for most vulvar malignancies is surgery to the vulva with lymphadenectomy to the inguino-femoral areas, plus radiotherapy or/and chemotherapy for locally advanced, or recurrent disease. Treatment is associated with significant physical, sexual, and psychological morbidity (Wills & Obermair, 2013).

4. Radiotherapy / chemotherapy / vaccination

Surgical resection is the gold standard treatment but radical vulval resections are in association with significant morbidity such as wound breakdown, lymphoedema, infection and psychosexual consequences. Over the past decade there was a shift to less mutilating procedures for early vulval cancer in combination with applications of new surgical methods such as sentinel lymph node testing, more directed radiotherapy and chemotherapy. Most vulval cancers are squamous cell in origin but, there are other histological subtypes including Paget's

disease and vulval melanoma which may require different management approaches (Platt et al., 2016). Approximately 30% of patients present locally advanced disease, which is irresectable or require radical surgical resection, possibly with a stoma. This is necessitating alternative forms of treatment such as chemoradiation and targeted therapies to minimise psychosexual morbidity of radical surgery. Investigation of the molecular biologies of the two different pathways to vulvar squamous cell carcinoma (human papillomavirus-associated and non-human papillomavirus-associated) will lead to the development of targeted therapeutic agents (Rogers, 2022).

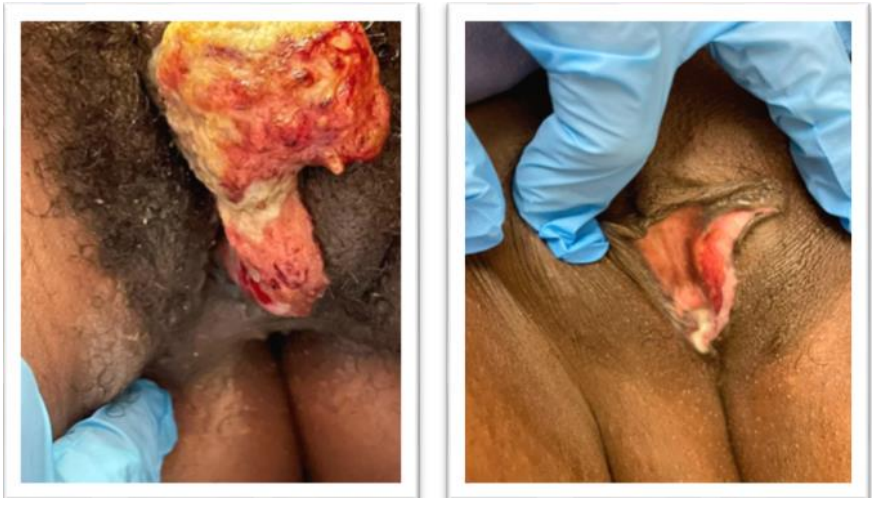

Figure 1. Prior to treatment (left) and after 3 cycles of carboplatin/paclitaxel (right) (Rogers, 2022).

It is not clear if definitive chemoradiation results in improved overall survival compared to radiation therapy alone in patients with vulvar cancer who are not candidates for surgery. Rao et al., (2017) compared these strategies in the National Cancer Database. They identified 1.352 patients with pathologically-confirmed squamous cell carcinoma of the

vulva treated with definitive radiation therapy (n = 353) or definitive chemoradiation (n = 999) between 2003-2014 in the National Cancer Database. Exclusion criteria were metastatic disease at diagnosis, radiation therapy dose less than 4000 cGy, follow-up less than six months, and surgical treatment. Median age was 66 (23–90) years. Chemoradiation group was younger with more advanced FIGO staging compared to the group of radiation therapy. Median radiation dose was 5940 (4000–7920) cGy. Median follow-up for living patients was longer for chemoradiation group (45 months; 6–132) compared to radiation therapy group (34 months; 6–128). The five-year overall survival was higher in the chemoradiation group than radiation therapy group (50% vs. 27%). Chemoradiation was related with less hazard of death than radiation therapy. On subgroup analysis, patients with FIGO stage I only had a trend towards improved survival with chemoradiation. As conclusion, in the National Cancer Database, definitive chemoradiation was associated with higher overall survival than radiation alone in patients with squamous cell carcinoma of the vulva who did not receive surgery. Concurrent chemoradiation can be beneficial for select patients in the definitive settings.

Al-Mansouri et al., (2018) reported an elderly women with a two-year history of intermittent vaginal bleeding which later developed a vulvovaginal mass. Core biopsy histology of the mass and left inguinal lymph node was suggested metastatic adenocarcinoma of breast origin. Breast lesion was not detected on mammography, with negative axillary nodes. Histopathologic features and the expression of GATA3,

cytokeratin (CK)7, mammaglobin staining and estrogen and progesterone receptors led to a diagnosis of breast cancer originating from the ectopic mammary tissue in the vulva. Rarity of these lesions and lack of standard treatment guidelines, management of the patient was extrapolated from the breast cancer treatment guidelines. Radiotherapy and chemotherapy followed by hormone therapy with aromatase inhibitor were administered to this patient in the metastatic setting with good palliation.

The advent of a vaccination programme against human papillomavirus 16 and 18, the main aetiological causes of vulval intraepithelial neoplasia and cervical intraepithelial neoplasia, may reduce the incidence in future generations (Platt et al., 2016).

5. Quality of life

Vulvar cancer treatment has high risk severe late effects which may have negative impacts on quality of life. Patient-reported outcome measures are increasingly used when evaluating disease- specific and treatment-specific effects. However, the adequacy of measures used to assess sequelae and quality of life in vulva cancer remains unclear (Froeding et al., 2018).

Jefferies & Clifford, (2011) examined the physical, psychological and sexual consequences for women after diagnosis and treatment for vulvar cancer with the help of 15 studies in the literature between 1983-2011. Involved approximately 400 women at this condition. They highlighted a paucity of published studies on this patient group, design

and analytical method weaknesses of the studies. The lack of recent evidence to support care practices offers limited help in contemporary health care today.

Froeding et al., (2018) evaluated disease-related and treatment-related effects measured by patient-reported outcomes for vulvar cancer patients to identify available specific patient-reported outcome measures. Systematic literature search between 1990-2016 was performed with inclusion criteria of report of disease-related and treatment-related effects in vulvar cancer patients using patient-reported outcome measures. Study was performed as a part of development phase 1 of ”European Organisation for Research and Treatment of Cancer Quality of Life” questionnaire for vulva cancer patients. 11 articles including total 535 women with vulva cancer were identified. 21 different instruments assessed quality of life. Most of the questionnaires were generic. Different issues (sexuality, body image, lymphedema, vulva-specific symptoms, urinary and bowel function) were reported as potentially important. As a conclusion, vulvar cancer treatment was found associated with significant morbidity deteriorating quality of life. A vulvar cancer-specific quality of life instrument with sensitive scales that allows for broad cross-cultural application for use in clinical trials is needed.

6. CONCLUSIONS

Vulvar malignancy diagnosis is dependent on biopsy and pathologic evaluation. Overall survival varies by diagnosis. Early stage vulvar cancer can be treated and cured by surgical excision. Advanced level

disease requires treatment either with mutilating surgery or a combination of chemotherapy and radiotherapy. For locally advanced vulval cancer, there is no consensus for the management. Complication incidence is high in vulvar cancer. Surgical resection is the gold standard treatment but radical vulval resections are in association with significant morbidity. Alternative forms of treatment such as chemoradiation and targeted therapies minimise psychosexual morbidity of radical surgery.

Definitive chemoradiation was associated with higher overall survival compared to radiation alone in patients with squamous cell carcinoma of the vulva who did not receive surgery.

It is needed to increase the number of multi centered randomized controlled trials to improve the quality of evidence and studies focused on complications of surgeon complication.

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CHAPTER 7

BENIGN UTERINE TUMORS: A REVIEW

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1. INTRODUCTION

Correct biomechanical function of the uterus is important for the execution of human reproduction. There is a general agreement that submucosal fibroids negatively affect fertility compared to women without fibroids. Uterine adenomyosis is responsible for chronic pelvic pain, abnormal uterine bleeding, and infertility. Endometriosis is characterized by heavy menstrual bleeding, pain and infertility. Therapeutic options with fertility preservation are challenging and require non-surgical management of benign endometrial hyperplasia.

Since they can progress to carcinoma, benign uterine tumors are clinically important. Benign uterine tumors are “Uterine fibroids”, “Uterine adenomyosis”, “Uterine endometriosis”, “Endometrial hyperplasia”, “Cervical polyp” and “Hydatidiform moles”.

This review is aiming to provide new data on the benign tumors of female genital system.

Correct biomechanical function of the uterus is important for the execution of human reproduction. These functions include aiding the transport of the embryo to the implantation site, remodeling tissue walls to host the placenta, protecting the fetus during gestation, contracting forcefully for a safe parturition and postpartum and remodeling back to its nonpregnant condition to renew the cycle of menstruation (Myers & Elad, 2017). Human uterus has no pacemaker or motor innervation, but develops rhythmic, strong contractions which increase intrauterine pressure to dilate the cervix and force the fetus through the pelvis. To

achieve the synchronous contractions required for labor, the muscle cells of the uterus act as independent oscillators that become increasingly coupled by gap junctions toward the end of pregnancy (Smith et al., 2015).

As cancer survival rates improve, understanding and preventing the adverse off-target and long-term impacts of cancer treatments, including impacts on fertility, have become increasingly important. Cancer therapy-mediated damage to the ovary and depletion of the primordial follicle reserve are well characterised. However, our knowledge of the full extent of damage to the rest of the female reproductive tract, in particular the uterus, is limited (Griffiths et al., 2020).

Since they can progress to carcinoma, benign uterine tumors are clinically important. Benign uterine tumors are “Uterine fibroids”, “Uterine adenomyosis”, “Uterine endometriosis”, “Endometrial hyperplasia”, “Cervical polyp” and “Hydatidiform moles”.

2. Benign myometrium tumors

2.1. Uterine fibroids (uterine leiomyomas, leiomyoma of uterus)

Uterine fibroids are the most frequent tumors of women and their prevalence is higher in infertility patients. At present, their classification is according to anatomical location, as no classification system includes their size or number. There is a general agreement that submucosal fibroids negatively affect fertility compared to women without fibroids. Intramural fibroids above >4 cm, even without cavity

distortion, can also influence fertility negatively. However, presence of subserosal myomas has no or little effect on fertility. Many theories were proposed to explain how fibroids impair fertility: 1) mechanisms involving alteration of local anatomical location, 2) mechanisms involving functional changes of the myometrium and endometrium, 3) endocrine and paracrine molecular mechanisms. But, any of the these mechanisms can cause reduced reproductive potential, thereby leading to impaired gamete transport, reduced ability for embryo implantation, and creation of a hostile environment. Myomectomy appears to have an effect in fertility improvement in certain cases. Excision of submucosal myomas seems to restore fertility with pregnancy rates after surgery similar to normal controls. Removal of intramural myomas affecting pregnancy outcome might be associated with increased pregnancy rates compared to non-operated controls. Treatment of subserosal myomas of reasonable size is not necessary for fertility reasons. The results of endoscopic and open myomectomy are similar; thus, endoscopic treatment is the recommended approach due to its advantages in patient's postoperative course (Zepiridis et al., 2016).

Risk factors associated with the development of fibroids include age, endogenous and exogenous hormonal factors, race, obesity, uterine infection, diet, alcohol consumption, smoking, caffeine consumption and stress (Pavone et al., 2018).

Chen et al., (2015) observed 9.988 cases and determined that ultrasound ablation treatment for uterine fibroid and adenomyosis was highly

effective and safe. Adverse reactions to ultrasound ablation under conscious sedation were low and temporary for both diseases.

Repeated 12-week courses of daily oral ulipristal acetate (5 and 10 mg) effectively control bleeding and pain, reduce fibroid volume, and restore quality of life in symptomatic fibroid patients (Donnez et al., 2015).

Since 1995 uterine artery embolization has been described as an alternative for hysterectomy in patients with symptomatic fibroids. Many studies including several randomized controlled trials established uterine artery embolization as a valuable treatment. A study of de Bruijn et al., (2016) was compared clinical outcome and health-related quality of life 10 years after uterine artery embolization or hysterectomy in the treatment of heavy menstrual bleeding caused by uterine fibroids. They determined that, in about 2/3 of uterine artery embolization–treated patients with symptomatic uterine fibroids a hysterectomy can be avoided. Health-related quality of life 10 years after uterine artery embolization or hysterectomy remained comparably stable. Uterine artery embolization was found a well-documented and less invasive alternative to hysterectomy for symptomatic uterine fibroids on which eligible patients should be counseled.

2.2. Uterine adenomyosis

Uterine adenomyosis is a benign disease, frequently encountered in reproductive-aged women. It is responsible for chronic pelvic pain, abnormal uterine bleeding, and infertility. Exact origin and pathogenic

mechanisms involved in adenomyosis still need to be elucidated but important progress are made over years. The theory of endometrium invaginating the myometrium via a traumatized interface was first proposed, many molecular mechanisms were reported as participated in this process. An alternative theory was suggested de novo development of adenomyotic lesions from metaplasia of Müllerian remnants or adult stem cells (Stratopoulou et al., 2021).

Atypical polypoid adenomyoma diagnosis is based on pathological and immunohistochemical analysis. Individuals diagnosed with atypical polypoid adenomyoma are at risk to coexist with endometrial carcinoma and atypical endometrial hyperplasia. For desire to retain fertility, treatment strategy is performing transcervical resection to completely remove the lesions and tight follow-up for possible progressive atypical polypoid adenomyoma recurrence. For individuals without fertility desire, hysterectomy may be preferred (Zhu et al., 2021).

Magnetic resonance imaging is the current imaging gold standard to diagnose adenomyosis, but is often limited due to high costs and availability. Transvaginal ultrasound is a cost-effective, accurate and readily available alternative (Sam et al., 2020).

The safety and effectiveness of percutaneous microwave ablation and ultrasound-guided radiofrequency ablation in the treatment of uterine adenomyosis were similar; however, the mean ablation time of percutaneous microwave ablation was shorter than that of ultrasound-guided radiofrequency ablation (Lin et al., 2020).

Donnez & Donnez, (2020) compared the efficacy of a selective progesterone receptor modulator, ulipristal acetate, and a gonadotropin-releasing hormone antagonist, linzagolix, in a case of severe uterine adenomyosis. New oral gonadotropin-releasing hormone antagonist (linzagolix) significantly reduced lesion size and improved quality of life in a patient with severe adenomyosis, who was previously nonresponsive to treatment with a selective progesterone receptor modulator, ulipristal acetate.

A once-daily regimen of 200 mg linzagolix for 12 weeks and then 100 mg for another 12 weeks decreased adenomyotic uterine volume and improved associated symptoms (Donnez et al., 2021).

2.3. Uterine endometriosis

Endometriosis is presence of functional endometrium outside of uterine cavum. As a pluripotent tissue, endometrium has possibility to implant itself everywhere even implantation in abdominal wall was described (Vuksic et al., 2016). This diseases is characterized by heavy menstrual bleeding, pain and infertility. Uterine disorders coexistence should be considered for assessing women with endometriosis to define treatment strategy better for infertility especially for older women than 35 years (Capezzuoli et al., 2020).

According to the Ministry of Health of Uzbekistan, frequency of occurrence of stomach cancer is in second place after breast cancer. For more than 50% of cases, primary detection of endometriosis of the

uterus in these patients occured in advanced stages (Khatamova & Bobokulova, 2020).

Perfluorinated substances are chemicals with endocrine disruptive properties which may interfere with female reproductive system. Exposure to high levels of perfluorinated substances in drinking water was determined that associated with increased risk of polycystic ovarian syndrome and possibly uterine leiomyoma, but not endometriosis (Hammarstrand et al., 2021).

A diagnosis of uterine leiomyoma increase the risk of endometriosis. Patients presenting with uterine fibroids should be encouraged to give informed consent for possible simultaneous surgical treatment of endometriosis (Lin et al., 2021).

Ziadeh et al., (2020) sheds light on the potential increased risk of uterine rupture during pregnancy who had a prior resection of deep-infiltrating endometriosis. If these patients are considered high-risk pregnancy cases, their care should be managed by high-risk obstetric specialists.

A number of dysregulated mechanisms are believed to contribute to adenomyosis development and symptoms. These include sex steroid signaling, endometrial proliferation and invasiveness, and aberrant immune response. Abnormal sex steroid signaling, particularly hyperestrogenism and subsequent progesterone resistance, are known to play a pivotal role in its pathogenesis. This is the reason to use various antiestrogenic agents to manage adenomyosis-related symptoms. Among them, gonadotropin-releasing hormone antagonists

are gaining ground, with studies reporting efficient lesion regression and symptom alleviation (Donnez et al., 2021).

Uterine myomas and endometriosis are benign hormone-dependent diseases affecting women of reproductive age and substantial efforts have been made to develop innovative medical options for treating these gynecologic diseases. Elagolix and relugolix were approved in some countries for treating endometriosis and myomas, respectively (Dababou et al., 2021).

3. Benign endometrium tumor: "Benign endometrial hyperplasia"

Endometrial hyperplasia is a spectrum of changes in the endometrium ranging from a slightly disordered pattern that exaggerates the alterations seen in the late proliferative phase of the menstrual cycle to irregular, hyperchromatic lesions that are similar to endometrioid adenocarcinoma. Generally, endometrial hyperplasia is caused by continuous exposure of estrogen unopposed by progesterone, polycystic ovary syndrome, tamoxifen, or hormone replacement therapy. Since it can progress, or often occur coincidentally with endometrial carcinoma, endometrial hyperplasia is clinically important. Reversion of hyperplasia to normal endometrium represents the key conservative treatment for prevention of the development of adenocarcinoma. Currently, cyclic progestin or hysterectomy is the major treatment option for endometrial hyperplasia without or with atypia, respectively. But, clinical trials of hormonal therapies and definitive standard treatments remain to be established for the management of endometrial hyperplasia. Therapeutic options with

fertility preservation are challenging and require non-surgical management (Chandra et al., 2016).

Endometrial hyperplasia, particularly with atypia, is a significant concern due to being a potential precursor of endometrial cancer. Accurate diagnosis of precancerous lesions of the endometrium and exclusion of coexisting endometrial carcinomas are highly required for the optimal management of patients. According to the classification of WHO, based on glandular complexity and nuclear atypia, endometrial hyperplasia is divided into four groups: non-atypical endometrial hyperplasia (simple, complex) and atypical endometrial hyperplasia (simple, complex). Estimated risk of progression of atypical hyperplasia to endometrial cancer is 8-29% (Sobczuk & Sobczuk, 2017).

4. Benign cervix tumor: "Cervical polyp"

Polyps of the uterine cervix are among the most common benign hyperplastic lesions of the female genital tract that usually arise from the endocervical canal. It probably a result of reactive changes due to long-standing chronic inflammation, multiparty, and foreign bodies. Cervical polyps are usually small sized (<4 cm) are common in adult women. But few cases of giant polyps and rare occurrence in children were also reported. Heterotopias and malignant transformation in cervical polyps are very rare (Esmat et al., 2021). Cervical polyps are a common finding on routine vaginal exams (Planer, 2020) and most commonly seen in the female with uterine bleeding (Ota et al., 2017).

Fibroepithelial cervical polyps are benign growths from the inner surface of the cervix. They are typically asymptomatic and minority can undergo malignant change. Cervical polyps develop as a result of focal hyperplasia of the columnar epithelium of the endocervix (Rexhepi et al., 2019). Fibroepithelial stromal polyps is usually seen in reproductive age group. They exhibit bizarre cytomorphology, atypical mitoses, or hypercellularity, raises the possibility of malignancy and continue to be underrecognized (Hasan et al., 2018).

Mullerian adenosarcoma of the uterine cervix generally displays cervical polyps and can be often misdiagnosed as benign endocervical polyps both clinically and pathologically (Yu et al., 2020).

Hasegawa-Nakajima et al., (2020) reported a case in which a polypoid lesion with a diameter of 5 mm was diagnosed as a cervical polyp due to a negative Papanicolaou smear in the cervix, and polypectomy revealed a diagnosis of villoglandular papillary adenocarcinoma on histopathological examination. Even if an asymptomatic cervical polyp with a negative Papanicolaou smear is diagnosed, in some patients villoglandular papillary adenocarcinoma of the uterine cervix may coexist with cervical intraepithelial neoplasia.

5. Benign placenta tumor: “Hydatidiform moles”

Androgenetic complete hydatidiform moles are human pregnancies with no embryos and affect 1/1.400 pregnancies. They have mostly androgenetic monospermic genomes with all the chromosomes originating from a haploid sperm and no maternal chromosomes

(Nguyen et al., 2018). DNA genotyping studies have established that most partial hydatidiform moles are diandric dispermic triploid conceptions. Rare triandric tetraploid partial hydatidiform moles have been described, but genotyping cannot determine the manner in which three paternal chromosome complements are derived (one sperm with triplication, two sperm with one duplication, three different sperm, or one diploid and one haploid sperm). Tetraploid partial hydatidiform moles arise when three different sperm fertilize a single, normal ovum. SNP array is useful to determine the parental contributions in triploid/tetraploid conceptuses. It also allows for direct visualization of meiotic crossover frequency and sites in these conceptions, providing insight into their biology (Bynum et al., 2020).

As around 1/3 of complete hydatidiform moles and 2/3 of partial hydatidiform moles are not diagnosed by ultrasound in cases of missed miscarriage, histopathological examination of all products of conception in case of early pregnancy failure is essential to detect molar changes. This is particularly important for the management of women with complete hydatidiform moles who have a higher risk of developing a gestational trophoblastic neoplasia (Memtsa et al., 2020).

Up to 20% of hydatidiform moles are followed by malignant transformation in gestational trophoblastic neoplasia and require chemotherapy. Syncytin-1 is involved in human placental morphogenesis and is also expressed in various cancers. Variations of Syncytin-1 protein localization and down-regulation of hASCT1 (human neutral amino acid transporter 1) and TLR4 (toll-like receptor

4) transcription are likely to reflect altered functions of Syncytin-1 in the premalignant context of complete moles (Bolze et al., 2016).

Hydatidiform moles are characterized by an abnormal proliferating trophoblast with a potential for a malignant transformation. Similar to other tumors, trophoblastic pathogenesis is probably a multistep process involving many molecular and genetic alterations. Altered expression of Bcl-2 (oncoprotein), p53 (tumor suppressor protein), p63 (tumor suppressor protein) and Ki-67 (cell proliferation marker) reflects the hydatidiform moles pathological development. Immunohistochemical analysis is beneficial to recognize the hydatidiform moles molecular and pathogenic mechanisms. Furthermore, it could serve as a useful adjunct to conventional methods for refining hydatidiform moles diagnosis (Missaoui et al., 2019).

6. CONCLUSIONS

About 2/3 of uterine artery embolization–treated patients with symptomatic uterine fibroids a hysterectomy can be avoided. New oral gonadotropin-releasing hormone antagonist (linzagolix) significantly reduced lesion size and improved quality of life in a patient with severe adenomyosis, who was previously nonresponsive to treatment with a selective progesterone receptor modulator, ulipristal acetate. Elagolix and relugolix were approved in some countries for treating endometriosis and myomas, respectively. Generally, endometrial hyperplasia is caused by continuous exposure of estrogen unopposed by progesterone, polycystic ovary syndrome, tamoxifen, or hormone replacement therapy.

Since it can progress, or often occur coincidentally with endometrial carcinoma, endometrial hyperplasia is clinically important. Reversion of hyperplasia to normal endometrium represents the key conservative treatment for prevention of the development of adenocarcinoma. Mullerian adenosarcoma of the uterine cervix generally displays cervical polyps and can be often misdiagnosed as benign endocervical polyps both clinically and pathologically.

Therefore, future studies should focus on evaluation of new treatment strategies and novel compounds that could simultaneously target pathways involved in the pathogenesis of estradiol-induced endometrial hyperplasia. Novel therapeutic agents precisely targeting the inhibition of estrogen receptor, growth factor receptors, and signal transduction pathways are likely to constitute an optimal approach for treatment of endometrial hyperplasia.

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CHAPTER 8

ABNORMAL UTERINE BLEEDING: A REVIEW

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1. INTRODUCTION

Abnormal uterine bleeding describes variations from normal bleeding patterns in nonpregnant, reproductive-aged women beyond menarche lasting for at least 6 months (Marnach et al., 2019). Up to 30% of women seek medical assistance for this problem during their reproductive years (Singh et al., 2018). It is a common condition leading increased health care costs and decreased quality of life (Marnach et al., 2019). Common causes of abnormal uterine bleeding are endometrial polyps, endometrial hyperplasia, submucous fibroids and anovulation (Goyal et al., 2015). Uterine fibroids, a common cause of abnormal uterine bleeding, are estimated to cost the USA $6 to $34 billion annually (Chodankar & Critchley, 2019). Abnormal uterine bleeding is a common complaint that affects many women from puberty to menopause. It affects health negatively by causing anemia, and impacts the quality of life of affected women (Levy-Zauberman et al., 2017).

Common causes of abnormal uterine bleeding are endometrial polyps, endometrial hyperplasia, submucous fibroids and anovulation. PALM–COEIN is a classification system of FIGO designed for abnormal uterine bleeding. In a gynecologic setting, the first step is most often to identify structural abnormalities with common diagnostic options such as ultrasonography, blood test, endometrial sampling, and hysteroscopy. Age, desire for pregnancy in future and etiology for abnormal uterine bleeding are important factors to consider before

initiating a treatment. Treatment for abnormal uterine bleeding can be medical and/or surgical depending on the cause.

Here in this review, some common and special causes, diagnostic options and treatment methods of abnormal uterine bleeding are reviewed by the help of articles published after 2015.

2. Palm–Coeın Of Fıgo

"The International Federation of Gynaecology and Obstetrics" working group on menstrual disorders was developed a classification system named as "PALM–COEIN" for the causes of the abnormal uterine bleeding in non-pregnant women (Mishra & Sultan, 2017). PALM-COEIN is an acronym for "Polyp; Adenomyosis; Leiomyoma; Malignancy and hyperplasia; Coagulopathy; Ovulatory dysfunction; Endometrial; Iatrogenic; and Not yet classified" for abnormal uterine bleeding (Munro et al., 2011).

The "PALM" group comprises the structural entities, which can be measured visually or by using imaging techniques and histopathology. The "COEIN" group comprises the nonorganic types which can not be defined by imaging or histopathology (Vasava et al., 2021). In a gynecologic setting, the first step is most often to identify structural abnormalities (PALM causes). Common diagnostic options for the identification of the PALM are ultrasonography, endometrial sampling, and hysteroscopy. These options are sufficient sole or in combination for diagnosis of many women with abnormal uterine bleeding. Contrast sonography with saline or gel infusion, 3D-ultrasonography, and

magnetic resonance imaging can be included (Dueholm & Hjorth, 2017). A structured approach for establishing the PALM-COEIN classification system will facilitate accurate diagnosis and inform treatment options (Whitaker & Critchley, 2016).

3. Diagnosis of abnormal uterine bleeding

Investigations may include blood test, hysteroscopy, ultrasound. Endometrial sampling is required in certain situations (Levy-Zauberman et al., 2017). Accurate diagnosis of the cause reduce the frequency of hysterectomy (Goyal et al., 2015). Transvaginal sonography is recommended as first line investigation in abnormal uterine bleeding. If transvaginal sonography shows normal cavity, further evaluation can be omitted and medical treatment for symptoms can be started directly (Goyal et al., 2015). For women with abnormal uterine bleeding, once a thorough history, physical examination, and indicated imaging studies are performed and all significant structural causes are excluded, medical management is the first-line approach. Determining the acuity of the bleeding, the patient's medical history, assessing risk factors, and establishing a diagnosis will individualize their medical regimen (Bradley & Gueye, 2016). Transvaginal color doppler sonography may be beneficial in detecting the etiology of abnormal uterine bleeding in premenopausal women (Bayram et al., 2021).

4. Common treatment

Age, desire for pregnancy in future and etiology for abnormal uterine bleeding are important factors to consider before initiating a treatment. Treatment for abnormal uterine bleeding can be medical and/or surgical depending on the cause. Medical treatment is based on iron supplementation, hormonal and non-hormonal therapies. Surgical treatments include removal of a focal lesion, endometrial resection or destruction and hysterectomy. Treatment efficiency can be assessed using the same tools as pretherapeutic evaluation (Levy-Zauberman et al., 2017).

Zupi et al., (2015) compared long-term efficacy of laparoscopic supracervical hysterectomy and hysteroscopic endometrial ablation in treating persistent abnormal uterine bleeding. Lower reintervention rate and better physical and mental health make laparoscopic supracervical hysterectomy a better procedure to treat recurrent abnormal uterine bleeding when compared with hysteroscopic endometrial ablation.

Gopimohan et al., (2015) evaluated the efficacy and safety of a new variant of the Levonorgestrel–Intrauterine System (LNG-IUS)—Emily—for the treatment of abnormal uterine bleeding. Among women with abnormal uterine bleeding, use of the Emily LNG-IUS significantly reduced menstrual bleeding and improved quality of life.

5. Cause-specific treatment

5.1. Adenomyosis

Damage to the uterine junctional zone is a primary contributor to adenomyosis. Diagnosis may be reliable by well-performed ultrasonography or magnetic resonance imaging. Medical managements need to be useable for prolonged durations, with the "Levonorgestrel Intrauterine Device" as best option to date. Conservative surgical management is feasible but requires high technical skill. Interventional sonography and radiological techniques are emerging and beneficial alternatives to surgery (Abbott, 2017).

5.2. Fibroids

An very common cause of "abnormal uterine bleeding/heavy menstrual bleeding" are fibroids (leiomyomas, myomas). Uterine fibroids are the most common benign tumours in women at reproductive age. Although hysterectomy is a permanent solution to the "abnormal uterine bleeding/heavy menstrual bleeding" complaint, a significant ratio of symptomatic fibroids are at younger women who desire uterine and/or fertility preservation and hence medical treatments have an important role. Endometrial ablation (2nd-generation) and transcervical resection of the endometrium are non-excisional methods to treat "abnormal uterine bleeding/heavy menstrual bleeding" and are an alternative to hysterectomy in women who do not desire fertility preservation. Both procedures are effective, and satisfaction rates are high (Chodankar & Critchley, 2019).

Abnormal uterine bleeding frequently co-exists with fibroids but the relationship between these are still incompletely understood and also at many women the identification of fibroids may be incidental to a menstrual bleeding complaint. Office hysteroscopy and increasing sophisticated imaging may assist provision of robust evidence for the underlying cause. Availability increases of medical options has expanded the choice for women and many will no longer need complicated surgery. Treatment must remain individualised and encompass the impact of pressure symptoms, desire for retention of fertility and contraceptive needs and improve quality of life (Whitaker & Critchley, 2016).

Sayyah-Melli et al., (2016) compared the usefulness of vaginal danazol and diphereline in the management of intra-operative bleeding during hysteroscopy. Both vaginal danazol and diphereline were effective to control uterine bleeding during operative hysteroscopy. However, vaginal danazol provided a clearer visual field.

Transcervical radiofrequency ablation with the Sonata® System offers a minimally invasive, incisionfree, organ-preserving therapy, with intraoperative visualization of fibroids using intrauterine ultrasound guidance. Sonata® System is a simple, minimally invasive, rapid and successful method that shows significant improvement of symptoms even in large myomas ≥5 cm (Piriyev et al., 2021).

Episodes of acute abnormal uterine bleeding related to uterine fibroids can cause significant morbidity. Traditional management with high-dose hormonal regimens can not be as effective when used in women

with fibroids. Ulipristal acetate has been shown to induce amenorrhea rapidly in women with uterine fibroids, and it may be a good treatment at the emergency management of fibroid-related acute abnormal uterine bleeding (Arendas & Leyland, 2016).

5.3. Ovulatory dysfunction

Abnormal uterine bleeding is a frequent cause of emergency department visits and a major concern reason for adolescents and families. Most cause of abnormal uterine bleeding in adolescents is ovulatory dysfunction and 5–36% of adolescents who present with heavy menstrual bleeding have an underlying bleeding disorder (Deligeoroglou & Karountzos, 2018).

Hokenstad et al., (2015) evaluated the efficacy and safety of endometrial ablation for the treatment of abnormal uterine bleeding related to ovulatory dysfunction. Endometrial ablation was effective in women with AUB-O and used as an alternative to hysterectomy or to medical management of AUB-O in patients with contraindications.

5.4. Von Willebrand Disease

The most common form of bleeding disorders is von Willebrand Disease, representing 13% of abnormal uterine bleedings of adolescents. Management of abnormal uterine bleeding depends on the bleeding severity, underlying etiology and hospitalization requirement. Treatment of adolescents with an underlying coagulopathy depends on the severity of the bleeding disorder. A coagulopathy is the cause of

abnormal uterine bleeding more usually than generally recognized (Deligeoroglou & Karountzos, 2018).

5.5. Polycystic ovary syndrome

Maslyanskaya et al., (2017) evaluated if polycystic ovary syndrome related ovulatory dysfunction is a frequent underlying etiology of abnormal uterine bleeding in adolescents required hospitalization and also to explore etiology, treatment, and complications of abnormal uterine bleeding with severe anemia in adolescents. Polycystic ovary syndrome was found major underlying etiology in adolescents hospitalized with abnormal uterine bleeding. Screening for hyperandrogenemia is important to diagnose polycystic ovary syndrome early to allow ongoing management and to prevent comorbidities. Endometritis was frequently underestimated as an etiology for abnormal uterine bleeding.

5.6. Myoma

Abnormal uterine bleeding is the major complaint in approximately 1/3 of gynecological visits in pre-menopausal women, and in >70% of appointments of postmenopausal and perimenopausal women. Uterine myoma is a major cause of abnormal uterine bleeding during menacme, especially if it is submucosal. The association of myoma and abnormal uterine bleeding may be tied to many factors, from locally alterated angiogenic and vasoactive substances to changed uterine contractility. There exist a correlation between penetration degree of the submucosal myoma and abnormal uterine bleeding intensity. Size of the submucosal

myoma is a secondary parameter in correlating the degree of bleeding (Lasmar & Lasmar, 2017).

5.7. Antiplatelet therapy

Increasing number of pre-menopausal women are using antithrombotic or/and antiplatelet therapy for diversified cardiovascular indications. Their usage may result with or exacerbate abnormal uterine bleeding and consequent anemia worsen cardiac symptoms. Collaboration is required between gynecologists and cardiologists to increase awareness on abnormal uterine bleeding and related consequences for optimally personalized management. Heavy and irregular menstrual bleeding is common in women in their 40s and may have diversified underlying causes that require different treatment options (Maas et al., 2015).

Abnormal uterine bleeding is a common complication of anticoagulant therapy in premenopausal women affected with acute venous thromboembolism. Abnormal uterine bleeding reduces quality of life, and can lead to premature cessation of anticoagulation. There is increasing data suggesting that direct oral anticoagulants used for the treatment of venous thromboembolism have differences for menstrual bleeding profile (Godin et al., 2017).

5.8. Immature hypothalamic-pituitary-ovarian axis

Most of abnormal uterine bleeding cases in adolescencets are due to an immature hypothalamic-pituitary-ovarian axis, but current approach to investigate adolescents with abnormal uterine bleeding frequently include pelvic ultrasound to exclude rare structural causes. Results

strongly suggest that pelvic ultrasound examination is not required in the initial investigation of abnormal uterine bleeding in the adolescent population because it did not alter treatment in any of studied patients (Pecchioli et al., 2017).

5.9. AUB-M

A structured history and associated other symptoms can indicate the potential underlying cause of abnormal uterine bleeding. AUB-M should always be considered especially in women with a raised body mass index, hypertension, diabetes, polycystic ovary syndrome, age >45 years, late menopause, nulliparity, tamoxifen use, unopposed oestrogen exposure, family history of breast, endometrial, colon cancer, Lynch syndrome etc (Chodankar & Critchley, 2019).

In acute abnormal uterine bleeding with a normal uterus, parenteral estrogen, a multidose progestin-only regimen, a multidose combined oral contraceptive regimen, and tranexamic acid are viable options, for the appropriate clinical scenario. Heavy menstrual bleeding may be treated with a levonorgestrel-releasing intrauterine system, continuous oral progestins, combined oral contraceptives, and tranexamic acid with high efficacy. Nonsteroidal antiinflammatory drugs may be utilized with hormonal methods and tranexamic acid to decrease menstrual bleeding. Gonadotropin-releasing hormone agonists are indicated in patients with leiomyoma and abnormal uterine bleeding in preparation for surgical interventions. In women with inherited bleeding disorders all hormonal methods as well as tranexamic acid can be used to treat abnormal uterine bleeding. Women on anticoagulation therapy should

consider using progestin-only methods as well as a gonadotropin-releasing hormone agonist to treat their heavy menstrual bleeding. By these options for medical treatment of abnormal uterine bleeding, many patients can avoid surgical intervention (Bradley & Gueye, 2016).

Progestin-only contraceptives induce abnormal uterine bleeding, accompanied by prothrombin leakage from dilated endometrial microvessels and increased thrombin generation by human endometrial stromal cell-expressed tissue factor. Studies on the thrombin-treated human endometrial stromal cell secretome identified increased levels of cleaved "chondroitin sulfate proteoglycan 4", impairing pericyte–endothelial interactions. Disruption of "human endometrial endothelial cells" tube formation by thrombin induces aberrant angiogenesis and abnormal uterine bleeding in "Depo medroxyprogesterone acetate" users (Shapiro et al., 2017).

5.10. Endometrial hyperplasia

To determine the feasibility, efficacy, and long-term clinical outcomes of resectoscopic endometrial ablation as primary treatment of simple endometrial hyperplasia and complex endometrial hyperplasia without atypia in women with abnormal uterine bleeding. When performed by surgeons experienced in hysteroscopy, resectoscopic endometrial ablation is feasible, safe, and effective for treatment of simple endometrial hyperplasia and complex endometrial hyperplasia without atypia in women with abnormal uterine bleeding (Vilos et al., 2015).

Abnormal uterine bleeding is usually hormonally managed by progestogens. Progestogens are used to regulate intermenstrual bleeding and decrease heavy menstrual bleeding in women of reproductive age or who are perimenopausal. In menopausal women, progesterones and progestogens prevent endometrial hyperplasia and aim to reduce the development of endometrial cancer. Progesterone also acts in concert with other hormones to affect breast, cardiovascular system, lipid profile and bone. Investigation of long-term effect of progestogen-releasing intrauterine systems is needed (Jewson et al., 2020).

6. CONCLUSIONS

Transvaginal sonography is recommended as first line investigation in abnormal uterine bleeding. Adenomyosis diagnosis may be reliable by well-performed ultrasonography or magnetic resonance imaging. Most cause of abnormal uterine bleeding in adolescents is ovulatory dysfunction. Screening for hyperandrogenemia is important to diagnose polycystic ovary syndrome early in the adolescents. A coagulopathy is the cause of abnormal uterine bleeding more usually than generally recognized. Association of myoma and abnormal uterine bleeding may be tied to many factors, from locally alterated angiogenic and vasoactive substances to changed uterine contractility.

Lower reintervention rate and better physical and mental health make laparoscopic supracervical hysterectomy a better procedure to treat recurrent abnormal uterine bleeding when compared with hysteroscopic endometrial ablation. Efficacy and safety of Emily LNG-IUS is high.

Availability increases of medical options for fibroids has expanded the choice for women and many will no longer need complicated surgery.

Investigation of long-term effect of progestogen-releasing intrauterine systems is needed. More safety data on uterine bleeding with novel anticoagulants in premenopausal women should be obtained.

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CHAPTER 9

BENIGN TUMORS OF FEMALE GENITAL SYSTEM: A REVIEW

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1. INTRODUCTION

World Health Organization classification of ovarian tumours is on histological criteria, but most of the neoplasms are basicly grouped into three major and mostly discrete subsets based on their cells of origin. These are 1) surface epithelial-stromal tumours, 2) sex cord-stromal and steroid cell tumours, 3) germ cell tumours (Muronda & Russell, 2018).

All ovarian tumors are fall into groups of epithelial tumors, mesenchymal tumors, mixed epithelial and mesenchymal tumors, sex cord-stromal tumors, mixed sex cord-stromal tumors, germ cell tumors, monodermal teratoma and somatic-type tumors arising from a dermoid cyst, germ cell-sex cord-stromal tumors, miscellaneous tumors, mesothelial tumors, soft tissue tumors, tumor-like lesion, lymphoid and myeloid tumors, secondary tumors (Kurman et al., 2014).

2. Benign Ovarian Tumors

2.1. Ovarian endometriosis

Epithelial ovarian tumors are complex and clinically, diagnostically and therapeutically challenging due to the difficulty of early detection, lack of known precursor lesions and high mortality rates. Endometrioid ovarian carcinomas are frequently associated with endometriosis, but the mechanism for this association remains unknown (Dinulescu et al., 2005). Endometriosis is associated with inflammatory reaction, and reactive oxidative species are highly pro-inflammatory factors (Chen et al., 2019). The severity of dysmenorrhea and postoperative pregnancy were independent risk factors for the recurrence of ovarian

endometriomas after surgery during long-time follow up (Li et al., 2019). Circular RNAs (circRNAs) are candidate factors for the activation of ovarian endometriosis and are promising diagnostic biomarkers and treatment targets (Xu et al., 2018).

2.2. Ovarian serous cystadenoma

Serous cystadenomas are usually oval, between 3–10 cm in diameter, contain a glistening surface and from clear to yellowish cystic fluid. They have a single microscopical layer of simple cuboidal non-ciliated epithelium or ciliated simple columnar. Simple papillary projections may be observable, stroma has fibroblasts at different degrees (Abu Sulb et al., 2016). Inhibins are glycoproteins produced mostly by ovarian granulosa cells and corpus luteum across the menstrual cycle. Inhibin production was demonstrated in malignant epithelial ovarian tumours. High amounts of dimeric inhibins presence in ovarian serous cystadenoma was also determined (Reis et al., 2000). Laparoscopic fertility sparing ovarian cystectomy is safe and applicable to large ovarian cystic masses, which are presumed to be benign pre-operatively, such as ovarian serous cystadenomas. It should be the preferred surgical approach for young women and adolescents for ovarian tissue conservation (Fahmi et al., 2015).

2.3. Ovarian mucinous cystadenoma

Ovarian mucinous cystadenomas are cystic neoplasms lined by mucin-producing epithelial cells. Majority are benign (80%) and mostly asymptomatic during early stages. Average diameters ranges between

15-30 cm (Alobaid et al., 2019). Ovarian mucinous cystadenomas are mostly unilateral (95%), and their peak incidence occurance among women are between ages of 30-50. Intraoperative cyst rupture and cystectomy instead of adnexectomy are two risk factors for recurrence for ovarian mucinous cystadenoma (Ben-Ami et al., 2010). Mucinous cystadenomas are rare in children with very rare recurrence. Patients undergoing cystectomy should be carefully followed up for recurrence. Risk of recurrence is key factor to decide on treatment. Preservation of fertility must be considered during treating young patients (Fujishima et al., 2021).

2.4. Brenner tumor

Brenner tumors are ovarian tumors, frequently benign, including epithelium that resembles transitional epithelium. As with other epithelial tumors there exist frankly malignant tumors and tumors that display greater proliferation than the benign Brenner tumors but lack destructive infiltrative growth, and these have been designated ‘atypical proliferative’ (borderline) Brenner tumors. There is not any well-documented cases of atypical proliferative Brenner tumor which exhibited malignancy. Based on shared morphologic features it is generally believed that atypical proliferative Brenner tumors develop from benign Brenner tumors (Kuhn et al., 2014). The immunoprofile of mucinous tumors associated with Brenner tumors shares the lack of Mullerian markers PAX2 and Paired box gene 8 with the Brenner tumor but differs in the expression of GATA3 only in the Brenner tumor component (Roma & Masand, 2015).

2.5. Sex cord tumor with annular tubules

Sex cord tumors with annular tubules are very rare neoplasms and comprise less than 1% of sex cord ovarian tumors. They usually occur at reproductive aged women and tend to be associated with Peutz Jeghers Syndrome, be bilateral, multifocal, and small. When diagnosed in old patients they are often sporadic, unilateral, predominantly cystic and bigger. It is important to be aware that sex cord tumors with annular tubules can also be present in older women, they can be bilateral despite not being related to Peutz Jeghers Syndrome syndrome and must be considered as a differential diagnosis in ovarian tumors (Luna-Limon et al., 2020).

Sex cord stromal tumor with annular tubules is distinguished by its ring-shaped tubules. It has morphological features between Sertoli cell tumor and granulosa cell tumor. Sex cord stromal tumor with annular tubules has low malignant potential with late recurrence. Oophorectomy is the main stay of treatment. Long term follow-up is important (Kwong et al., 2019). It is difficult to recognize sex cord tumors with annular tubules clinically and there is no standard treatment (Qian et al., 2015). They may be hormonally active, was detected in a case of premature ovarian failure (Garcia-Galiana et al., 2001).

2.6. Ovarian fibroma

Ovarian fibromas are the most frequent solid primary tumors of ovarium but are often found in the perimenopausal period incidentally. Bilateral involvement and ascites are found in 3–10% and 10–15% of

cases with larger lesions, respectively. Ovarian fibromas are benign neoplasms that arise from the stromal connective tissue of the ovary and constitute 4% of all ovarian neoplasms. Ovarian fibroma with Meigs syndrome can be differentiated from ovarian malignancy with the help of pelvic sonography, laparoscopy and intraoperative frozen section study of the tumor. Once ovarian malignancy is ruled out, ovarian fibroma can be excised vaginally (Chang et al., 2005). Ovarian fibromas are gonadal stromal cell origin and account for 3-4% of all ovarian tumors. Cystic degeneration is frequent but calcification was rarely reported. Successfully removing a large, stony hard mass via minimally invasive surgery is a big challenge. In a case of a large, torsioned calcified fibroma with its consistency harder than human bones was excised laparoscopically and was removed using rongeur through ultraminilaparotomy (Moon et al., 2010).

2.7. Ovarian follicular cyst

Imaging modalities including ultrasonography and magnetic resonance imaging play a pivotal role in the differential diagnosis of cystic ovarian mass lesions. Imaging modality collaboration with the histopathological findings may lead to accurate diagnosis of cystic ovarian mass. Ultrasonography and magnetic resonance imaging play a vital role to narrow differential diagnosis, which can be further confirmed on histopathological investigations (Sharma et al., 2020). Henes et al., (2018) showed a significant decrease in anti-Müllerian hormone levels after surgery on the ovaries.

From the pathological point of view there are no overwhelming data that could clearly differentiate a cystic granulosa cell tumor from a follicular cyst (Nocito & Sarancone, 2020). In reproductive age females, the majority of ovarian cysts are physiological or functional in nature and encompass dominant follicles, follicular cysts and luteal cysts. Key differential diagnoses of haemorrhagic ovarian cysts include endometrioma, dermoids and mucinous cystic tumours (Tonolini et al., 2019). Cystic abdominal lesions are extremely common in adolescent girls and are now diagnosed more frequently due to the availability of better imaging modalities (Rajput et al., 2014).

2.8. Leydig cell tumor

Leydig cell tumors of the ovary are very rare, mostly associated with symptoms of virilization in postmenopausal patients. Sometimes it is difficult to localize the tumor precisely even with modern imaging techniques. When precise tumor location is not determined pre-operatively, selective ovarian venous hormonal sampling may help to make accurate diagnosis (Ozgun et al., 2008). Selective ovarian vein catheterization and hormonal sampling is effective to localize small ovarian tumors (Dickerson et al., 2005). Leydig cell tumors are usually small and resemble normal ovarian stroma, so they are often difficult to localize. Combining these dynamic contrast-enhanced and diffusion-weighted magnetic resonance imaging techniques may be useful for diagnosing a Leydig cell tumor (Okamura et al., 2020). Leydig cell tumors are rare, and even when they are small, they can cause

symptoms related to androgen excess. As a result, diagnosing them often is challenging (Bala et al., 2021).

2.9. Sertoli cell tumor

Ovarian sertoli cell tumors are rare, and their morphologic spectrum, behavior, and influencing factors are not clear. They can be mimicked by different tumors, some are more frequent than Sertoli cell tumors. Immunohistochemistry may aid to differentiate (Oliva et al., 2005). Sertoli cell tumors are rare occurrences and should be considered in the differential diagnosis for a prepubescent girl with an abdominal mass (D'Souza et al., 2007).

2.10. Sertoli–Leydig cell tumor

Sertoli-Leydig cell tumors are sex-cord stromal tumors that account less than 0,5% of primary ovarian neoplasms. They are frequently benign and occur in reproductive aged women. Variants with heterologous mesenchymal elements are exceptionaly rare. The usual presentation of Sertoli-Leydig cell tumors is with signs of androgen excess as majority of them produce androgens (Papler et al., 2016). Ovarian sex cord-stromal tumors include Sertoli-Leydig cell tumor, juvenile granulosa cell tumors and gynandroblastoma among others. These ovarian sex cord-stromal tumors as well as other tumors including pleuropulmonary blastoma may be associated with DICER1 mutations (Schultz et al., 2017). Variants of Sertoli-Leydig cell tumors with heterologous elements account for 20%. Ovarian Sertoli-Leydig cell tumors with heterologous mesenchymal elements are exceptional and mainly

associated with poorly differentiated tumors and are often fatal (Grove & Vestergaard, 2006). The most common mode of presentation is with hormonal-related symptoms in the form of secondary amenorrhea, irregular menses and features of virilization (Bhat et al., 2013). A simple numeric chromosomal abnormality in Sertoli-Leydig cell tumors may be associated with a malignant phenotype (Manegold et al., 2001).

2.11. Ovarian Thecoma

Thecoma-fibroma group of ovarian stromal tumors represent a spectrum of neoplasms composed of “entirely lipid-containing cells resembling theca interna cells” to those containing “predominantly spindle-shaped cells with variable intercellular collagen" (Streblow et al., 2007).

Elevated serum inhibin B is a classic marker of adult granulosa cell tumors, however, extremely rare and informative case of elevated inhibin B was associated with ovarian thecoma (Carballo et al., 2020). Thecoma sometimes has positive “fluorodeoxyglucose F18” uptake on positron emission tomography–computed tomography, which indicates a need for caution regarding false-positive positron emission tomography–computed tomography in patients with benign solid ovarian tumor (Bono et al., 2017). Combining conventional morphologic and signal intensity characteristics with the findings from diffusion-weighted image or perfusion-weighted image may assist differentiating ovarian fibroma, fibrothecoma, and thecoma from ovarian malignancies (Chung et al., 2015).

2.12. Luteoma

Pregnancy luteomas are rare, nonneoplastic lesions of the ovary probably caused by the hormonal effects of pregnancy. Many patients are asymptomatic with the ovarian enlargement incidentally discovered by imaging or surgery. Some patients develop hirsutism or virilization at late pregnancy. Luteomas spontaneously regress postpartum. Its diagnosis and management may be challenging as it may mimic the presentation of malignant ovarian tumors (Verma et al., 2016). Successive pregnancy luteomas associated with maternal hyperandrogenism may cause female disorders of sex development (Chen et al., 2009). High maternal serum testosterone levels due to a luteoma can result in virilization in the female newborn (Spitzer et al., 2007).

2.13. Teratoma

Teratoma is the most frequent ovarian germ-cell tumor, probably arises from a single germ cell and is composed of tissues representing all germ layers (ectoderm, mesoderm, and endoderm). Benign cystic teratomas (dermoid cyst) include 95% of ovarian teratomas and are comprised of entirely mature adult tissues. When malignant, almost all mature teratomas contain squamous carcinoma (Noumoff et al., 2001). Up to 1/3 of ovarian masses originate from germ cells, and many are mature cystic teratomas. Secondary development of malignancy is rare but a well known phenomenon in ovarian teratoma patients. Squamous-cell carcinoma represents 80% of secondary malignant transformations of ovarian teratomas (Hackethal et al., 2008).

Early detection is important for long-term survival. Old age, large tumor size, and solid portion in mature cystic teratoma seem to predict the malignant transformation of mature cystic teratoma (Park et al., 2008).

2.14. Struma ovarii

Malignant struma ovarii is a rare ovarian neoplasm which is generally asymptomatic. There are many approaches fort he treatment based on staging. A few case studies have described associated thyrotoxicosis. Follow-up with surveillance thyroglobulin levels in cases of malignant struma ovarii for at least 10 years is recommended (Makani et al., 2004). Struma ovarii has some characteristic magnetic resonance images of a multilobulated complex mass with thickened septa, multiple cysts of variable signal intensities, and enhancing solid components (Kim et al., 2000).

In cases of metastatic struma ovarii, total thyroidectomy in conjunction with radioiodine scanning and radioiodine ablation is recommended. Thyroglobulin levels should be followed as a tumor marker, and diagnostic radioiodine scans should be performed to screen for residual or recurrent disease. Although this treatment strategy is well established for thyroid cancer, long-term outcomes of this treatment for struma ovarii are still unknown (McGill et al., 2009).

2.15. Corpus luteum cyst

Corpus luteum cyst is a functional cyst formed during the second phase of ovarian cycle. Its natural history typically includes regression in the

absence of pregnancy or regression after the first trimester of pregnancy and maturation of placenta. It has a very vascular structure and occasionally a subject of rupture. Blood loss is usually self-limited, but rarely can lead to massive hematoperitoneum and even death. Due to variable clinical presentation and sonographic appearance, misdiagnosis potential is high (Vidakovic et al., 2013).

Hemorrhagic corpus luteum cysts are frequently seen during sonography of the female pelvis, but diagnosis is generally challenging due to variations in size, thickness of the cyst wall, and internal echo pattern depending on the formation and lysis of the clot. In some cases, hemoperitoneum is the most obvious finding. The differential diagnosis is extensive and includes ectopic pregnancy, adnexal torsion, neoplasm, and pelvic inflammatory disease (Swire et al., 2004).

Ruptured corpus luteum cyst of pregnancy manifesting massive hemoperitoneum is a rare but life-threatening disorder that can occur even in a young girl. Ovarian conservative treatment can laparoscopically be performed with intraoperative autologous blood transfusion (Takeda et al., 2007).

3. Benign myometrium tumors

3.1. Uterine fibroids (uterine leiomyomas, uterine leiomyomata)

Uterine fibroids (also known as leiomyomas or myomas) are a common benign tumor of the female genital tract (Cha et al., 2011). These are common clonal neoplasms of the uterus. Fibroids have both smooth muscle and fibroblast components, in addition to a substantial amount

of fibrous extracellular matrix, and all contribute to the pathogenesis. Fibroids are highly heterogeneous in their pathophysiology, location, size, and clinical symptomatology. They are also a part of a range of disease in which a few variants have facets of malignant behaviour but overall are benign. Risk for fibroids is associated with race. Black women have elevated risk to develop fibroids early in life than white counterparts. Clinically, fibroids account for one-third to half of all hysterectomies and are associated with substantial morbidity and health care costs for women of reproductive age (Stewart et al., 2016).

Uterine fibroids are associated with DNA damage and genomic instability. Hypovitaminosis D is a known risk factor for uterine fibroids, especially among African Americans. Studies demonstrate a novel link between DNA damage and the vitamin D3/VDR (Vitamin D3/Vitamin D receptor) axis in uterine fibroids. Vitamin D3 suppresses the UF phenotype through orchestrated targeting at multiple molecules in DNA repair pathways, which offers novel mechanistic insights into the clinical effectiveness of vitamin D3 on uterine fibroids (Ali et al., 2019).

3.2. Uterine adenomyosis (Uterus adenomyoma)

Adenomyosis is a benign uterine condition affecting women at various ages with different symptoms. The management of these patients is still controversial. No drug is labelled for adenomyosis currently. But many nonsteroidal anti-inflammatory drugs and hormonal treatments (progestins, gonadotropin-releasing hormone analogues and oral contraceptives) are currently used off-label for pain symptom control

and abnormal uterine bleeding in adenomyosis. Gonadotropin-releasing hormone analogues are indicated before fertility treatments to improve the chances of pregnancy in infertile women with adenomyosis. An antiproliferative and anti-inflammatory effect of progestins (dienogest, danazol and norethindrone acetate) suggests to control pain symptoms. Also intrauterine device releasing levonorgestrel is extremely effective in resolving abnormal uterine bleeding and reducing uterine volume in a long-term management plan (Vannuccini et al., 2018).

Uterine adenomyoma differs from uterine adenomyosis due to its relatively localized characteristics (i.e., focal adenomyosis) or its related disease, adenomyosis (Wang et al., 2009). Appropriate surgical treatment of adenomyosis, a benign invasion/infiltration of endometrial glands within the underlying myometrium, remains a subject of discussion. Since 1990, in place of the classical V-shaped resection method, various kinds of surgical management have been attempted, including a uterine muscle flap method that emphasizes fertility preservation, an asymmetric dissection method, and various modified reduction methods. Laparoscopic adenomyomectomy has also become an alternative to laparotomy for surgically managing the focal type of adenomyosis, although it seems to be associated with a higher risk of uterine rupture than laparotomy (Osada, 2018).

3.3. Uterine endometriosis

Endometriosis is a condition characterized by the presence of endometrial tissue outside the uterus. Although it is common, cause is still unclear. Two primary mechanisms were proposed as explaination

of the pathogenesis of endometriosis: 1) in situ development by metaplasia, 2) development as a consequence of abdominal dissemination of endometrial cells at the time of menses (retrograde menstruation). Endometriosis may result from abnormal myometrial contractility through tubal transportation, dissemination, and implantation of endometrial viable cells into the abdomen (Bulletti et al., 2002).

Endometriosis has been related to menstruation since Sampson formulated the hypothesis that menstrual regurgitation and implantation of endometrial debris are the principal causes of the disease. If this hypothesis is accepted, its onset cannot precede menarche when endometrial shedding and menstrual bleeding begin to occur. However, endometriosis was documented in normal young girls before menarche and, in these cases it was assumed that its pathogenesis and pathophysiology differ from adolescent and adult endometriosis. Endometriosis can be present for a long time before a diagnosis is established (Brosens & Benagiano, 2013).

4. Benign fallopian tube tumors

4.1. Adenomatoid tumor

The adenomatoid tumor is the most common benign neoplasm of the fallopian tube (Terada, 2012). Adenomatoid tumors of the female and male genital tracts are well characterized as mesothelial origined (Sangoi et al., 2009). Adenomatoid tumor in female genital tract shows typical morphologic features with bland nuclei (Pongsuvareeyakul et al., 2021). Gynecologists may take care of the diagnosis of adenomatoid

tumor of the female genital tract, a pathology which is often mistaken for leiomyoma, and in addition to warn of the malignant appearance of adenomatoid tumor (Huang et al., 1995).

4.2. Fallopian tube endometriosis (tubal endometriosis)

Tubal endometriosis refers to ectopic endometrium on the fallopian tubes. Tubal endometriosis can cause fractural and functional dysfunction of the fallopian tubes, which may trigger the appearance of masses, dysmenorrhea, and tubal endometriosis-related infertility (Wang et al., 2017). Endometriosis is a disease affecting millions of women around the world. Ovary is the most common organ site involved by endometriosis. The fallopian tube epithelia may be one of the tissue sources contributing to ovarian endometriosis (Yuan et al., 2014).

5. Benign vulva tumors

5.1. Papillary hidradenoma

Papillary hidradenoma is also known as hidradenoma papilliferum, is an uncommon lesion usually occuring in women aged 30-49 years. It is a rare benign tumor of apocrine glands. Papillary hidradenoma of the vulva is a rare, benign neoplasm arising from apocrine sweat glands of the skin. Mostly, this lesion has been mistaken for carcinoma (Udawat et al., 2015). Papillary hidradenomas of vulva arises from specialized anogenital mammary-like glands in and around the intralabial sulcus. These are benign lesions, which present slow growing circumscribed cystic masses. Histologically, papillary hidradenomas are characterized

by glandular structures and complex branching papillae with fibrovascular stalks. Glands are lined by myoepithelial cells and epithelial secretory cells with a surrounding fibrous stroma. Oestrogen and progesterone receptors are potential markers to differentiate between anogenital sweat glands and conventional sweat glands (Akhtar et al., 2017).

5.2. Vulvar intraepithelial neoplasia

Lichen sclerosus is considered to be the precursor lesion of vulvar squamous cell carcinoma, of which only 2–5% progress to squamous cell carcinoma. Differentiated vulvar intraepithelial neoplasia was proposed as the direct precursor lesion, but this is a recently recognized, and a difficult to diagnose, entity, which may easily be mistaken for a benign dermatosis. Differentiated vulvar intraepithelial neoplasia diagnosis is frequently missed and associated with rapid progression to squamous cell carcinoma. Patients with lichen sclerosus with dyskeratosis and parakeratosis, hyperplasia and/or basal cellular atypia should be kept under close surveillance as these lesions also tend to progress to squamous cell carcinoma (Van De Nieuwenhof et al., 2011). Differentiated vulvar intraepithelial neoplasia is a unique precursor to vulvar squamous cell carcinoma that is typically HPV-negative and frequently associated with nuclear p53 staining. These features imply a mode of pathogenesis involving somatic mutations (Pinto et al., 2010).

6. Benign endometrium tumor

6.1. Benign endometrial hyperplasia

The differential diagnosis of endometrial hyperplasia and well-differentiated endometrioid adenocarcinoma is complicated not only by the resemblance of these lesions to each other, but also by their tendency to be overdiagnosed (particularly hyperplasia) on the background of polyps, endometritis, artifacts, and even normally cycling endometrium. Atypical hyperplasia may also be overdiagnosed when epithelial metaplastic changes occur in simple or complex hyperplasia without atypia. Low-grade adenocarcinomas are best recognized by architectural evidence of stromal invasion, usually in the form of stromal disappearance, desmoplasia, necrosis, or combinations of these findings between adjacent glands (Silverberg, 2000).

7. Benign cervix tumor

7.1. Cervical polyp

Inflammatory lesions of the uterine cervix are very common, and although lymphomas in this location are rare, the differential diagnosis between both diseases must be considered in some cases and may be difficult to achieve (Alameda et al., 2005). Cervical polyps occur in up to 5% of women and 1,7% contain carcinomatous changes. Most malignant polyps result from the progression of localized dysplasia, but distant metastases were reported. An unusual finding of a lung cancer metastatic to a cervical polyp at a 69-year-old female was described (Omrani et al., 2004).

Adenolipoleiomyoma, also known as adenomyolipoma (a unique cervical polyp), is a hamartomatous tumor composed of an admixture of smooth muscle tissue, adipose tissue and cystically dilated benign glands. This entity has only rarely been reported in the uterine corpus or fallopian tube (Selvarajan et al., 2017).

8. Benign placenta tumor

8.1. Hydatidiform moles

Recurrent hydatidiform moles are aberrant human pregnancies characterized by absence of, or abnormal, embryonic development, hydropic degeneration of chorionic villi, and hyperproliferation of the trophoblast. Biallelic mutations in two maternal-effect genes, NLRP7 and KHDC3L, underlie the causation of recurrent hydatidiform moles in 60% of patients (Qian et al., 2018). Murdoch et al., (2006) reported five mutations in the maternal gene NALP7 in individuals with familial and recurrent hydatidiform moles. NALP7 is a member of the CATERPILLER protein family involved in inflammation and apoptosis. NALP7 is the first maternal effect gene identified in humans and is also responsible for recurrent spontaneous abortions, stillbirths and intrauterine growth retardation.

Immunohistochemical analysis of cyclin-dependent kinase inhibitor 1C (CDKN1C, p57, Kip2) expression and molecular genotyping accurately classify hydatidiform moles into complete and partial types and distinguish these from non-molar specimens. Accurate subclassification of molar specimens into complete hydatidiform mole and partial hydatidiform mole and distinction of these from non-molar

specimens are important for clinical management and for accurate assessment of the risk of persistent gestational trophoblastic disease (Banet et al., 2014).

9. Benign vagina tumor

9.1. Vaginal cysts

Benign anterior-vaginal-wall cysts (0,5–1% prevalence) often mimic other structures, such as cystoceles. No algorithm for their diagnosis, treatment, recurrence or complication prediction is found. Careful preoperative diagnosis may minimize intraoperative surprises and complications due to differences in cyst origin. Anterior-compartment vaginal cysts can be found incidentally during pelvic organ prolapse assessment and surgery, as they can mimic anterior-vaginal-wall prolapse (Esber et al., 2021).

10. CONCLUSIONS

Circular RNAs (circRNAs) are candidate factors for the activation of ovarian endometriosis and are promising diagnostic biomarkers and treatment targets. It is important to be aware that sex cord tumors with annular tubules can also be present in older women, they can be bilateral despite not being related to Peutz Jeghers Syndrome syndrome and must be considered as a differential diagnosis in ovarian tumors. Ovarian fibroma with Meigs syndrome can be differentiated from ovarian malignancy with the help of pelvic sonography, laparoscopy and intraoperative frozen section study of the tumor. Significant decrease in anti-Müllerian hormone levels after surgery on the ovaries

was determined. Leydig cell tumors are rare, and even when they are small, they can cause symptoms related to androgen excess. As a result, diagnosing them often is challenging.

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CHAPTER 10

ENDOMETRIAL CANCER

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INTRODUCTION

Endometrial cancer is the most frequent gynecological cancer in developed countries, with a global incidence of 417,367 cases per year (Sung). It is the second most frequent cancer in underdeveloped countries, after cervical cancer. It is most common in postmenopausal women, with a mean diagnostic age of 60. Postmenopausal bleeding is the most common reason for endometrial cancer admission. Only 5-10% of postmenopausal bleeding cases are detected with endometrial cancer, despite the fact that it is quite common (Clarke MA , Walker). Endometrial cancer has a good prognosis in general since it is identified at an early stage in patients. The prognosis, however, varies depending on the extent of extrauterine dissemination and stage of endometrial cancer (4).

Risk factors

Polycystic ovarian syndrome, estrogenic hormone therapy, early menarche, late menopause, tamoxifen use in breast cancer treatment, anovulatory cycles, and obesity are the most major risk factors. Additional risk factors for endometrial cancer include a family history of the disease, Lynch syndrome, hypertension, diabetes mellitus, and thyroid disease (Braun MM , Siegel , Buchanan EM , Saso). Endometriosis is still being debated as a risk factor for endometrial cancer (Terzic). Furthermore, it has been demonstrated that modifiable lifestyle variables can influence the risk of endometrial cancer (Avgerinos KI). A higher BMI, poor eating habits, excessive alcohol intake, and physical inactivity have all been linked to an increased risk

of endometrial cancer in various studies (Gierach GL , Kawachi A , Dunneram Y). Smoking, parity, and oral contraceptives are all protective factors in endometrial cancer. (Lu).

Pathophysiology

The action of unopposed estrogen on the uterine endometrium is the most common cause of endometrial cancer. The aromatase enzyme is responsible for the peripheral aromatization of steroids, which is the main source of estrogen in postmenopausal women. Many tissues, including the placenta, adipose tissue, and human tissues such as skin, granulosa ovarian cells, skin fibroblasts, muscle, bone, and brain, contain this enzyme. Furthermore, the transcription and activation of this enzyme appears to be closely related to the patient's age and BMI, which explains why postmenopausal obese and elderly women have a higher chance of developing endometrial cancer. The aromatase enzyme's genetic expression is considerably elevated in endometrial cancer tissue, and it serves as a measure of tumor cell proliferation and survival (Boruban MC , MacDonald , Bulun SE , Grodin JM). Endometrial hyperplasia and cancer transformation result from chronic estrogen stimulation of the endometrium without progesterone antagonism (Doherty MT , Jordan SJ).

Endometrial cancer premalignant lesions

Endometrial hyperplasia is a frequent gynecological condition that causes irregular vaginal bleeding, infertility, and the development of cancer (Clarke MA). Endometrial hyperplasia, one of the endometrial

cancer precursor lesions, is a proliferative endometrial lesion that can lead to certain kinds of endometrial cancer. Endometrial hyperplasia affects 133/100,000 women per year, and atypical endometrial hyperplasia affects 54/100,000 women per year (Reed). Atypical hyperplasia / endometrial intraepithelial neoplasia is a precancerous lesion that needs to be treated differently from other forms of hyperplasia and adenocarcinoma. Invasive carcinoma formation, on the other hand, is extremely rare in situations of hyperplasia without atypia (less than 5%). (Ryan).

Atypical endometrial hyperplasia (AEH) is a classification system that employs architectural traits and cytological atypia (glandular complexity and nuclear atypia) to identify precursor lesions (Kurman RJ). They were grouped into four groups by the World Health Organization in 1994 (WHO 1994) classification:

1. Simple endometrial hyperplasia is the most common type of endometrial hyperplasia.
2. Complex Endometrial hyperplasia
3. Simple atypical endometrial hyperplasia
4. Complex atypical endometrial hyperplasia

The WHO categorization of 1994 is descriptive, does not include a special management strategy, and is difficult to replicate (Baak JP). As a result, in 2000, a new classification system based on quantitative morphological data was proposed, which included the term Endometrial intraepithelial neoplasia (EIN). The EIN classification was split into two categories in 2000:

- Hyperplasia of the endometrium
- Intraepithelial neoplasia of the endometrium (EIN).

The World Health Organization, on the other hand, developed a new, simplified categorization of endometrial hyperplasia in 2014, which divided the condition into two categories: hyperplasia with and without atypia. The requirement to eliminate a significant number of misleading terminology led to the reduction to these two groups. The new WHO categorization (Emons G) which was released in 2014, is divided into two categories:

1. Non-atypical endometrial hyperplasia (benign hyperplasia)

2. Atypical endometrial hyperplasia or Endometrial Intraepithelial Neoplasia (EIN)/well differentiated carcinoma

Atypical hyperplasia and EIN had equal sensitivity and negative predictive values for associated endometrial cancer (Salman). Atypical hyperplasia and EIN have the same clinical management. Finally, cancer progression rates of endometrial hyperplasia have been found to be 1-5 percent (Kurman RJ , Lacey JV Jr) for hyperplasia without atypia and between 8% and 27% for hyperplasia with atypia. In 36-59 percent of women who had hysterectomy for atypical hyperplasia, there was a risk of concurrent endometrial cancer (Zaino R , Kurman RJ , Lacey JV Jr , Antonsen SL , Rakha).

Histologic and molecular types

Endometrial cancer is classified into two histological kinds based on clinicopathological characteristics: estrogen-dependent type 1 and estrogen-independent type 2. The most frequent type of endometrial cancer is estrogen-dependent endometrioid adenocarcinomas with type 1 histology, which account for 75-90 percent of cases (Gao Y). Clear cell carcinoma and serous adenocarcinomas are examples of type 2 histologic cancers, which are estrogen-independent (Zhang). Cancers of type 1 are low-grade and have a favorable prognosis. Type 2 tumors, on the other hand, are high-grade and frequently identified at an advanced stage, accounting for 70% of endometrial cancer deaths (Lu). Using genomic, transcriptomic, and proteomic analyses, four molecular subtypes with differing prognostic markers were found in the 2013 Cancer Genome Atlas (TCGA) study on the molecular etiology of endometrial cancer (Cancer Genome Atlas Research Network). Ultramutated/DNA polymerase epsilon (POLE) mutated group (POLE mut), Hypermutated/microsatellite unstable group (MMRd), low copy number group (NSMP), and high copy number (serous-like) group (POLE mut) are the molecular subtypes (p53abn).

Phosphatase and tensin homologous (PTEN) tumor suppressor gene mutations, DNA mismatch repair problems, and the near-diploid karyotype CTNNB1, KRAS, and POLE oncogene mutations are all linked to a high rate of type 1 carcinomas (Amant F , Lu , Arend RC). TP53 mutations and ERBB-2 (HER2/neu) overexpression are linked to type 2 cancers (Amant F).

The European Society of Gynecological Oncology (ESGO), European Society of Radiotherapy and Oncology (ESTRO), and European Society of Pathology (ESP) guidelines for 2020 identify the risk group and treatment options based on these known molecular subtypes (Concin N).

Histologic classification

The endometrioid type is the most prevalent histology, accounting for 75 to 80 percent of cases, according to the World Health Organization (WHO) for histological classification of endometrial cancer (WHO Classification of Tumours Editorial Board (2020). Female Genital Tumours):

• Endometrioid carcinoma: adenocarcinoma; adenocarcinoma variants (with squamous differentiation; secretory variant; villoglandular variant and ciliated cell variant)

• Mucinous adenocarcinoma

• Serous adenocarcinoma

• Clear cell adenocarcinoma

• Undifferentiated carcinoma

• Neuroendocrine tumors

• Mixt carcinoma (multiple types of carcinoma with at least 10% of each component).

• Adenomyoma

• Atypical polypoid adenomyoma

• Adenofibroma

• Adenosarcoma

• Carcinosarcoma: Currently, carcinosarcomas in which both epithelial and mesenchymal components are malignant and aggressive tumors are considered metaplastic carcinomas and treated as aggressive carcinomas.

Endometrioid cancer: The most prevalent histology is endometrioid, which accounts for 75 to 80 percent of cases. The majority of endometrioid types are low-grade (grade 1 or 2), are identified early, and have a favorable prognosis (Singh). The International Federation of Gynecology and Obstetrics (FIGO) classification system is used to classify endometrioid tumors based on the structural model and nuclear grade .

- Grade1: Less than 5 percent solid area
- Grade 2: 6 to 50 percent solid area
- Grade 3: More than 50 percent solid area

Serous endometrial cancer: It is the second most common type of endometrial cancer, but only accounts for about 10 percent of cases. Clinically, occult extrauterine disease is usually present at the time of diagnosis (Huang CY).

Clear cell cancer: A rare subtype of endometrial cancer and clinically aggressive.

Mixed cancer: It typically has at least two different histological components, an endometrioid and a high-grade non-endometrioid pattern (usually serous, sometimes clear cell).

Undifferentiated cancer: It is undifferentiated cancer of the endometrium and is the least known type.

Carcinosarcoma (malignant mixed mullerian cancer): is a rare, aggressive biphasic carcinoma.

Other types of cancer: It is mesonephric and mesonephric-like adenocarcinoma of the uterine corpus.

Clinical and diagnostic methods

Postmenopausal bleeding is a red flag symptom for endometrial cancer (Funston G). Pelvic pain, abdominal bloating, early satiety, changes in bowel or bladder function, pain during sexual intercourse, and shortness of breath due to pleural effusion are common complaints in advanced patients. It's crucial to remember, however, that up to 5% of endometrial cancer patients are asymptomatic (Passarello). Therefore, women with postmenopausal bleeding should be promptly evaluated to rule out endometrial cancer (Jones ER). The procedures performed in the evaluation were transvaginal ultrasonography, dynamic hysteroscopy, and endometrial biopsy (Sundar). Furthermore, reported rates of endometrial neoplasia vary widely among patients assessed for persistent or recurrent postmenopausal bleeding, from 4% to 21% (Twu

, Ronghe). . In addition, conventional Pap smears are 40% to 55% sensitive for cervical cancer screening in patients with endometrial cancer with abnormal cytology; fluid-based tests are 60% to 65% more sensitive (Guidos BJ, Selvaggi SM. Detection of endometrial adenocarcinoma with the ThinPrep Pap test. Diagn Cytopathol. 2000 Oct;23(4):260-5., Schorge , Gu M). Extensive metastatic disease after computed tomography or magnetic resonance imaging, or a mass confined to the uterus, increased endometrial thickness and myometrial invasion, or a mass extending into the cervix may suggest endometrial cancer and may also be postoperatively in cases of hysterectomy with benign cause discovered incidentally in the pathology report. In a database study of approximately 230,000 patients undergoing hysterectomy for benign indications, 0.96% had occult endometrial cancer, of which 75% reported endometrial cancer and 22% sarcoma (Desai VB).

Genetic predisposition

Sporadic mutations are responsible for the majority of endometrial cancer cases; in addition, approximately 5% of endometrial cancer cases are caused by inherited genetic mutations. Endometrial cancer due to genetic susceptibility typically occurs 10 to 20 years before sporadic endometrial cancer (Passarello). The following syndromes are known to predispose to endometrial cancer:

1. Lynch syndrome (LS), an autosomal dominant syndrome, is caused by a mutation in one of four DNA mismatch repair genes (MLH1, MSH2, MSH6 or PMS2) (Passarello). It is associated with a

significantly increased lifetime risk of colorectal, endometrial cancer, and some other cancers (Passarello , Hutt S).

2. Cowden syndrome: It is an autosomal dominant syndrome characterized by PTEN mutations. It is associated with a 19% to 28% risk of endometrial cancer by age 70 (Passarello).

Currently, there is no effective screening program to screen for endometrial cancer (Passarello). In these genetic cases, prophylactic and screening endometrial biopsy and risk-reducing hysterectomy may be performed to reduce the risk of endometrial cancer. Evaluation of the patient should include a detailed medical history, especially family history and possible risk factors(Passarello).

International Classification of Endometrial Cancer (table 1) (Amin MB):

Table 1. International classification of endometrial cancer

Stage I		Tumor confined to the corpus uteri,including endocervical glandular involvement
	IA	Tumor limited to the ednometrium or invading less than half the myometrium
	IB	Tumor invading one half or more of the myometrium
Stage II		Tumor invading the connective tissue of the cervix but not extending beyond the uterus.
Stage III		Tumor involving serosa, adnexia, vagina, or parametrium
	IIIA	Tumor involving the serosa and/or adnexa (direct extension or metastasis)
	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
	IIIC	Pelvic and/or paraaortic lymph node(s) metastasis
	IIICI	Pelvic lymph node(s) involvement (less 0,2 mm in diameter)
	IIICII	Paraaortic lymph node metastasis (less 0,2 mm in diameter), with or without positive pelvic lymph nodes
Stage IV		Bladder and/or bowel mocosa involvement and/or diastant mestastasis
	IVA	Tumor invading the bladder mocosa and/or bowel mucosa
	IVB	Distant metastasis (includes to inguinal lymph nodes intraperitoneal disease, lung, liver, or bone

Surgical treatment

Primary treatments are total abdominal hysterectomy and bilateral salpingo-oophorectomy, usually by evaluating the lymph nodes using a minimally invasive approach. Progestins may be considered for patients who are not candidates for surgery or who wish to preserve fertility (Lu). Approximately 80% to 90% of cases are diagnosed at an early stage, when the prognosis is usually very good, with appropriate surgical treatment and staging evaluation (Fader AN , Morice). Today, endometrial cancer can be treated with open surgery, laparoscopic surgery, or robotic surgery. Compared with open surgery, laparoscopic surgery provides the same oncological outcomes while reducing operative and postoperative morbidity (Walker).

Lymphadenectomy

The assessment of lymph nodes is crucial in the treatment of endometrial cancer. However, there is still no consensus on the therapeutic value, indications, and extent of surgery (para-aortic to pelvic, inferior mesenteric artery, or para-aortic to left renal vein) (Benedetti Panici P , Todo). Endometrioid endometrial cancer cases confined to the lymph node-negative uterus have an excellent survival rate of greater than 80-90% at 5 years. In patients with lymph node-positive cancer, the survival rate decreases to 60-70% in 5 years (Bogani G). The sentinel lymph node is the first lymph node in the lymphatic basin into which the lymph of the primary tumor flows. Sentinel lymph node sampling is performed in early-stage endometrial cancer without suspicious lymph node and/or extrauterine spread on

imaging (Bedyńska M). Recently, sentinel node mapping has replaced systematic lymphadenectomy in the surgical staging of endometrial cancer (Bogani G , Bogani G).

Survival

In early-stage endometrial cancer, 5-year survival rises to 96%. However, it causes poor clinical outcomes in cases such as delayed diagnosis, recurrence and metastatic. The 5-year survival rate in stage 4 endometrial cancer is 17% (Zong). Endometrial cancer: FIGO surgical stage and overall survival are given (table 2) (Lewin).

Table 2. FIGO surgical stage and overall survival chart

FIGO stage	5-year overall survival (%)
1A	90,3
1B	80,8
II	80,5
IIIA	68,5
IIIB	53,1
IIIC1	58,3
IIIC2	51,2
IVA	22,0
IVB	21,1

(4, 75, 76).

Prognostic factors in treatment

Indications for adjuvant therapy primarily depend on clinical and pathological factors such as age, grade, histological type, depth of myometrial invasion, and presence of lymphovascular space invasion (Colombo N).

The presence of lymphovascular space invasion is a strong prognostic factor for pelvic recurrence, distant metastasis, and decreased overall survival (Bosse T). Based on these prognostic factors, low, intermediate, high-intermediate and high risk groups were defined, each with a different prognosis and indications for adjuvant therapy (Table 3) (Colombo N , Creutzberg CL).

Table 3. The risk groups of endometrial cancer:

Risk group	ESMO-ESGO-ESTRO concensus (Colombo N)	GOG-99	PORTEC-1(Creutzberg CL)
Low risk	Endometrioid endometrial cancer, grade 1-2, <%50 myometrial invasion, lymphovascular space invasion negative	Endometrioid endometrial cancer, no myometrial invasion	endometrioid endometrial cancer, any age, grade 1-2, <50% myometrial invasion
Low-intermediate risk group	Endometrioid endometrial cancer, grade 1-2, ≥50% myometrial invasion, lymphovascular area invasion negative	endometrioid endometrial cancer, not medium risk	endometrioid endometrial cancer, grade 1-2, age <60, ≥50% myometrial invasion
high-intermediate risk	Endometrioid endometrial cancer, grade 3, <50% myometrial invasion, any lymphovascular space invasion	endometrioid endometrial cancer ≥50% with two factors: lymphovascular space invasion, grade 3, ≥66% myometrial invasion ≥70% by age or a factor	endometrioid endometrial cancer, grade 1-2, age ≥60, ≥50% myometrial invasion

	Endometrioid endometrial cancer, grade 1-2, definitely lymphovascular space invasion positive, any myometrial invasion	endometrioid endometrial cancer, any age with all factors: 3rd grade, ≥66% myometrial invasion and lymphovascular space invasion	endometrioid endometrial cancer, grade 3, age ≥60, <50% area invasion
High	Endometrioid endometrial cancer, grade 3, ≥50% myometrial invasion, any lymphovascular space invasion	Stage II-III endometrioid endometrial cancer	endometrioid endometrial cancer, grade 3, ≥50% myometrial invasion
	Stage II-III endometrioid endometrial cancer, residual no disease	Stage I-III non-endometrioid endometrial cancer	Stage II-III endometrioid endometrial cancer
	non-endometrioid endometrial cancer stage I–III (serous, clear cell or undifferentiated carcinosarcoma)		Stage I-III non-endometrioid endometrial cancer (serous or clear cell)
Advanced/metastatic	Stage III with residual disease and stage IVa Stage IVb	Stage 4	Stage 4

ESGO, European Society of Gynecological Oncology; ESMO, European Society of Medical Oncology; ESTRO, European Community; GOG, Gynecological Oncology Group; PORTEC, Postoperative Radiation Therapy for Endometrial Carcinoma

Treatment methods according to risk groups

Low risk endometrial cancer

The standard initial approach to women with newly diagnosed endometrial cancer is total hysterectomy + bilateral salpingo-oophorectomy (BSO) + lymph node assessment and surgical staging with extrauterine disease assessment. However, women who want their fertility preserved may be candidates for medical treatment. Progestin therapy can be given as adjuvant therapy until she completes her fertility. However, women who are candidates for drug therapy should be informed about the risks and benefits so that they can make an informed decision. However, a meta-analysis of four studies found no difference in risk of death at five years between adjuvant progestin therapy and no further therapy (RR 1.00, 95% CI0.85-1.18) (Martin-Hirsch).

Low-intermediate and high-intermediate risk endometrial cancer

Considering the benefits and harms of radiotherapy or chemotherapy in addition to surgical treatment in low-intermediate risk endometrial cancer cases, observational treatment is sufficient. The recommended treatment in the management of this group is usually brachytherapy or pelvic radiotherapy, but chemotherapy is not recommended. Prognosis Women with low-intermediate risk endometrial cancer have an excellent prognosis, with recurrence rates of approximately 5-6% without any adjuvant therapy. In patients with clinical features that define high-intermediate risk endometrial cancer, there is a risk of

recurrence ranging from 5% (with adjuvant radiation) to 30% (if not treated after surgery) (Creutzberg CL).

High risk endometrial cancer

Approximately 15-20% of women with endometrial cancer have an increased risk of distant metastasis and disease-related death, and are therefore classified as high-risk (Colombo N). If diagnosed at an early stage, survival rates similar to grade 3 endometrioid endometrial cancer have been reported for both serous and clear cell endometrial cancer (Creasman WT).

Advanced/metastatic endometrial cancer

The clinical picture for metastatic endometrial cancer may be local, regional or sistemic complaints depending on the endometrial cancer localization. In cases with clinical or radiological signs of metastatic cancer, surgical treatment is applied to establish a definitive diagnosis, reduce symptoms and signs of cancer, and improve oncological outcomes (Barlin JN). Surgical cytoreduction is typically recommended for this group, followed by systemic therapy. Such patients have a poor prognosis, with a reported 5-year relative survival is less than 20%. Management of advanced, metastatic, or recurrent endometrial cancer remains difficult as there is no standard treatment available. Although the combination of carboplatin and paclitaxel is an effective standard regimen as first-line therapy, alternative treatment strategies, especially biomarkers, have shown promise in selected populations. Researchers

are investigating new combinations of immunotherapy to improve oncologic outcomes .

Post-treatment follow-up

Most relapses occur within three years of treatment. About 70 percent of cases develop symptoms at relapse (eg, vaginal bleeding, abdominal pain, cough, weight loss). Although post-treatment follow-up protocols may vary by clinic, clinical examination (including symptom review, physical examination for symptoms, and pelvic examination) is performed at quarterly intervals for two years, then semi-annually or annually.

Special clinical situations

Preservation of fertility

Young premenopausal patients under the age of 40 often have early-stage endometrial cancer and low-grade tumors (Biler A). Fertility-sparing therapy in endometrial cancer includes hysteroscopic resection and/or curettage in combination with hormonal therapy with progestin. In this situation, complete remission rates of 50-75% have been reported (Park , Gunderson CC) and close follow-up evaluation with hysteroscopic examination and endometrial sampling is recommended. The most common approach for women who are candidates for fertility preservation is progestin therapy and deferring surgical staging (including hysterectomy and bilateral salpingo-oophorectomy) until after the completion of fertility. However, since the safety of fertility preservation in terms of genetic mutation is unknown (especially

because of the increased risk of developing ovarian cancer in a patient with Lynch syndrome), cases should be evaluated for potential risks of endometrial cancer as a result of Lynch syndrome.

Covid 19 pandemia and endometrial cancer

After the declaration of the Covid 19 pandemic by the World Health Organization on March 11, 2020, screening practices and regular periodic examinations were adversely affected (Bogani G , Castanon A). Although it should be diagnosed early, delay in diagnosis and treatment may lead to advanced stage of the cancer and poor outcomes (Cortiula F , Bilgi A.). In a retrospective national cohort study, it was shown that gynecological cancer surgery can be performed with an acceptable perioperative rate of SARS-CoV-2 infection in the Covid-19 pandemia, if staff and patients strictly adhere to established infection control measures (Ayhan A).

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CHAPTER 11

PRECANCEROUS LESIONS OF THE CERVİX AND HPV

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INTRODUCTION

The cervicocolumnar junction, also known as the transformation zone, is the location where the ectocervix's squamous epithelium meets the endocervix's columnar epithelium. It's a dynamic zone that's always changing, and histologically, it's where the glandular epithelium meets the squamous epithelium. At the same time, this region is recognized as the site of carcinogenesis caused by infection with carcinogenic human papillomavirus subtypes (HPV). According to one study, the principal source of carcinogenic HPV-associated CIN and cervical cancer is a tiny population of cuboidal cells at the squamocolumnar junction, rather than the entire transformation zone (Herfs). The gene expression profile of these cells is identical to that of squamous and glandular high-grade CIN and carcinomas.

Mild, moderate, and severe cervical dysplasia were traditionally used to describe premalignant squamous alterations of the cervix. The Bethesda system, which was adopted a new terminological nomenclature in 1988, was revised in 1991, 2001, and 2015. Different terms are used for cytological (Pap test) and histological (biopsy) findings in this system (Solomon , Luff R. D. (1992). The Bethesda System for reporting cervical/vaginal cytologic diagnoses. Report of the 1991 Bethesda workshop. American journal of clinical pathology , Nayar). Squamous intraepithelial lesion (SIL) is a cytological finding, whereas cervical intraepithelial neoplasia (CIN) is a histological alteration. There are three levels of CIN classification:

1. CIN 1 is a low grade lesion. It is used for mild atypical cellular changes in the lower third of the epithelium and usually HPV cytopathic effect (koilocytotic type).
2. CIN 2 is a high-grade lesion. It includes moderately atypical cellular changes limited to the basal two-thirds of the epithelium (formerly called moderate dysplasia) with preservation of epithelial maturation.
3. CIN 3 is a high-grade lesion. It includes severe atypical cellular changes involving more than two-thirds of the epithelial thickness and includes full-thickness lesions (called severe dysplasia or carcinoma in situ in older terminology).

However, in 2012, the Lower Anogenital Squamous Terminology (LAST) project of the American College of Pathology and the American Society of Colposcopy and Cervical Pathology published a new terminology system for HPV-related squamous lesions of the anogenital tract (Waxman , Darragh). In this new system, histological cervical findings are used using the same terminology as cytological findings, as follows:

1. In the old system, CIN 1 was called a low-grade squamous intraepithelial lesion (LSIL).
2. CIN 2 was named according to p16 immunostaining to identify precancerous lesions. LSIL for p16 negative pathologies and high grade squamous intraepithelial lesions (HSIL) for p16 positive pathologies.
3. CIN 3 was named HSIL

This form of terminology is used as the CIN terminology is used in the 2019 American Society of Colposcopy and Cervical Pathology guidelines for the evaluation and management of cervical cytological and histological abnormalities (Perkins).

Incidence

According to Globocan 2018, the age-standardized incidence rate for women under the age of 29 is 0.46 per 100,000, and for women under the age of 24 it is as low as 0.06 per 100,000 (9). In the United States, the annual incidence of cervical cancer cases screened is predicted to be 4% for CIN 1 and 5% for CIN 2,3 (Insinga). With a global prevalence of 11.7 percent, HPV infection is the most frequent sexually transmitted infection (Bruni). It demonstrates that women under 25 years of age have a larger rate of HPV infection than women over 45 years of age; nevertheless, the proportion of persistence is higher in this age group, possibly due to the increased risk of precancerous lesions (Pett , Williams). As a result, screening in asymptomatic women should not begin until the age of 25, regardless of the age at which sexual activity/sources began. Screening after the age of 30 is suggested in resource-constrained contexts. If just one round of screening is possible, it should focus on women between the ages of 35 and 40 (Sankaranarayanan).

Pathogenesis of HPV

HPV is epitheliotropic, meaning it can stay in the cytoplasm or integrate into the host genome after it infects the epithelium. A low-grade lesion

occurs when HPV is episomal-integrated. High-grade lesions and cancer can occur when the virus integrates into the human DNA (Pett). An important factor of the early stages of infection is the susceptibility to the host's immune system to oncogenic HPV types (Snijders). Viral integration into the host genome results in disruption of the E1 and E2 open reading parts and thus results from loss of transcriptional regulation of E6 and E7 resulting in overexpression of oncoproteins. (Beutner). HPV E6 protein binds to p53 and induces cellular degradation of p53, while E7 interacts with retinoblastomaprotein (Rb), resulting in degradation of the transcription factor E2F and promotion of cell cycle progression (de Villiers E. M. (2003). Relationship between steroid hormone contraceptives and HPV , Münger). The deactivation of these two major tumor suppressor genes, p53 and Rb, is thought to be central to HPV-induced host cell transformation and immortalization of infected cell lines. The presence of extracellular E7 also activates cervical endothelial cells, resulting in overproduction of interleukin 6 and 8, two cytokines associated with significant malignant progression of CIN 2,3 in more than 80 percent of cancers (D'Anna , Klaes) .

HPV is the main etiological cause of cervical precancer and cancer (Schiffman , Kaufman). There is a very close relationship between HPV and cervical neoplasia. In addition, behavioral, sexual, and socioeconomic variables are often associated with HPV infection and are not considered independent risk factors (Schiffman , Khan). HPV infection is required for cervical neoplasia, but HPV alone is not

sufficient to cause these diseases, as the vast majority of patients with HPV infection do not develop high-grade cervical lesions or cancer (Böhmer , Ylitalo , Moscicki).

Molecular mechanism of HPV

The clinical manifestations that may occur following acute HPV infection are:

1. It is an occult infection with no physical, cytological or histological signs. This is the clinic where HPV infection is most common and is detected in more than 90% of infections.
2. It may be a form of active infection in which HPV undergoes nutritional replication but fails to integrate into the genome.
3. Actively replicating HPV produces characteristic cellular changes such as nuclear enlargement, multinucleation, hyperchromasia, and perinuclear cytoplasmic depletion (halos) (Nucci). Cytological findings are also cytological features of low-grade squamous intraepithelial lesion (LSIL) and atypical squamous cells of uncertain significance (ASC-US); therefore, LSIL and HPV-positive ASC-US can be defined as active HPV Cytological manifestations of infection. Resolution of infection was associated with resolution of cytological changes. Solubility is at least partially related to the formation of HPV antibodies and the recruitment of macrophage natural killer cells and activated CD4+ T lymphocytes (Carter , Bontkes , Arany). In most cases, the immune response is the predominant process, so the infection remains latent or rapidly suppressed; in addition, these antibodies

may take months to develop, or may not develop at all (Association of Reproductive Health Professionals. Clinical Proceedings. Human Papillomavirus (HPV) and cervical cancer).

HPV types

There are more than 100 HPV types; about 40 types are specific to the anogenital epithelium and have different potentials for causing malignant changes (de Villiers). The distribution of HPV in the population varies by geographic area (Li). Sequential infection with different HPV subtypes and co-infection with more than one HPV subtype are common (Plummer). HPV types show clinical symptoms and oncogenic potential (low or high) of HPV infection (Hariri). These types are:

1. Low-risk types such as HPV 6 and 11 do not integrate into the host genome and cause only low-grade lesions (CIN 1) and genital warts in the form of benign condyloma (Mao). HPV 6 and 11 are the cause of 10 percent of low-grade lesions and 90 percent of condylomatous genital warts.
2. High-risk HPV types 16, 18, 31, 33, 45, 52, and 58 were strongly associated with high-grade lesions (CIN 2.3) and risk of developing invasive cancer. HPV 16 and 18 are the HPV types with the highest risk of developing lesions of CIN 3 or higher, causing 25 % of low-grade lesions, 50% to 60 % of high-grade lesions, and 70 % of cervical cancers. (Demarco , Bosch).
3. High oncogenic risk HPV subtypes are more persistent than low oncogenic risk types (Ho).

In one study, the two-year cumulative absolute risk of developing CIN 3 or higher lesions was higher in patients with HPV 16 infection than in patients with other high-risk subtypes (30% to 40% vs 8% to 10%). HPV 18 has a higher risk of CIN 3 or higher lesions compared with non-high-risk HPV types (3.3% vs 1.3%) (Demarco).

Factors affecting HPV persistence

Cervical HPV infection is usually transient and occurs in younger patients. Persistent infection with oncogenic HPV subtypes is an important factor in the development of high-grade cervical lesions (Rodríguez , Koshiol , Wallin) and cervical cancer (Koshiol). In addition, clearance of HPV infection predicts regression of CIN lesions (Nobbenhuis). In most cases, HPV infection is subclinical, especially in young women, and in more than 80% of cases, the infection resolves spontaneously within 1 to 2 years. However, approximately 10% of HPV infections may persist, and approximately 3% to 4% may progress to intraepithelial lesions. Of these, 0.7% to 1% may progress to high-grade disease (CIN 2/3), and an estimated 0.1% will progress to invasive carcinoma if left undetected and treated (Shepherd). The exact reason why HPV infection persists is not known. Persistent HPV infection is known to be present for at least 6 to 12 months. The longer the HPV persists in the cervix, the greater the risk of developing CIN. 21% of cases with highly oncogenic HPV infection persisting for more than 12 months have been reported to have CIN 2 or more lesions at age 30 months of follow-up (Rodríguez). In addition, in the analysis of

cases aged 13-24 with CIN 2 lesions, 38 percent had regression within one year, 63 percent at 2 years, and 68 percent at 3 years (Moscicki).

HPV is a virus transmitted through sexual contact. Cervical cancer and precursor lesions are almost undetected in cases who have not had sexual intercourse (Shepherd). The risk of HPV is associated with the number of lifetime sex partners, but is relatively high (4 to 20 percent) even for those with a single partner. At least 75 to 80 percent of sexually active cases will have genital HPV infection by age 50 (Workowski). While 50 percent of high-risk HPV infections persist in cases older than 55 years of age, there is a 20 percent persistence rate in cases under 25 years of age (Bosch).

Clinical course

The clinic of cervical HPV infections is usually asymptomatic. However, clinical picture occurs when symptoms related to genital condylomas or cervical lesions occur. The clinic of cervical HPV infections is usually asymptomatic. However, clinical picture occurs when symptoms related to genitalcondylomas or cervical lesions occur . HPV infection is universally accepted as a causative agent in the development of cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesions. These may be benign, but are considered precancerous and often develop into invasive cervical carcinoma (Ziegert). As precursors of invasive squamous carcinoma, more than one-third of all high-grade squamous intraepithelial lesions (HSIL) and CIN grades II and III progress to cervical cancer within a 10 to 15-year period (Sankaranarayanan R).

Cofactors in pathogenesis

Persistent infection with high-risk HPV genotypes is a necessary but not sufficient condition for disease progression and is the main epidemiological factor of high-grade intraepithelial lesions (HSIL) and invasive carcinoma (Oliveira).

HIV infection and immunosuppressive therapy

Incidence of CIN increases from patients with HIV (human immunodeficiency virus) (Duerr). The risk of both HPV infection and CIN increases with increasing degrees of immunosuppression (as measured by lower CD4 counts and higher HIV RNA load) (Jamieson). In addition, cervical cancer is one of the most common acquired immunodeficiency syndrome (AIDS) associated cancers (Maiman). Patients with chronic conditions requiring long-term immunosuppressive therapy are at high risk of developing CIN (Williams). This association has been described in transplant recipients and patients with systemic lupus erythematosus (Tam , Malouf).

Smoking

Smoking and HPV infection have synergistic effects on the development of CIN and cervical cancer (Luhn). Compared with HPV-negative non-smokers, the risk of developing CIN 2.3 with smoking alone, HPV infection alone, and both smoking and HPV infection was approximately 2-fold, 15-fold, and 66-fold, respectively. (Olsen).

Herpes simplex virus and chlamydia

Infection with chlamydia (Madeleine), herpes simplex virus (Smith) , or other sexually transmitted infections may be mediators of exposure to HPV rather than a causative factor itself (Jha). However, these infections can modulate host immunity, thereby facilitating persistence of oncogenic HPV (Silins I).

Oral contraceptives

Long-term use of oral contraceptives has been reported as a cofactor that increases the risk of cervical carcinoma in HPV-positive cases (Luhn). However, the risk of serious cervical cancer decreases after discontinuation of oral contraceptives and returns to the initial risk of 10 years in non-users (International Collaboration of Epidemiological Studies of Cervical Cancer).

Other factors

Often genetic, familial, dietary, and endogenous hormonal factors are not thought to play a role in the development of CIN or cervical cancer (García-Closas , Shields). Although familial factors played a role in some studies on the pathogenesis of squamous cell cervical cancer, familial aggregation due to shared environmental exposures could not be excluded (Zelmanowicz). Several studies have reported that certain types of human leukocyte antigen (HLA) may affect the risk of acquiring HPV, thus making some patients more susceptible to HPV infection based on a genetic factor (Mahmud). It found that high parity

increased the risk of squamous carcinoma of the cervix in HPV-positive patients (Muñoz).

Screening for preinvasive lesions

There are many initiatives that focus on primary HPV screening for cervical cancer prevention, for example conventional or liquid-based cytology, which represents a successful reduction in cervical cancer prevention of up to 80% (recherches sur le cancer, 166, 277–297.). Screening programs that include HPV testing have consistently been associated with reduced incidence of cervical cancer, potentially reducing morbidity and mortality (Chan).

The most common screening methods are conventional cytology, liquid-based cytology and HPV testing, or a combination of the last two.

Although Pap smear testing has improved the detection of cervical cancer, there is some disadvantages such as high specificity but low sensitivity, so it is important to develop more sensitive and specific techniques to improve prevention algorithms (Rizzo).

In addition, women vaccinated after exposure to HPV16 or 18 are still at risk for HPV16 and HPV18-associated cervical cancer, as vaccination does not alter the clearance of pre-existing HPV infections (Hildesheim).

However, as the immunization status of the population targeted for screening changes in time, and as more vaccinated groups reach screening age, the reduction in the prevalence of cervical lesions has the potential to adversely affect the test performance characteristics of

cytology screening adapted to detect cytological screening for signs of HPV infections.(Schiffman M. (2007). Integration of human papillomavirus vaccination).

Results from international randomized controlled trials have shown that, compared with cytology, primary HPV testing has an increased sensitivity for high-grade precancerous lesion (cervical intraepithelial neoplasia grade 2 or more severe diagnoses; CIN2+) in increased detection of high-grade abnormalities in the first round of screening (Rijkaart , Kitchener , Elfström).

Various options have been proposed in the context of primary HPV screening for the treatment of oncogenic HPV-positive women. These include cytology triage, partial genotyping with direct referral of women who test positive for HPV16/18 to colposcopy, and the use of dual staining (DS) of liquid-based cytology (LBC) preparations for the molecular markers p16INK4a (p16) and Ki-67 to triage women with detected oncogenic HPV (Wentzensen , Petry , Bergeron C).

The natural history of cervical cancer are well known and the carcinogenesis process is slow. The presence of precancerous lesions, the availability of sensitive screening tests of detection and effective treatment methods have made highly effective secondary prevention possible using screening programs (Tsikouras).

Management

New risk-based management consensus guidelines will be used to determine the appropriate management process of cervical screening

abnormalities, based on risk and clinical action thresholds. To address these changes, the 2019 guidelines have shifted from results-oriented management to risk-based management. In this algorithm, for each management scenario and past/current test result combination, a risk profile of CIN grade 2 or higher CIN 2+), CIN 3+, and cancer risks was generated from the current test time to 5 years after the current test. Risk profiles, CIN 3+, and cancer risks from time of current testing to 5 years after current testing, transition to risk-based management using consensus clinical action thresholds (Perkins , Egemen , Demarco).

For each scenario and combination of past/current test results, we generated a risk profile of CIN 2+, CIN 3+, and cancer risks for annual time points from the time of current testing (immediate risk) to 5 years after current testing (5-year risk). We focused on estimating the risk of CIN 3+ because CIN 3 identifies a true precancerous condition more likely than CIN 2, whose removal may prevent future cancers (McCredie). Validity consisted of comparing risk and risk-based management with 3 new groups/trials and 1 previous comparison (Gage).

Management options and clinical action thresholds in this risk-based algorithm will require local decision making based on the benefits, harms and efficacy appropriate for the situation. (Cheung).

Prevention methods

The recognition of HPVs as the primary etiologic agent for human cancers has increased their medical importance and has spurred research to develop strategies for screening, diagnosis, prevention and

treatment of HPV-related diseases (Bekele , Bradford). These methods are categorized in 3 ways:

1. Priority prevention

The primary approach to cervical precancerous lesions are vaccination against oncogenic HPV types. Condoms can be used as a method of protection, but there is no definite protection.

2. Secondary prevention

It is used for appropriate monitoring and treatment to prevent progression to cervical cancer.

3. Tertiary prevention

Since it is an advanced cancer, it consists of rehabilitation and palliative treatment.

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CHAPTER 12

ANATOMY OF FEMALE GENITAL: A REVIEW ON RELATION OF SEX & REPRODUCTION ROLES

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1. INTRODUCTION

Female genitalia are the primary structures used to receive and store sperm during copulation and secondary structures that make contact with males. External genitalia of female is intersting due to the fact it is made up of both urinary tract and reproductive structures. Female genitalia have been largely neglected in studies of genital evolution but it has some of the fastest evolving characters in the animal kingdom. The majority of anatomic descriptions for these organs have been from the context of reproduction. Wide variability exists in the appearance of female external genitalia. Aesthetic genital surgery seems to have become a fashionable issue nowadays. Through history, knowledge of female genital anatomy has been discovered and rediscovered. Renewed interest in anatomical research over the last two decades has increased by photography and magnetic resonance imaging.

Female genitalia are the primary structures used to receive and store sperm during copulation. However, female genitalia can also include secondary structures that make contact with males but do not necessarily receive intromittent organs or play a primary role in reproduction. Such secondary structures may have evolved either to facilitate copulation or to resist mating when not in the female's best interests, and are widely accepted as being genital structures (Sloan & Simmons, 2020). The female external genitalia is intersting due to the fact it is made up of both urinary tract and reproductive structures. These structures collectively fall under the term vulva. The definition of "vulva" is covering or wrapping. From the exterior observation of the

female external genitalia, it does appear to be covered or wrapped by skin folds. These skin folds are called the labia majora and labia minora. Both labia majora and labia minora are part of the vulva. The components of the entire vulva are the mons pubis, labia minora, labia majora, clitoris, urethra, vulva vestibule, vestibular bulbs, Bartholin's glands, Skene's glands, and vaginal opening. The external female genitalia serves the purposes of reproduction and urination (Nguyen & Duong, 2021).

2. Evolution

Genitalia are some of the fastest evolving characters in the animal kingdom. Female genitalia have been largely neglected in studies of genital evolution, perhaps due to the belief that they are relatively invariable and taxonomically and evolutionarily uninformative in comparison with male genitalia (Sloan & Simmons, 2019). Male genitalia exhibit patterns of divergent evolution driven by sexual selection. In contrast, for many taxonomic groups, female genitalia are relatively uniform and their patterns of evolution remain largely unexplored. Results eliminate the notion that female genitalia do not show the same patterns of divergent evolution as male genitalia, and suggest that female genitalia are under sexual selection through their role in female choice (Simmons & Fitzpatrick, 2019).

3. Sexual function

The majority of anatomic descriptions for these organs have been from the context of reproduction. Yet, there is a growing awareness that while sharing some same anatomical structures and hormonal milieu,

sexual function and reproductive function are distinct, with unique physiological responses (Ginger & Yang, 2011). The physiology and anatomy of female sexual function are poorly understood. The differences in sexual function among women may be partly attributed to anatomical factors. Gravina et al., (2008) used ultrasonography to evaluate the anatomical variability of the urethrovaginal space in women with and without vaginal orgasm. The urethrovaginal space thickness as measured by ultrasound was chosen as the indicator of urogenital anatomical variability. The urethrovaginal space and distal, middle, and proximal urethrovaginal segments were found thinner in women without vaginal orgasm. A direct correlation between the presence of vaginal orgasm and the thickness of urethrovaginal space was found. Women with a thicker urethrovaginal space were more likely to experience vaginal orgasm. A direct and significant correlation between the thickness of each urethrovaginal segment and the presence of vaginal orgasm was found, with the best correlation observed for the distal segment. Researchers concluded that, the measurement of the space within the anterior vaginal wall by ultrasonography is a simple tool to explore anatomical variability of the human clitoris-urethrovaginal complex, also known as the G-spot, which can be correlated to the ability to experience the vaginally activated orgasm.

4. Aesthetics of the female genital

Wide variability exists in the appearance of female external genitalia. Sexual function does not appear to be associated with genital dimensions. This information is important for both women and

surgeons when considering cosmetic vulvar surgery (Krissi et al., 2016). Aesthetic genital surgery is a fashionable issue nowadays (Dobbeleir et al., 2011). Vaginal rejuvenation was on the rise for the past 10 years. Women seem to prefer no pubic hair and minimal if any labia minora dangling beyond the majora. Labiaplasty or labia minora reduction is the most common procedure requested by women concerned with the appearance of their vulvar area. Safe and effective surgical procedures exist to trim the labia minora and the labia majora and clitoral hood as indicated (Hamori, 2014).

Aesthetic surgery of the external genitalia in women encompasses many procedures and may address the labia minora, clitoral hood, labia majora, mons pubis, or vaginal opening. During the initial evaluation, the surgeon should consider all aspects of the external genitalia to develop an appropriate surgical plan. It may be necessary to perform two or more procedures during the same surgical session to achieve the desired aesthetic result. Aesthetic surgery of the clitoral hood may involve straight-line resection, extended wedge resection, or inverted V hoodoplasty. The mons pubis may be treated with mons pubis pexy, wedge resection, or lipomodeling. The labia majora can be managed with direct resection or lipomodeling, and hymenoplasty may be performed to correct a wide vaginal opening (Triana & Robledo, 2015). Labia minora and clitoral hood reduction as performed by the trim/edge resection method does not result in diminished sensitivity (Placik & Arkins, 2015).

5. Knowledge of female genital anatomy

Anatomical terminology is a cornerstone of medical terminology and was a norm, regularly revised, extended, and updated. The latest official version issued by the "Federative International Program on Anatomical Terminology" was approved by the "International Federation of Associations of Anatomists" in 1998 as "Terminologia Anatomica". Second edition of the "Terminologia Anatomica 2" has now been prepared for approval (Kachlik, 2021). Through history, knowledge of female genital anatomy has been discovered and rediscovered, with previous knowledge being lost. Renewed interest in anatomical research over the last two decades has provided objective media such as photography of sections, and magnetic resonance imaging has complemented historical work based on diagrams of dissections (O'Connell & Vikraman, 2015).

When a healthy woman expresses concerns about her vulva, the doctor's response should be informed by clinical knowledge. For many doctors, accumulation of such knowledge would have begun with undergraduate teaching and medical textbooks. Andrikopoulou et al., (2013) studied medical textbooks to examine the information on female genital morphology. Total 59 gynaecology and anatomy textbooks were searched for information on the dimensions of vulval constitutent parts. No textbook gave measurements for all vulval structures. Vaginal length was reported in 21 textbooks, clitoral size in 15 and labia minora in 1. Where measurements appear, they suggest narrower ranges than recent reports. Information of vulval morphology is scanty and

inaccurate in medical textbooks. The general lack of professional resources means that doctors may consciously or non-consciously rely upon personal experiences and popular culture to form their opinions.

In sexology textbooks, the embryology and the anatomy of the female erectile organs are neglected. A true knowledge of female sexual anatomy and functioning is important in sexual therapy and education. Only the body of the uterus and the uterine tubas are formed by the Müllerian ducts; the vagina develops from the urogenital sinus. The female external genital organs develop from the phallus, from the urogenital folds and from the labioscrotal swellings. Vulva is constituted by the labia majora and the vaginal vestibule, with an erectile apparatus: clitoris, bulbs and corpus spongiosum, labia minora, corpus spongiosum of the female urethra. Corpus spongiosum of the female urethra is present in every woman and the female urethral sensibility was not well investigated. The vagina is mainly a reproductive organ; the vaginal orgasm and G-spot are not based on scientific evidence. In sexology textbooks the female genital anatomy should include all the erectile structures responsible for the female orgasm (Puppo et al., 2008).

O'connell et al., (2005) presented clitoral anatomy, its component structures, neurovascular supply, relationship to adjacent urethra, vagina and vestibular glands, and connective tissue supports, histology and immunohistochemistry. The clitoris is a multiplanar structure with a broad attachment to the pubic arch and via extensive supporting tissue to the mons pubis and labia. Centrally it is attached to the urethra and

vagina. Its components include the erectile bodies (paired bulbs and paired corpora, which are continuous with the crura) and the glans clitoris. The glans is a midline, densely neural, nonerectile structure that is the only external manifestation of the clitoris. All other components are composed of erectile tissue with the composition of the bulbar erectile tissue differing from corpora. The clitoral and perineal neurovascular bundles are big, paired terminations of the pudendal neurovascular bundles. The clitoral neurovascular bundles ascend along ischiopubic rami, meet each other and pass along the superior surface of the clitoral body supplying the clitoris. The neural trunks pass largely intact into the glans. These nerves are at least 2 mm diametered even in infancy. The cavernous or autonomic neural anatomy is microscopic and difficult to define consistently. Clitoral pharmacology and histology appears to parallel those of penile tissue, although the clinical impact is vastly different. Typical textbook descriptions of the clitoris lack detail and include inaccuracies. It is impossible to convey clitoral anatomy in a single diagram showing only 1 plane, as is typically provided in textbooks, which reveal it as a flat structure. MRI provides a multiplanar representation of clitoral anatomy in the live state, which is a major advantage, and complements dissection materials. The bulbs appear to be part of the clitoris. They are spongy in character and in continuity with the other parts of the clitoris. The distal urethra and vagina are intimately related structures, although they are not erectile in character. They form a tissue cluster with the clitoris. This cluster appears to be the locus of female sexual function and orgasm.

Ostrzenski, (2021) described the bulbus vestibuli anatomy in detail, compared previous bulbus vestibuli descriptions and illustrations to the current study's findings and photograms to show bulbus vestibuli topographic relation to the urethral meatus. The bulbus vestibuli was located within the posterior-distal vagina and composed of two vertical legs, which fused to one another. The inferior pars intermedia fused both descending legs to the anterior-proximal perineal urethral wall, and bulbus vestibuli embraced the anterior-proximal urethra. The superior pars intermedia connects the bulbus vestibuli to the posterior-distal clitoral body. The bulbus vestibuli legs traversed parallel to and aside from the vaginal introitus and the lateral urethra and not crossing the anterior-distal urethra. The tile-end was a tapered end which terminates in the vicinity of Bartholin glands. Laterally, the bulbus vestibuli legs outspread to the medial labia minora and attach to the ischiopubic ramus. The anatomical site-specific defects occurs within the bulbus vestibuli. The present study resolves the bulbus vestibuli anatomical controversy and shows that the bulbus vestibuli runs parallel to and aside from the anterior-distal urethra and the bulbus vestibuli. The site-specific defects can occur within the bulbus vestibuli. Little information is available regarding the sensory nerve endings within the glabrous skin of the external female genitalia. The diversity of possible sensations suggests a variety of receptor types. Comprehensive knowledge of the sensory stimuli, including stimulus position, changes in temperature, pressure and pain, is critical for addressing pain and sexual function disorders clinically. Free nerve endings in the papillary dermis appeared as thin fibers, varicose, branched or single processed,

straight or bent. In the labia minora, free nerve endings were identified in the strata basale, spinosum and granulosum of the epidermis. Non-capsulated corpuscles in the dermal papillae interdigitated with epidermal ridges of the skin. Capsulated corpuscles protruded from the deep dermis into the epidermis. Free nerve endings, Meissner's corpuscles and Pacinian corpuscles are present in the female labia minora and exhibit characteristic staining patterns (Schober et al., 2015).

The intimate relationship between the genitalia and the muscles, ligaments, and fascia that provide support is complex. The external female genitalia include the mons pubis, labia majora and minora, clitoris, vestibule with glands, perineal body, and the muscles and fascia surrounding these structures. Through the perineal membrane and the perineal body, these superficial vulvar structures are structurally related to the deep pelvic muscle levator ani with its fascia. The levator ani forms the pelvic floor with the coccygeus muscle and provides vital support to all the pelvic organs and stability to the perineum. The internal female genital organs include the vagina, cervix, uterus, tubes, and ovaries with their visceral fascia. The visceral fascia also called the endopelvic fascia, surrounds the pelvic organs and connects them to the pelvic walls. It is continuous with the paraurethral and paravaginal fascia, which is attached to the perineal membrane. Thus, the internal and external genitalia are closely related to the muscles and fascia, and work as one functioning unit (Yavagal et al., 2011).

6. Premenopausal females

In the past, a few attention was paid in literatures and social informations towards the normal and abnormal female clitoris and prepuce, only during the second half of the twentieth century, the stream of data and debates about external female organs start to emerge. But sometimes these informations are inaccurate or not conclusive. At the main time the absence of accepted terms of the intimate parts of the female genitalia can influence the meaning of descriptions. The normal pediatric female genital anatomy was not well described, even there is no universal agreement about the terminology of some parts of these organs, also in many researches and illustrations there is some confusion between clitorial and preputial anatomy, anomalies and functions. The female prepuce, which is homologue to the male prepuce has a special and intricate anatomy. It projects at the front of the labial commissure, where the edges of the labia meet at the base of the clitoris. It forms as part of the external folds of the labia minora and partially covers the clitorial glans and external shaft. There is considerable variation in how much of the glans protrudes from the hood and how much is covered by it, ranging from completely covered to fully exposed. Many textbooks describe the female prepuce as the only distal portion, the clitorial hood. But actually the prepuce in female is formed of three distinct parts: the base, which is in continuity proximally with mons pubis and cover the most proximal part of the clitoris, preputial body covering the shaft of the clitoris, and the term clitorial hood is reserved for the only cutaneous and nearly circular fold at the loose end of this prepuce (Fahmy, 2020).

Female adolescents often present to health care providers with concerns about the appearance of their external genitalia. These patients might experience significant distress about their genital appearance and might request surgery to correct a perceived abnormality. Accurate descriptions of normal adolescent female genital anatomy are lacking in the literature. Role of labiaplasty in adolescents should be considered with extreme caution because of the wide range in size and morphology and paucity of data in this population (Brodie et al., 2019). Suh et al., (2003) used contrast enhanced magnetic resonance imaging of the female genital organs to describe normal anatomy and differences between premenopausal and postmenopausal women. The clitoris and vestibular bulbs were well delineated on T1-weighted post-contrast images. The clitoral unit formed a brightly enhancing, wishbone-shaped structure lying just anterior to the inverted V of the bulbs, which surrounded the urethra and vagina. The urethra, vagina and rectum formed a distinct complex within uniformly enhancing soft tissue. The vagina was well visualized in premenopausal subjects but without distinguishable mucosal rugae or clearly separate layers in postmenopausal subjects. Postmenopausal subjects were also observed to have smaller labia minora width, vestibular bulb width, vaginal width and wall thickness, and cervical diameter. Pelvic and genital structures were not well visualized on T1 noncontrast images. They described detailed female genital anatomy for the first time using magnetic resonance imaging with MS-325 contrast medium. The clitoris, vestibular bulbs, labia majora and minora, urethra, vagina, cervix and rectum are well visualized on T1 post-contrast images. The observed

genital anatomy on magnetic resonance imaging was consistent with descriptions in current anatomical texts. Differences in the female genitalia between premenopausal and postmenopausal women were discernible on magnetic resonance imaging. These data are important for future studies using magnetic resonance imaging for evaluating anatomical anomalies, postoperative changes and female sexual function.

Pediatric female genitalia size and morphology was not previously been well described. Brodie et al., (2016) conducted a study to take following measurements from female patients between 0-16 years of age with normal external genitalia: 1) Length of clitoral hood. 2) Length of sides of clitoral hood. 3) Clitoral diameter. 4) Apex of clitoral hood to base of pubic symphysis. 5) Apex of clitoral hood to urethral orifice. 6) Distance of clitoral hood to labia majora. 7) Length and depth of labia minora. 58 patients were grouped into four age ranges: 0–3 years, 4–8 years, 9–12 years, and 13–16 years. There was a linear relationship between age and genital structure size. In the majority of patients, the labia minora converged under the clitoral glans, separate to the clitoral hood. Four shapes of clitoral hood were observed: horseshoe, trumpet, coffee bean, and tent. Great variation in size and morphology of pediatric female genitalia was observed. The study demonstrated that the clitoral hood and labia minora are anatomically distinct structures.

Characterization of the anatomical changes and relationships of external genitalia in postmenopausal women is important for functional and perioperative evaluation. In addition to reconstructive surgical

procedures, determination of the objective measurements of anatomical landmarks in postmenopausal external genitalia might also be useful for assessing the results of treatment of 'atrophic' changes in women. Basaran et al., (2008) determined measurements to determine differences between the external genital organs of pre-menopausal and postmenopausal women. 50 premenopausal and 50 postmenopausal patients were recruited. The length of the vagina and the width of the labium minus were found significantly different between two groups. Mean vaginal length was significantly longer in premenopausal women compared to postmenopausal women (90.3 ± 14.8 mm vs. 82.3 ± 11.2 mm, respectively). The labia minora were wider in premenopausal women than in postmenopausal women (17.9 ± 4.1 mm vs. 15.4 ± 4.7 mm).

7. CONCLUSIONS

The physiology and anatomy of female sexual function are poorly understood. The differences in sexual function among women may be partly attributed to anatomical factors. A direct correlation between the presence of vaginal orgasm and the thickness of urethrovaginal space was found. Labia minora and clitoral hood reduction as performed by the trim/edge resection method does not result in diminished sensitivity. Free nerve endings, Meissner's corpuscles and Pacinian corpuscles are present in the female labia minora and exhibit characteristic staining patterns. The internal and external genitalia are closely related to the muscles and fascia, and work as one functioning unit. Many textbooks describe the female prepuce as the only distal portion, the clitorial hood.

But actually the prepuce in female is formed of three distinct parts: the base, which is in continuity proximally with mons pubis and cover the most proximal part of the clitoris, preputial body covering the shaft of the clitoris, and the term clitorial hood is reserved for the only cutaneous and nearly circular fold at the loose end of this prepuce.

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CHAPTER 13

DIAGNOSTIC IMAGING METHODS IN GYNECOLOGY: A REVIEW

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1. INTRODUCTION

Women frequently present to the emergency room with subacute or acute symptoms of gynecologic origin. The imaging findings are important when evaluating acute gynecologic diseases because the symptoms and physical examination findings are often nonspecific and limited. Although obstetric and gynecological ultrasound are two of the most commonly performed imaging studies, artificial intelligence have huge potential to assist repetitive ultrasound tasks, such as automatic identifying. Ultrasound should be considered the first-line imaging modality in women with acute or chronic pelvic pain because many gynecologic/obstetric causes of pelvic pain are easily diagnosed by ultrasound. Doppler ultrasound gives real-time information regarding anatomy and blood vessel location to guide needle placement for gynecologic interstitial brachytherapy. MR imaging has become central in selecting treatment options and therapy for patients with gynecologic malignancies. Dual-energy CT is a new technology that acquires datasets essentially simultaneously at two different photon spectra in a single CT acquisition. Molecular imaging has various impacts in different clinical scenarios. Narrow band imaging is a new endoscopic technique in which images of mucosal microstructures and capillary structures are enhanced.

Gynecologic emergencies include various diseases that result from adnexal and uterine disorders. Adnexal disorders may be classified into the following three categories: 1) disorders that cause hemorrhage (hemorrhagic ovarian cysts and ectopic pregnancies); 2) disorders

related to adnexal tumors (adnexal torsion and rupture of ovarian tumors); 3) disorders related to pelvic inflammatory disease. Uterine disorders in gynecologic emergencies may be classified into two categories: 1) acute fibroid complications, including red degeneration of a uterine leiomyoma, torsion of subserosal myomas, and torsion of the uterus; 2) causes of acute uterine bleeding, including retained products of conception and uterine arteriovenous malformations. Some gynecologic diseases are self-limited, while others cause infertility or life-threatening infection or bleeding if left untreated. Therefore, prompt and accurate diagnosis is important for appropriate treatment and preservation of fertility. The imaging is important when evaluating acute gynecologic diseases because the symptoms and physical examination findings are often nonspecific and limited. Ultrasonography is the first-line imaging modality. However, when a definitive diagnosis cannot be established, computed tomography (CT) and magnetic resonance (MR) imaging may narrow the differential diagnosis. Appropriate management requires radiologists to be familiar with the CT and MR imaging features of gynecologic emergencies. With respect to rare conditions, radiologists should take into account the representative findings to increase diagnostic accuracy. CT and MR imaging are helpful in gynecologic emergencies, especially when ultrasound findings are indeterminate. CT is ideal for emergency use and can demonstrate internal bleeding, such as hemoperitoneum. CT also allows easy detection of pelvic mass lesions and a presumed diagnosis of a gynecologic emergency. However, CT findings are occasionally nonspecific and may lead to misinterpretation. MR

imaging can narrow the differential diagnosis, particularly when adnexal masses or uterine leiomyomas are related to the conditions. Radiologists play an important role in diagnosing acute gynecologic diseases for appropriate treatment (Iraha et al., 2017).

The list of medical image-analysis artificial intelligence applications with "USA Food and Drug Administration" or "European Union Medical Device Regulation" approval is growing rapidly. It covers diverse clinical needs, such as detection of arrhythmia using a smartwatch. Deep learning, a tool of artificial intelligence, performs particularly well in image pattern recognition. Therefore, sonologists, radiographers and pathologists can benefit who rely heavily on images. Although obstetric and gynecological ultrasound are two of the most commonly performed imaging studies, artificial intelligence have huge potential to assist repetitive ultrasound tasks, such as automatically identifying good-quality acquisitions and providing instant quality assurance (Drukker et al., 2020).

2. Ultrasound

Ultrasound should be considered the first-line imaging modality in women with acute or chronic pelvic pain because many gynecologic/obstetric causes of pelvic pain are easily diagnosed by ultrasound. Since the clinical presentation of gynecologic causes of pelvic pain overlaps with gastrointestinal and genitourinary pathology, referral to CT or MRI, especially in pregnant patients, should be considered if the ultrasound examination is nondiagnostic (Cicchiello et al., 2011).

There is wide inequality in the practice of brachytherapy for cervical cancer around the world. Although select well-resourced centers advocate use of MRI for all insertions, planar X-ray imaging remains the most commonly used imaging modality to assess intracavitary implants. Incorporating soft tissue imaging into brachytherapy programs improve technical accuracy of implants, which led to improved local control and decreased toxicity. A modality with good soft tissue imaging capabilities, widely available, portable, and economical, is needed. Ultrasound fulfils these requirements and offers the potential of soft tissue image guidance to a much wider brachytherapy community. Although use of ultrasound is the standard of care in brachytherapy for prostate cancer, it only seems to have limited uptake in gynecologic brachytherapy (Van Dyk et al., 2015).

Concerns exist regarding the potential thermal and mechanical effects of ultrasound on the developing embryo/fetus (Eskandar et al., 2010). Over the last decade, a massive technology development led to a dramatic improvement in the quality ultrasound imaging. If performed by an experienced sonographer, ultrasound has an significant role for the primary diagnosis of gynecological cancer, assessment of tumor extent in the pelvis and abdominal cavity, evaluation of the treatment response, and in follow-up. Ultrasound is also valuable for monitoring patients treated with fertility-sparing surgery. It is an ideal technique to guide tru-cut biopsy for the collection of material for histology. Besides its accuracy, ultrasound is a commonly available, non-invasive, and inexpensive imaging method which has no risk or discomfort for patients (Fischerova & Cibula, 2015).

Doppler ultrasound gives real-time information regarding anatomy and blood vessel location to guide needle placement for gynecologic interstitial brachytherapy. The use of Doppler ultrasound in the first trimester should be restricted to well-defined diagnostic purposes with the shortest possible exposure duration (Eskandar et al., 2010). Clinical use of color Doppler sonography has within many organ systems. Significant improvements was occurred to improving the visualization and evaluation of intraorgan vascularity, resulting from enhancements in delineation of tissue detail through electronic compounding and enhancements in signal processing of frequency-based and amplitude-based color Doppler sonography. Spatial representation of vascularity can be improved by utilizing 3D and 4D (live 3D) processing. Greater sensitivity of color Doppler sonography to macro- and microvascular flow has provided improved anatomic and physiologic assessment throughout pregnancy and for pelvic organs. The potential use of contrast enhancement is also mentioned to further differentiate benign from malignant ovarian lesions. The rapid development of these new sonographic techniques will continue to enlarge clinical applications in obstetric and gynecologic disorders (Fleischer & Andreotti, 2005). Color Doppler analysis added to transvaginal gray-scale ultrasonography is helpful in diagnosis of recurrent tumors in the central region of the pelvis (Testa et al., 2002). Transvaginal color Doppler ultrasound may give precise diagnosis for the obstetrical and gynecological emergency diseases. It is the preferred auxiliary method for the diagnosis of gynecological emergency diseases (Mai et al., 2007).

3. Transvaginal ultrasonography

Pavlik et al., (2013) examined the prevalence, incidence, persistence, and resolution of ovarian abnormalities using serial transvaginal ultrasonography. A group of 39.337 women in the University of Kentucky Ovarian Cancer Screening Program were monitored with 221.576 baseline and interval transvaginal ultrasonography. The transvaginal ultrasonogram was normal for first and all subsequent visits for 31.834 participants (81%), whereas 6.807 women (17%) had transvaginal ultrasonograms interpreted as abnormal and were monitored over 21.588 ultrasonograms. Ovarian cysts were more common in premenopausal (prevalence 35%, incidence 15%) than in postmenopausal women (prevalence 17%, incidence 8%). For the group with abnormalities, the initial transvaginal ultrasonogram was abnormal in 47% of the cases, of which 63% resolved to normal on subsequent ultrasonograms. Of 35.314 cases classified as normal on the first examination, 10% were abnormal on subsequent annual examinations. The abnormal findings were classified as follows: unilocular cysts (11,5%), cysts with septations (9,8%), cysts with solid areas (7,1%), and solid masses (1,8%). Many transvaginal ultrasonographic abnormalities were followed to resolution. Surgery was performed on 557 participants for 85 ovarian malignancies and 472 nonmalignancies. Over the duration of the study, the positive predictive value increased from 8% to 25%. As a conclusion, serial ultrasonography has shown that many ovarian abnormalities resolve, even if the initial appearance is complex, solid, or bilateral. Thus, it is advantageous to avoid a single transvaginal ultrasonographic abnormality as the sole trigger for

surgery and to take a measured serial approach to reduce false-positive results and increase the ositive predictive value.

4. Magnetic Resonance Imaging (MR / MRI)

MR imaging has an important role from the initial evaluation of the extent of the disease to appropriate treatment selection and follow-up. With growing role of radiologists in multidisciplinary treatment planning teams, it is crucial to recognize that MR imaging has become central in selecting treatment options and therapy for patients with gynecologic malignancies. In endometrial carcinoma, MR can provide local staging by accurate assessment of the depth of myometrial invasion and cervical stromal invasion. This in turn correlate with lymph node metastases and overall patient survival. If possible, tumor grade and histology should be considered before reporting an MR imaging case of endometrial carcinoma. Grade 3 endometrioid adenocarcinomas and serous papillary and clear cell carcinomas demonstrate more aggressive biologic behavior and, therefore, have a 50% pretest probability of advanced disease and/or peritoneal spread at the time of presentation. In cervical cancer, MR is the best single imaging method for determining tumor location and size, involvement of parametria, pelvic side wall, adjacent organs, or nodal enlargement, and the high negative predictive value of MR imaging in excluding parametrial invasion is important for selecting patients for radical surgery. In young women with small invasive cervical cancer who wish to preserve fertility, in whom a more conservative surgical procedure can be performed, MR is the best method for determining eligibility in

terms of tumor size, cervical length, and distance of tumor from the internal cervical os. In ovarian cancer, the extent and location of peritoneal spread dictates the choice between cytoreductive primary surgery versus neoadjuvant chemotherapy. Therefore, accurate mapping of the disease with imaging plays a crucial role in treatment selection and directly influences patient outcome. In endometrial cancer, MR imaging improves pretreatment risk stratification. It enables accurate surgical planning and selection of patients for pelvic or paraaortic lymph node dissection in high-risk disease, while obviating extended surgery in patients with low-risk disease. DW MR imaging may play a role in more accurate mapping of the extent of the peritoneal disease when compared with CT. MR imaging certainly plays an important role for patients with recurrent ovarian cancer by enabling assessment of resectability in cases of solitary pelvic recurrences (Sala et al., 2013).

Progresses in MRI techniques increased the role of MRI in assessment of the pelvis in women (Nougaret et al., 2013). Outside gynaecologic oncologic MRI examinations are often submitted for a second-opinion review by GynOnc radiologists. One-fifth of MRIs had important discrepancies between initial and second-opinion interpretations. Second-opinion review of gynaecologic oncologic MRI is a valuable clinical service (Lakhman et al., 2016).

External-beam radiotherapy followed by high dose rate brachytherapy is the standard-of-care for treating gynecologic cancers. The enhanced soft-tissue contrast provided by magnetic resonance imaging makes it a

valuable imaging modality for diagnosing and treating these cancers. However, in contrast to computed tomography imaging, the appearance of the brachytherapy catheters, through which radiation sources are inserted to reach the cancerous tissue later on, is often variable across images (Zaffino et al., 2019).

There is a widespread lack of understanding among clinicians regarding the potential risks of magnetic resonance imaging (MRI) and ultrasound energy on the fetus. The use of MRI is not generally advisable during the first trimester of pregnancy. Although there is no scientific evidence of any adverse effects on the human embryo/fetus from the use of MRI during pregnancy, it is not advisable in the first trimester because of the potential hazards of hyperthermia and acoustic noise (Eskandar et al., 2010).

5. CT (Computed Tomography)

Women frequently present to the emergency room with subacute or acute symptoms of gynecologic origin. Although a pelvic exam and ultrasound are the preferred initial diagnostic tools for gynecologic entities, a CT is often the first line imaging modality in the emergency department (Tran-Harding et al., 2019). Gynecologic disorders causing pelvic pain in adolescents include hemorrhagic ovarian cysts, rupture or torsion of ovarian cyst or tumors, endometriosis, hematocolpos caused by vaginal obstruction, pelvic inflammatory diseases, cystic uterine adenomyosis, and pelvic inclusion cyst. The use of CT for the evaluation of pelvic pain is increasing, and CT is useful if ultrasound findings are not decisive and the lesion is extensive (Kim, 2012).

Dual-energy CT (DECT) is a new technology that acquires datasets essentially simultaneously at two different photon spectra in a single CT acquisition. By obtaining CT data at different photon energies, differences in material composition can be detected on the basis of differences in photon absorption. This may help to assess primary tumors and metastatic disease in patients with gynecologic malignancies. Dual-energy CT has the potential to improve diagnostic performance, may improve the ability to differentiate between simple cystic lesions and primary ovarian cancer, and may improve the detection of musculoskeletal and liver metastases (Benveniste et al., 2017).

6. PET (Positron Emission Tomography)

Molecular imaging (mainly PET and MRI) plays important roles in the management of gynecologic malignancies. Molecular imaging has various impacts in different clinical scenarios (Lai et al., 2014). Integrated positron emission tomography–computed tomography (PET–CT) is a major technologic advance in oncologic imaging of gynecologic malignancy patients. It improves localization of regions of increased 18F-fluorodeoxyglucose uptake and staging/restaging accuracy by allowing a near-simultaneous acquisition of co-registered, spatially matched metabolic and anatomic data in the same examination. However, physiologic processes, normal variants, and many benign lesions within the pelvis can accumulate fluorodeoxyglucose and may be confused with malignant neoplasms. Conversely, false-negative results due to malignancies with low

fluorodeoxyglucose uptake can be a diagnostic challenge in patients with gynecologic cancer. With the increased use of PET–CT in patients with gynecologic malignancies, misinterpretation of these potential pitfalls can have significant implications and alter staging/restaging and patient management (Gorospe et al., 2012). The main difference between PET and SPECT scans is the type of used radiotracers. While SPECT scans measure gamma rays, the decay of the radiotracers used with PET scans produce small particles called positrons.

A growing body of evidence defines PET/CT as one of the most powerful tools for tumor, nodal and metastasis cancer staging both in pre-treatment and in post treatment follow-up settings. At any phase of cancer evaluation, detection of metastasis is among the most critical impediments for the tumor cure. Traditional diagnostic imaging modalities, such as computed tomography, are frequently found to inadequately stage the tumor, based on subsequent outcomes. As a result, patients may undergo pointless surgery for disease that could be treated with local medical therapies. In the setting of restaging, the ability to describe primary lesion, lymph nodes, possible metastases to peritoneum, bone, lungs, liver, and brain renders PET/CT a potential alternative for a series of tests, including bone scanning, magnetic resonans imaging or ultrasound, diagnostic computed tomography, lymph node surgical sampling (Dalla Palma et al., 2012).

FDG-PET/CT has become more established in the management of gynecologic malignancies in the last decade. While the role in initial or pre-operative staging for FDG-PET/CT is controversial, it allows

noninvasive detection of equivocal or distant metastases, may alter stage and prognosis, and can guide or help eliminate unnecessary interventions that may not be beneficial. FDG-PET/CT is a useful adjunct to traditional staging with MR and CT (Akin et al., 2018). MR imaging and 18F-FDG PET/CT play central and complementary roles in the care of patients with gynecologic cancer. Because treatment often requires combinations of surgery, radiotherapy, and chemotherapy, imaging is central to triage and to determining prognosis (Lee et al., 2015).

Cervical cancer is typically very FDG avid, and FDG-PET/CT appears to be most valuable for initial staging, radiation therapy planning, and detection of recurrent disease. For ovarian cancer, the most value of FDG-PET/CT is for detecting recurrent disease in the setting of rising CA-125 level and negative or equivocal anatomical imaging studies. FDG uptake in both nonmalignant and physiological processes in the pelvis can make interpretation of FDG-PET/CT in this region challenging and knowledge of these entities and patterns can avoid misinterpretation. Some of the most common findings relate to the cyclic changes that occur as part of the menstrual cycle in premenopausal women. Mucinous tumors and low-volume or peritoneal carcinomatosis are causes of false-negative results on FDG-PET/CT studies. As new tracers are developed, comparisons with patient outcomes and standards of care (eg, FDG-PET/CT) will be needed (Grant et al., 2014).

MR imaging and PET using FDG are both useful in the evaluation of gynecologic malignancies. MR imaging is superior for local staging of disease whereas fludeoxyglucose FDG PET is superior for detecting distant metastases. Integrated PET/MR imaging scanners have great promise for gynecologic malignancies by combining the advantages of each modality into a single scan (Ohliger et al., 2017). Positron emission tomography (PET) with FDG, the most commonly used functional imaging for staging, treatment planning, and therapy response evaluation in gynecological cancers, is limited in providing information about the unique biological features of these tumors. There is an increasing need to noninvasively determine the patient's distinct tumor biological features in order to select the most appropriate therapy (Ponisio et al., 2019).

PET/MR imaging offers superior soft tissue contrast, improved assessment of primary tumor involvement because of high-resolution multiplanar reformats, and functional MR techniques such as diffusion-weighted MR imaging and dynamic contrast-enhanced MR imaging (Ponisio et al., 2016). Instruments that combine PET and MR imaging have recently been assembled for use in humans, and may have diagnostic performance superior to that of PET/CT for particular clinical and research applications. MR imaging has major strengths compared with CT. These are, superior soft-tissue contrast resolution, multiplanar image acquisition, and functional imaging capability through specialized techniques such as diffusion-tensor imaging, diffusion-weighted (DW) imaging, functional MR imaging, MR elastography, MR spectroscopy, perfusion-weighted imaging, MR

imaging with very short echo times, and the availability of some targeted MR imaging contrast agents. Furthermore, the lack of ionizing radiation from MR imaging is highly appealing, particularly when pediatric, young adult, or pregnant patients are to be imaged. Also the safety profile of MR imaging contrast agents compares very favorably with iodinated CT contrast agents. MR imaging also can be used to guide PET image reconstruction, partial volume correction, and motion compensation for more accurate disease quantification and can improve anatomic localization of sites of radiotracer uptake (Torigian et al., 2013).

Virarkar et al., (2020) performed a meta-analysis of the literature to compare the diagnostic performance of FDG PET/CT versus 18F-FDG PET/MRI for gynecological malignancies of the pelvis. Nine studies were included. Compared with PET/CT, PET/MRI had slightly better diagnostic performance to that of 18F-FDG PET/CT in the gynecological malignancies on lesion level (44 vs 26) and patient level analysis (28 vs 17). However, the differences between results showed no statistical significance.

7. Narrow band imaging (NBI)

Narrow band imaging is a new endoscopic technique in which images of mucosal microstructures and capillary structures are enhanced by shifting the light spectrum to a narrow band. Image-enhanced gastrointestinal endoscopy using narrow band imaging improves the qualitative diagnosis of the grade and depth of invasion of an atypical lesion. Narrow band imaging is currently not commonly used in

gynecological endoscopy, but has recently been applied in laparoscopy and hysteroscopy. The utility of narrow band imaging for diagnosis of endometrial lesions and endometriosis was also shown. In gynecological endoscopy, narrow band imaging provides enhanced images of mucosal microstructures and capillary structures and improves visual identification of lesions. Therefore, image-enhanced observation using narrow band imaging is likely to be useful for improved detection of lesions in endoscopic diagnosis. However, this technique remains experimental so far, and no study has demonstrated improved clinical outcome (Kisu et al., 2012).

8. CONCLUSIONS

MRI and FDG PET-CT play central and complementary roles in gynecologic cancer care. Because treatment often requires combinations of surgery, radio- and chemotherapy, imaging is central to triage and to determine prognosis. Artificial intelligence have huge potential to assist repetitive ultrasound tasks, such as automatically identifying. Ultrasound should be considered the first-line imaging modality in women with acute or chronic pelvic pain because many gynecologic/obstetric causes of pelvic pain are easily diagnosed by ultrasound. Doppler ultrasound gives real-time information regarding anatomy and blood vessel location to guide needle placement for gynecologic interstitial brachytherapy. MR imaging has become central in selecting treatment options and therapy for patients with gynecologic malignancies. Dual-energy CT is a new technology that acquires datasets essentially simultaneously at two different photon spectra in a

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CHAPTER 14

PELVIC PAIN IN WOMEN: A REVIEW

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1. Chronic pelvic pain

Women bear a disproportionate burden of persistent pain conditions compared to men. Chronic pelvic pain in women is defined as persistent, noncyclic pain perceived to be in structures related to the pelvis and lasting more than six months. Irritable bowel syndrome is the most frequent chronic, noncancer abdominal pain condition. Genito-pelvic pain/penetration disorder can be extremely bothersome for patients, and a challenge for assessment and treatment of professionals. Dilated, refluxing pelvic veins may be a cause of chronic pelvic pain and treatment by trans-venous occlusion is increasingly performed when gynecological causes are excluded. It is typically associated with other functional somatic pain syndromes and mental health disorders.

Women bear a disproportionate burden of persistent pain conditions compared to men. Low androgen levels were consistently associated with increased pain (Evans et al., 2021). Irritable bowel syndrome is the most frequent chronic, noncancer abdominal pain condition (Zhou et al., 2018). Chronic pelvic pain conditions often overlap with nonpelvic pain disorders (eg, fibromyalgia, migraines) and nonpain comorbidities (eg, sleep, mood, cognitive impairment) to contribute to pain severity and disability (Lamvu et al., 2021). Genito-pelvic pain/penetration disorder can be extremely bothersome for patients, and a challenge for assessment and treatment of professionals. Professionals should be familiarized with the underlining factors of the problem, and should be able to provide helpful guiding suggestions (Dias-Amaral & Marques-

Pinto, 2018). There is wide variation in reported outcomes and applied outcome measures in chronic pelvic pain studies. Commonly reported outcomes were pain (pelvic pain, dyspareunia, dysmenorrhoea), life impact (quality of life, emotional functioning, physical functioning), clinical effectiveness (efficacy, satisfaction, cost effectiveness, return to daily activities) and adverse events (surgical, perioperative observations, nonsurgical) (Ghai et al., 2021a). Patient-centred approach for the management of chronic pelvic pain may target acceptance of pain, quality of life, communication and support (Ghai et al., 2021b).

Chronic pelvic pain is a considerable economic burden on women and healthcare systems globally. Productivity loss contributes a substantial portion of the total costs (Le et al., 2021). Chronic pelvic pain is a challenging condition affecting approximately 1/4 of the global female population. Chronic pelvic pain accounts for 40% of laparoscopies and 12% of hysterectomies in the US annually even though the origin of chronic pelvic pain is not gynecologic in 80% of patients. Patients and clinicians are frequently frustrated by a perceived lack of treatments. Chronic pelvic pain conditions often overlap with nonpelvic pain disorders (eg, fibromyalgia, migraines) and nonpain comorbidities (eg, sleep, mood, cognitive impairment) to contribute to pain severity and disability. Musculoskeletal pain and dysfunction are found in 50% to 90% of patients with chronic pelvic pain. Traumatic experiences and distress have important roles in pain modulation. Complete assessment of the biopsychosocial factors contribute to chronic pelvic pain requires a thorough history, patient education on pain mechanisms, and

extending visit times. A single-organ pathological examination should be avoided. As a conclusion, chronic pelvic pain is like other chronic pain syndromes in that biopsychosocial factors interact to contribute and influence pain. To manage this type of pain, clinicians must consider centrally mediated pain factors as well as pelvic and nonpelvic visceral and somatic structures that can generate or contribute to pain (Lamvu et al., 2021).

Chronic pelvic pain affects 24% of women worldwide. The cause cannot be identified in 40% despite invasive investigations. Dilated, refluxing pelvic veins may be a cause of chronic pelvic pain and treatment by trans-venous occlusion is increasingly performed when gynecological causes are excluded. To determine effectiveness of this applications, a systematic review of the literature was conducted by Hansrani et al., (2015). Two authors independently reviewed 13 studies including total 866 women. Technical success was reported in 865 of 866 (99,8%) with low complication rates: coil migration in 14 women (1,6%), abdominal pain in ten women (1,2%) and vein perforation in five (0,6%). In a study on varicose veins of the legs, recurrence was seen in 13% of 179 women 5-years following coil embolization.

Chronic pelvic pain in women is defined as persistent, noncyclic pain perceived to be in structures related to the pelvis and lasting more than six months. Often no specific etiology can be identified. It can be conceptualized as a chronic regional pain syndrome or functional somatic pain syndrome. It is typically associated with other functional somatic pain syndromes (such as irritable bowel syndrome, nonspecific

chronic fatigue syndrome) and mental health disorders (such as posttraumatic stress disorder, depression). Diagnosis is based on findings from the history and physical examination. Pelvic ultrasonography is indicated to rule out anatomic abnormalities. Referral for diagnostic evaluation of endometriosis by laparoscopy is usually indicated in severe cases. Curative treatment is elusive, and evidence-based therapies are limited. Patient engagement in a biopsychosocial approach is recommended, with treatment of any identifiable disease process such as endometriosis, interstitial cystitis/painful bladder syndrome, and comorbid depression. Potentially beneficial medications include depot medroxyprogesterone, gabapentin, nonsteroidal anti-inflammatory drugs, and gonadotropin-releasing hormone agonists with add-back hormone therapy. Hysterectomy may be considered as a last resort if pain seems to be of uterine origin, although significant improvement occurs in only about one-half of cases (Speer et al., 2016).

Gabapentin has potential analgesic benefits in patients with neuropathic pain, such as post-herpetic neuralgia and diabetic peripheral neuropathy neuropathic pain. However, its efficacy in women with chronic pelvic pain remains contradictory. Fan et al., (2021) performed a systematic review and meta-analysis of articles including active treatment for chronic pelvic pain in women. Four studies with total 469 participants were included. Results from analysis of secondary outcomes showed that gabapentin had no beneficial efficacy during the first 3 months of treatment. Although gabapentin treatment was associated with a higher risk of dizziness and somnolence, no statistically significant differences

were observed with regards to the total incidence of adverse events. The difference of 6-month pooled result was more clinically important. Overall, gabapentin was found to be a potential treatment option for chronic pelvic pain in women.

Psychological interventions are often added to medical treatment for women with chronic pelvic pain. Because women with chronic pelvic pain experience higher rates of mental health concerns and difficulties to cope with pain. However, recent systematic reviews have highlighted that the efficacy of psychological interventions is not conclusive in this population. Methodological concerns made identifying predictors of mental health outcomes and effective psychological interventions difficult. However, cognitive behavioural therapy and Mensendieck therapy emerged as therapeutic interventions with the best evidence for women with chronic pelvic pain (Brooks et al., 2020).

It was suggested that pelvic floor dysfunction may contribute to lumbopelvic pain development due to changes in trunk muscle control. Vesentini et al., (2020) analysed eight articles including 469 participants. There was no conclusive evidence that the addition of "pelvic floor muscle training" to usual physiotherapy care or minimal intervention is superior to minimal intervention and usual care alone.

Evidence for physical therapy and trigger point injections for treatment of myofascial components of chronic pelvic pain is increasing. Neuromodulation techniques, such as percutaneous tibial nerve stimulation and transcutaneous electrical stimulation, have limited but

favorable preliminary data in patients with chronic pelvic pain (Till et al., 2017).

2. Endometriosis related pelvic pain

Abdominal-pelvic pain is the dominant symptom in endometriosis, which is among the most common pathologies affecting women as a multifactorial disorder. Exploratory laparoscopy allows correct location assessment, severity and lesion extent, thus is the current gold standard in diagnosis. Surgical treatment (preferably performed laparoscopically) includes excision of the ectopic endometrium as primary objective to control persistent pain and remove all endometriotic foci. This procedure improve patient life quality, reduce relapses, control postoperative pain, and eliminate disease. There are cases of persisting abdominal-pelvic pain even after surgery. This makes endometriosis a challenge for specialist and patient. Nutritional education in these patients is essential to reduce the risk of endometrial pathology (Badiu et al., 2018).

3. Dyspareunia related pelvic pain

Childbirth is a risk factor for developing genito-pelvic pain and/or dyspareunia during the postpartum period and potentially in the longer term. These two types of pain can occur simultaneously or sequentially and affect women's lives, including sexual life. The prevalence of postpartum genito-pelvic pain is lower than postpartum dyspareunia pain. Postpartum genito-pelvic pain and dyspareunia are associated with impaired sexual functioning (Rosen & Pukall, 2016). Half of women with endometriosis are experiencing deep dyspareunia. Four

types of deep dyspareunia are proposed in women with endometriosis: type I (directly due to endometriosis); type II (related to a comorbid condition); type III (genito-pelvic pain penetration disorder is primary); type IV (secondary to a combination of types I to III) (Yong et al., 2017). Fear was suggested as diagnostic variable distinguishing vaginismus from dyspareunia. Fear and vaginal muscle tension are significantly greater in the vaginismus group compared to dyspareunia/provoked vestibulodynia. Moreover, behavioral measures of fear and vaginal muscle tension discriminate the vaginismus group from the dyspareunia/provoked vestibulodynia. Genital pain did not differ significantly between the vaginismus and dyspareunia/provoked vestibulodynia groups (Lahaie et al., 2015).

4. Fibromyalgia in chronic pelvic pain patients

Gallagher et al., (2016) aimed to describe a chronic pelvic pain population and to assess centralized pain by a validated fibromyalgia scale, and to evaluate correlation of fibromyalgia phenotype with patient clinical characteristics. 312 women included. Majority were white and employed, and mean age was 35.5±11.7 years. Women with higher fibromyalgia survey scores were younger (34±11), had more days of pain per month and missed days of work, higher pain intensity and interference scores, and significantly more pain with a full bladder and bowel movements. Women with a fibromyalgia phenotype were more likely to have depression, anxiety, and sleep problems. Higher fibromyalgia survey scores in a chronic pelvic pain population were found significantly associated with higher pain severity and pain

interference scores. Similar to other chronic pain conditions, the fibromyalgia phenotype among women with chronic pelvic pain is associated with greater pain morbidity.

5. Irritable Bowel Syndrome in Female Pelvic Pain

Lessa et al., (2013) determined the prevalence of irritable bowel syndrome in women with chronic pelvic pain. 1470 women were interviewed. Independent variables associated with irritable bowel syndrome were age, schooling, duration of pain, sedentary lifestyle, migraine, depression, insomnia, dysmenorrhea, back pain, dyspareunia, history of violence, depression, and intestinal symptoms. The prevalence of irritable bowel syndrome in women with chronic pelvic pain was 19,5%. Pain duration, back pain, history of physical or sexual abuse, and intestinal complaints were more prevalent in the group with irritable bowel syndrome and chronic pelvic pain.

Fibromyalgia and irritable bowel syndrome are common disorders which frequently coexist in women with chronic pelvic pain. Like pelvic pain, these disorders describe symptoms without pathologic findings. Women with chronic pelvic pain have a higher prevalence of fibromyalgia (4-31%) and irritable bowel syndrome (8-41%) than the general population. Aberrant pain processing and psychosocial stressors were implicated in the co-occurrence of these pain syndromes (chronic overlapping pain conditions). Gynecologists should have more education in diagnosis and treatment of these and other chronic overlapping pain conditions to improve care for women (Johnson & Makai, 2018).

6. Pelvic pain and depression

E Siqueira-Campos et al., (2019) investigated the prevalence of anxiety, depression, mixed anxiety and depressive disorder associated with chronic pelvic pain in women. Study was conducted with 100 women with chronic pelvic pain and 100 without chronic pelvic pain. The prevalence of anxiety was 66% in the chronic pelvic pain group and 49% in the controls. Depression was in 63% of the women with chronic pelvic pain and in 38% of the controls. Mixed anxiety and depressive disorder were present in 54% of the chronic pelvic pain group and in 28% of the controls. As a conclusion, prevalence of anxiety, depression and mixed anxiety and depressive disorder were found higher in women with chronic pelvic pain compared to the pain-free controls. Systematic management of psychological factors could improve mental health of these women.

7. Low-back pain and pelvic pain during pregnancy

Low back pain and pelvic girth pain are common in pregnancy and women commonly utilize complementary manual therapies such as massage, spinal manipulation, chiropractic, and osteopathy to manage their symptoms. There is currently limited evidence to support the use of complementary manual therapies as an option for managing low back and pelvic pain during pregnancy (Hall et al., 2016). More than 2/3 of pregnant women experience low-back pain and almost 1/5 experience pelvic pain. Separately or together low-back and pelvic pain increase with advancing pregnancy, interfering with work, daily activities and sleep. There is low-quality evidence that exercise may reduce

pregnancy-related low-back pain and moderate- to low-quality evidence suggest that any exercise improves functional disability. Evidence suggests that acupuncture or craniosacral therapy improves pregnancy-related pelvic pain, and osteomanipulative therapy or a multi-modal intervention (exercise and education) may also helpful (Liddle & Pennick, 2015). Given that pregnancy-related low back and/ pelvic pain occur across the world, and affects the majority of pregnant women, heath care providers need to ensure that standard care provided is meeting women's needs (Close et al., 2016).

8. Acute dysmenorrhoea related pelvic pain

Primary dysmenorrhoea is highly prevalent among women at reproductive age. It may have significant short-term and long-term consequences for women and society (Chen et al., 2015). Acute dysmenorrhoea in women which has been shown to be anatomically negative for endometriosis is a very common condition. It is frequently associated with chronic pelvic pain from uterine origin, including painful uterine contractions and deep dyspareunia.

9. Sexual violence as an acute pelvic pain reason

Almost 20% of women will suffer from sexual abuse at a time during their lives. This is a risk factor for chronic pelvic pain. Specific tools should be used to evaluate sexual abuse and chronic pelvic pain, since these two entities are seldomly reported by patients (Garza-Leal et al., 2021). An evaluation of history may help to prioritize differential diagnosis, which must include a sexual history. Direct questioning about contraception use, sexual activity, and previous sexually

transmitted infections can offer clues to stratify the patient's risk of pregnancy and pelvic inflammatory disease. Also health care professionals must remember to also ask about potential sexual violence. This is especially true for women with high-risk sexual behavior (DiPlacido, 2010). Suppression of unwanted thoughts and emotions and past abuse distinguishes chronic pelvic pain patients from healthy controls. Assisting patients to express distressing emotions may impact on pain levels (Thomas et al., 2006).

10. CONCLUSIONS

There is wide variation in reported outcomes and applied outcome measures in chronic pelvic pain trials. Commonly reported outcomes were pain (pelvic pain, dyspareunia, dysmenorrhoea), life impact (quality of life, emotional functioning, physical functioning), clinical effectiveness (efficacy, satisfaction, cost effectiveness, return to daily activities) and adverse events (surgical, perioperative observations, nonsurgical). There is a lack of studies examining postpartum genito-pelvic pain and dyspareunia together and integrating biomedical and psychosocial risk factors.

Gabapentin is a potential treatment option for chronic pelvic pain in women. Psychological interventions are often recommended added to medical treatment for women with chronic pelvic pain. Fear was suggested as diagnostic variable distinguishing vaginismus from dyspareunia. Higher fibromyalgia survey scores in a chronic pelvic pain population were found significantly associated with higher pain severity and pain interference scores. Fibromyalgia and irritable bowel

syndrome are common disorders which frequently coexist in women with chronic pelvic pain. Prevalence of anxiety, depression and mixed anxiety and depressive disorder were found higher in women with chronic pelvic pain compared to the pain-free controls.

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CHAPTER 15

ADNEXAL MASSES IN WOMEN: A REVIEW

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1. INTRODUCTION

Majority of the adnexal masses are benign but misdiagnosed or mismanaged adnexal masses may result with significant morbidity and mortality. Timely, appropriate laboratory and radiographic studies are important. Adnexal lesion occurrence are frequent in radiology practice and imaging plays a crucial role in appropriately triaging women. Biopsy of adnexal masses is not recommended generally since ovarian cancer is known to spread by direct peritoneal extension. Many tumor markers exist but majority of markers are not specific to one tumor or cancer and many benign conditions cause elevations in tumor markers. “ADNEX”, “ROMA”, “IOTA SR”, “O-RADS” protocols in combination with cancer antigens may help to distinguish benign from malignant tumors.

Adnexal masses are a common finding in women. They must be evaluated appropriately to determine the management course. Majority of the masses have a benign etiology. But, smaller percentage of malignant masses are worrisome and must be ruled out. Misdiagnosed and mismanaged adnexal masses may result with significant morbidity and mortality. Evaluation of an adnexal mass begins with a thorough history and physical exam. Imaging modalities with sonography can aid diagnosing and differentiating adnexal masses. Selected laboratory tests may also help distinguishing malignancy potential. Accumulation of information can set the course of surveillance, medical management, or surgical intervention. When surgical treatment is pursued, minimally invasive approach is needed to be the preferred method to maximize the

benefit and minimize the morbidity for patients. Surgical techniques and management vary with different adnexal mass types, which can range from simple ovarian cysts, endometriomas, ovarian remnants, or suspected ovarian malignancies. It is necessary to have a great breadth and depth of the various laparoscopic techniques for surgically treating the various adnexal mass types (Nezhat et al., 2021).

2. Symptoms

The initial detection and evaluation of an adnexal mass requires a high index of suspicion, a thorough history and physical examination, and careful attention to subtle historical clues. Timely, appropriate laboratory and radiographic studies are important. The frequent symptoms reported by women with ovarian cancer are pelvic or abdominal pain; increased abdominal size; bloating; urinary urgency, frequency, or incontinence; early satiety; difficul eating; and weight loss. These symptoms present for months in big part of patients with ovarian cancer. Occurrance of any of these symptoms daily for >2 weeks, or with failure to respond to appropriate therapy warrant further evaluation. Transvaginal ultrasonography is the standard for adnexal mass evaluation. Findings suggestive of malignancy in an adnexal mass are a solid component, thick septations (bigger than 2 mm), bilaterality, Doppler flow to the solid component of the mass, and presence of ascites. Family physicians can manage many nonmalignant adnexal masses but prepubescent girls and postmenopausal women with an adnexal mass should be referred to a gynecologist or gynecologic oncologist for further treatment. All women, regardless of menopausal

status, should be referred if they have evidence of metastatic disease, ascites, a complex mass, an adnexal mass greater than 10 cm, or any mass that persists longer than 12 weeks (Givens et al., 2009).

Accurate identification of an adnexal mass can ensure optimum management. The RMI (risk of malignancy index 1) can be used as a triaging tool and also for framing a referral policy for adnexal masses. For counseling patients with adnexal masses, the "risk of malignancy index 1" through a better option than the SI (symptom index) does not have a good positive or negative likelihood ratio to either rule out or rule in a diagnosis of malignancy in individual cases. Menopausal status, CA-125, and ultrasound features are much more predictive of the nature of an adnexal mass compared to symptoms making RMI a better tool for triaging and referral and counseling women with adnexal masses (Ray, 2018). The combination of a patient-reported symptom index and refined biomarker panel improves accuracy in the assessment of ovarian cancer in patients with an adnexal mass. This strategy may add a personalized approach to address risk of malignancy to triage patients with an adnexal mass to appropriate care (Urban et al., 2018). The risk of malignancy of benign appearing purely solid adnexal masses in asymptomatic postmenopausal women is low. Conservative management of these lesions might be an option (Alcazar et al., 2017).

3. Ultrasound & Imaging

Adnexal lesion occurrence are frequent in radiology practice and imaging has a crucial role in appropriately triaging women. Current trends toward early detection and characterization increased need for

accurate imaging assessment of adnexal lesions before treatment. Ultrasound is the first-line imaging modality for assessing adnexal lesions but, nearly 20% of lesions are characterized incompletely after ultrasound evaluation. Secondary assessment with MR imaging using the ADNEx MR Scoring System is demonstrated as highly accurate in the characterization of adnexal lesions and in excluding ovarian cancer (Sadowski et al., 2018). Approximately 1/4 of adnexal masses detected at ultrasonography are indeterminate for benignity or malignancy, posing a substantial clinical dilemma (Thomassin-Naggara et al., 2020).

Ovarian masses are among the most frequently identified entities in gynecological practice. Early differential diagnosis is a key factor in the medical management of each patient. Transvaginal ultrasound with additional preoperative testing, such as serum cancer antigen 125 (CA-125) levels and the Risk of Ovarian Malignancy Algorithm (ROMA) score, frequently provide adequate information for a presumptive diagnosis. Minimally invasive surgery as a therapeutic approach is the standard procedure for uncomplicated and benign adnexal masses. Histopathological examination alone, or with immunohistochemical testing supplies more certain diagnosis at the final step of management plan (Ionescu et al., 2018).

Many early stage cases with a large mass or worrisome clinical signs, but for a small subset, the initial presentation is a small, asymptomatic adnexal mass with no other factors that would raise suspicion of cancer. Biopsy of adnexal masses is not recommended generally since ovarian cancer is known to spread by direct peritoneal extension. Therefore, if

a mass is malignant, biopsy could theoretically worsen prognosis. As a result, concern that a mass in an older woman may represent an early cancer leads many women with small masses to undergo unnecessary surgery with accompanying morbidity, despite the fact that the overwhelming majority of these masses are found to be benign. The alternative to urgent surgery for masses of uncertain nature is ultrasound monitoring. Although ultrasound is found ineffective as ovarian cancer screening tool, it is frequently used to evaluate or follow ovarian or adnexal masses once they are detected (Suh-Burgmann & Kinney, 2016). Based on ultrasound examination, all adnexal masses can be divided into three cathegories: 1. Benign, 2. Malignant, 3. indeterminate. Indeterminate adnexal mass is the complex one which even after including color doppler cannot be placed into either cathegory or for which the site of origin cannnot be established. For women with indeterminate adnexal masses MR imaging is the method of choice. In these women, MRI imaging can reduce the number of unnecessary surgery for benign lesions and risk of missing a malignant lesion (Nikolic et al., 2017).

Suh-Burgmann & Kinney, (2016) reviewed the use of serial ultrasound for the management of adnexal masses and propose an approach to monitor overall risk of cancer. Ultrasound monitoring of adnexal masses was found valuable to identify early cancers among women with small masses and asymptomatic and do not demonstrate other signs of cancer such as elevated CA125 or ascites. But, overall risk of cancer for these women was very low. A short-term repeat ultrasound at 6–8 weeks to evaluate for either regression or growth helps to avoids

surgery on transient masses and does not appear to worsen prognosis in the event that the mass represents an early cancer. The presence of significant solid components that demonstrate vascular flow appears to be the ultrasound characteristic for specificity for malignancy. Masses demonstrating clear progression during monitoring should be removed. For stable masses, repeat ultrasound at 3-month intervals, to observe for worrisome growth or changes in complexity is appropriate. But, since the potential benefit in terms of cancer identification wanes with time, the duration of monitoring of stable masses should be limited to 1–2 years in order to limit potential harms from overtreatment and overdiagnosis.

Given the unique intra-peritoneal anatomic location of the adnexa, tubo-ovarian diseases can commonly spread into the peritoneal cavity. Peritoneal seeding may occur in a spectrum of adnexal conditions including infectious diseases, endometriosis, and benign or malignant primary or secondary ovarian tumors. CT is usually the imaging modality on which the concomitant involvement of the peritoneum and the ovary is depicted. First diagnosis to be considered by the radiologist is generally peritoneal carcinomatosis from ovarian cancer but other conditions cited above have also to be in mind and may be suggested on the basis of careful assessment of CT findings or on further MR findings. MRI may indeed help characterize the lesions in some cases (Ognong-Boulemo et al., 2017). Adnexal mass characterization on MRI without the administration of contrast medium has a high accuracy and excellent inter- and intra-reader agreement. Non-contrast studies may

offer a reasonable diagnostic alternative when the administration of intravenous contrast medium is not possible (Sahin et al., 2021).

Adnexal masses are a common presenting concern among women of all age groups. While the majority of adnexal masses are benign, the differentiation of a mass and diagnosis of malignancy can present a dilemma. The use of laboratory studies and tumor markers through minimally invasive means may aid the diagnosis of a mass or refer a decision to specialist. Many tumor markers exist. But the majority of markers are not specific to one tumor or cancer. Many benign conditions cause elevations in tumor markers, which can complicate distinguishing benign and malignant conditions. In recent years, the development of biomarker panels improved diagnostic accuracy for adnexal masses. Algorithms were developed to aid with triaging a patient to continued observation versus referral to a specialist. Merging clinical and laboratory data together is important when diagnosing and managing any patient with an adnexal mass given the many benign and malignant conditions that can cause elevations in tumor markers (Penick et al., 2019).

C-reactive protein serum levels independently predicted the presence of borderline tumor of the ovary and epithelial ovarian cancer in patients with suspicious adnexal masses. C-reactive protein serum levels seem to add value to CA-125 in the preoperative differential diagnosis of adnexal masses and might be particularly in combination with CA-125 clinically useful (Reiser et al., 2017). Elevated levels of CA125 or CA15-3 individually have a high diagnostic value for preoperative

discrimination of benign/malignant adnexal masses. Combination of CA125 and CA15-3 does not present addtive effect. CA19-9 is not an appropriate marker for discrimination of benign/malignant adnexal masses (Bacanakgil et al., 2017).

Adnexal masses can be of varied etiology. It may be benign like luteal cyst, infective like abscess or malignant like ovarian cancer. These masses can be detected on pelvic or abdominal examination and sometimes incidentally found on ultrasonographic evaluation. Adnexal masses have a wide spectrum of clinical, morphological and histological features. Cancer Antigen 125 is a marker in the blood elevated in women with ovarian cancer, but also in people with other medical conditions and in some healthy people. This biomarker can be useful when an ovarian mass is felt on examination or seen on ultrasound and the physician is unsure whether it is ovarian cancer (Dhillon et al., 2020).

4. Ovarian

While outcomes for ovarian cancer patients clearly benefit from centralised, comprehensive care in dedicated cancer centres, majority of patients still do not have access to appropriate specialist treatment. Any accuracy improvement in the current triaging and referral pathways by using new imaging tests or biomarkers is valuable to optimise appropriate selection of patients for such care. Current evidences show that such tests are now available, but still waiting for acceptance and widespread adoption (Kaijser, 2015). Distinguishing benign adnexal masses from malignant tumors is important to improve

patient survival rates. The International Ovarian Tumor Analysis (IOTA) group developed a model named the Assessment of Different NEoplasias in the adneXa (ADNEX) (Poonyakanok et al., 2021). MRI, coupled with the use of the ADNEX MR scoring system, can accurately classify adnexal masses into low-risk (ADNEX MR score <4) or high-risk (ADNEX MR score ≥4) group, thereby allowing for appropriate preoperative counseling and planning for surgery (Ruiz et al., 2016).

The ROMA (Risk of Ovarian Malignancy Algorithm) algorithm showed best diagnostic performance to distinguish epithelial ovarian cancer from benign ovarian disease in the study of Terlikowska et al., 2016). They found the high specificity of HE4 and CA125 while differentiating ovarian benign diseases from epithelial ovarian cancer in postmenopausal women and the high sensitivity of CA125 in detecting epithelial ovarian cancer in premenopausal patients. Xie et al., (2022) showed that a combination of International Ovarian Tumor Analysis Simple Rules (IOTA SR) or Ovarian-Adnexal Reporting and Data System (O-RADS) in combination with Cancer Antigen 125 (CA125) may improve the ability to distinguish benign from malignant ovarian tumors.

Poonyakanok et al., (2021) evaluated the performance of the ADNEX model to distinguish benign and malignant tumors at a cutoff value of 10%. The prospective diagnostic study included 357 patients with an adnexal mass who were scheduled for surgery. All patients recieved ultrasonography. Serum CA125 was also measured. Data were calculated by the ADNEX model via an IOTA ADNEX calculator. Of

the 357 patients, 296 had benign tumors and 61 had malignant tumors. The area under the receiver operating characteristic curve for using the ADNEX model was 0.97. At a 10% cutoff, the sensitivity was 98.4% and specificity was 87.2%. The best cutoff value was at 16.6% in our population. The performance of the ADNEX model in differentiating benign and malignant tumors was found excellent. Women with adnexal mass suspected of ovarian malignancy are likely to benefit from consultation with a gynecologic oncologist, but imaging and biomarker tools to ensure this referral show low sensitivity and may miss cancer at critical stages (Coleman et al., 2016).

5. Premenopausal

Practitioners may frequently encounter adnexal masses in premenopausal women. Adnexal masses can represent a wide variety of etiologies and may represent a diagnostic dilemma. Following the observation of adnexal mass, initial work up must focus on identifying acute pathology followed by determining the malignancy risk. Pelvic ultrasound is still the mainstay for adnexal mass evaluation in premenopausal patients. When ultrasounds findings are indeterminate, MRI is the next imaging choice. Malignancy evaluation should include serum marker screening. Aspiration of adnexal masses is frequently avoided due to the lack of therapeutic benefit and tumor seeding risk. If ultrasound findings are suggestive of benign disease, conservative management, including repeat imaging, should be considered. If the clinical suspicion for malignancy is high, gynecologic oncologist referral is warranted. In other patients (evaluation of their adnexal mass

remains unclear), surgical excision with care (not to disrupt the integrity of the mass) should be performed for pathologic diagnosis (Hall & Randall, 2015). Adnexal masses in the reproductive age group demonstrate the greatest histologic variance that is mostly benign. Clinical judgement is important to predict if a mass is likely to be benign or malignant based on risk factors, imaging appearances, and tumor markers. If suspicion of malignancy is high, referral to a gynecologic oncologist may improve patient's survival (Liwan & Hong, 2019).

HE4 have superior specificity compared to CA-125 for the differentiation of benign and malignant adnexal masses in premenopausal women (Holcomb et al., 2011). Alcazar et al., (2011) assessed if a single determination of the serum cancer antigen 125 (CA-125) level provides additional information to sonography for specific diagnosis of benign adnexal masses in premenopausal women. They conducted a retrospective study including 1.058 premenopausal women (mean age, 34.8 years) with histologically proven benign adnexal masses. All women had undergone transvaginal sonography and serum CA-125 determination within one week before surgery and tumor removal. Cancer antigen 125 screening did not add useful information for specific diagnosis of benign adnexal tumors, except for endometrioma. An elevated CA-125 level significantly increases the probability of such a lesion.

6. Pregnancy

Adnexal masses in pregnancy are often incidentally detected during sonography and most resolve spontaneously by early second trimester (Surampudi et al., 2015). The incidence of adnexal masses, due to large use of ultrasound during pregnancy, has considerably increased during last years. Large percentage of ovarian masses found during pregnancy consists in simple cysts and tend to disappear spontaneously at pregnancy. There are masses persist in 2nd and 3rd trimester that need to be monitored and, sometimes surgically removed. If the mass increases in size, it is sometimes an indication for delivery via cesarean section. Adnexal masses diagnosed in pregnancy are generally benign. Ovarian cancer is the second gynecological tumor for incidence after cervical cancer during pregnancy. Most patients are clinically asymptomatic and diagnosis is often a random finding during ultrasound for pregnancy follow-up. Sometimes, ovarian mass finding requires other imaging technique such as MRI. Computed tomography is avoided during pregnancy due to negative effects on fetus. For treatment option, a multidisciplinary approach is required considering both mother and fetus. Sometimes differential diagnosis between benign masses and malignancy is not feasible through imaging, so that surgical intervention with histological examination is mandatory, even during pregnancy. Although ovarian cyst torsion, hemorrhage, or rupture is not common during pregnancy, some women may require emergency surgery for these complications. Both open surgery and laparoscopy can be performed considering mass diameter, gestational age, and surgical expertise (Martone et al., 2021).

7. CONCLUSIONS

Biopsy of adnexal masses is not recommended generally since ovarian cancer is known to spread by direct peritoneal extension. Many tumor markers exist but majority of markers are not specific to one tumor or cancer and many benign conditions cause elevations in tumor markers. “ADNEX”, “ROMA”, “IOTA SR”, “O-RADS” protocols in combination with cancer antigens may help to distinguish benign from malignant tumors. If the clinical suspicion for malignancy is high, gynecologic oncologist referral is warranted. HE4 have superior specificity compared to CA-125 for the differentiation of benign and malignant adnexal masses in premenopausal women.

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CHAPTER 16

CERVICAL CANCER

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INTRODUCTION

Cervical cancer is the fourth most frequent malignancy in women all over the World (Fowler JR). In the United States, it is the third most common cause of gynecological cancer diagnoses and fatalities (Siegel). Human Papilloma Virus (HPV) can be detected in 99.7% of cervical cancers (Walboomers). In the fight against cervical cancer, both primary and secondary prevention are vital (Pimple). Primary prevention and screening is the best method to reduce cervical cancer and mortality from cervical cancer. Since HPV infection is a sexually transmitted infection, cervical cancer is a preventable disease. Prevention of HPV transmission constitutes primary prevention. Primary prevention is achieved through HPV vaccines and education of the population at risk. Treatment of cervical preinvasive lesions detected by screening with HPV test and cytology constitutes secondary prevention. The most common histological type of cervical cancer is squamous cell type with a frequency of 70%, while the second type is adenocarcinoma with a frequency of 25% (Ries L).

Epidemiology

According to the 2020 data of the World Health Organization's Global Cancer Observatory (GLOBOCAN), it is estimated that 604.127 women were diagnosed with new cervical cancer in 2020 and 342.000 women died due to cervical cancer. In the United States, approximately 4,000 women die annually from cervical cancer. Mortality rates are much higher in populations with low socioeconomic status, such as African-Americans and Hispanics. Cervical cancer is the second most

common cancer among women in developing countries, and the third in cancer-related deaths (Sung). Cervical cancer is a serious public health issue in Europe, with 61,072 diagnoses and 25,829 deaths reported in 2018 (Bruni L AG).

Risk factors

There are two main histological types of cervical cancer. These are squamous cell carcinoma and adenocarcinoma. These two types of cervical cancer have many of the same risk factors, along with preinvasive disease, which is the precursor to cervical cancer. These risk factors are divided into two groups as those associated with HPV and those without:

- Associated with HPV: early onset of sexual activity, multiple sexual partners, a high-risk sexual partner, history of sexually transmitted infections such as chlamydia trachomatis, genital herpes, first birth and multiparity at an early age, vulvar or vaginal squamous intraepithelial neoplasia or history of cancer are immunosuppressive conditions such as HIV(8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. International journal of cancer, 120(4), 885–891.).
- Those not associated with HPV are: low socioeconomic level (Yu L), use of oral contraceptives (International Collaboration of Epidemiological Studies of Cervical Cancer), smoking (increases the risk of squamous type cervical cancer, but does not increase the risk of adenocarcinoma) (8,097 women with squamous cell

carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. International journal of cancer, 120(4), 885–891.) and genetic predisposition (Hemminki). IL1B C511T and T-31C, especially higher interleukin-1β level, TNFA G-308A, HLA gene polymorphisms, IL12A rs568408 GA/AA and IL12B rs3212227 AC/CC variant genotypes are associated with increased risk of cervical cancer and DAPK1 promoter methylation; can be used as a biomarker during cervical carcinogenesis (Chen).

Pathogenesis

HPV is the main factor in the development of cervical neoplasia and can be detected in 99.7 percent of cervical cancers (Walboomers). Of the more than 40 identified genital mucosal HPV types, about 15 are known to be oncogenic. HPV is divided into two according to the oncogenic type:

- High-risk (oncogenic or cancer-related) types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82.
- Low-risk (non-oncogenic) types: 6, 11, 40, 42, 43, 44, 54, 61, 72, 81.

The beginning of the development of cervical cancer is the infection of the metaplastic epithelium in the cervical transformation zone (the junction between the squamous epithelium of the ectocervix and the glandular epithelium of the endocervical canal) with oncogenic HPV. It is well documented that approximately 90% of HPV infections clear

within 2 years of infection and remain in only 10% of women (Franco). With the persistence of this HPV infection, a clone of epithelial cells progresses to a precancerous lesion. As a result, carcinoma develops and invades beyond the basement membrane (Schiffman).

Histopathological types

Histopathological types of cervical cancer are shown in Table 1(Hitchcock A. Tumors of the cervix):

Table 1. Histopathologic types of cervical cancer

A. Squamous cell carcinoma
Large cell, keratinizing squamous cell carcinoma
Large cell, non-keratinizing squamous cell carcinoma
Verrucous carcinoma
Papillary squamous and transitional cell carcinoma
Lymphoepithelioma-like carcinoma
B. Adenocarcinoma
Mucinous, endocervical variant
Mucinous, intestinal type, signet ring variant
Mucinous, adenoma malignum (minimal deviation variant)
Mucinous, villoglandular adenocarcinoma (well differentiated)
Endometrioid type
Clear cell type
Papillary serous type
Mesonephric type
C. Adenosquamous carcinoma
D. Adenoid cystic carcinoma
E. Neuroendocrine (carcinoid, small cell, large cell)
F. Undifferentiated carcinoma
G. Mixed epithelial and mesenchymal tumors

While squamous cell carcinoma is detected with a frequency of 70-75%, adenocarcinoma is detected with a frequency of 25%. The incidence of adenocarcinoma has increased in recent years, especially in younger patients (Adegoke) and other types are rare.

Clinical findings

Although early cervical cancer is frequently asymptomatic, screening is critical. In asymptomatic patients, if a visible lesion is detected as a result of cervical cancer screening or pelvic examination, cervical cancer can be detected incidentally. The most common complaints are irregular or heavy vaginal bleeding and postcoital bleeding (Frumovitz M). Some patients present with vaginal discharge that may be watery, mucoid, or purulent and foul-smelling. This is a nonspecific finding and can be confused with vaginitis or cervicitis. Pelvic or low back discomfort that radiates to the backs of the lower extremities may be symptoms of advanced illness. Intestinal or urinary symptoms such as compression complaints, hematuria, hematochezia, or vaginal passage of urine or stool are rare and suggest advanced disease.

Diagnostic methods

Cervical cancer usually arises from the transformation zone (the junction between the squamous epithelium of the ectocervix and the glandular epithelium of the endocervical canal). The lesion may present as superficial ulceration, exophytic tumor of the exocervix, or infiltration of the endocervix. Endophytic tumors can result in an enlarged, smooth, and firm-looking cervix, often referred to as a

"barrel-shaped cervix." About half of cervical adenocarcinomas are exophytic, others enlarge or ulcerate the cervix extensively, and about 15 percent have no visible lesions as the carcinoma is within the endocervical canal. The diagnosis of cervical cancer is made based on the histological evaluation of the cervical biopsy.

Physical examination: Every patient with symptoms suggestive of cervical cancer should have a pelvic examination performed. Visualization of the cervix on speculum examination may reveal a normal appearance or a visible cervical lesion; large tumors may appear to completely replace the cervix. Any visible lesion should be biopsied regardless of previous benign cervical cytology results (Partridge). The only visible lesions that do not require biopsy are nabothi cysts only when this diagnosis is confirmed by an experienced examiner. A comprehensive pelvic examination, which includes a rectovaginal examination along with assessment of tumor size and vaginal or parametrial involvement, is required to stage cervical cancer.

Cervical cytology: Cervical cytology is the primary method for cervical cancer screening and is the method of choice when cervical cancer is suspected.

Cervical biopsy and colposcopy: In patients with a largely visible lesion, a suspected cancer diagnosis should be confirmed by biopsy of the lesion. We prefer to take the biopsy from the most suspicious-looking area of the lesion to avoid largely necrotic areas, as these are often non-diagnostic. Any unusually hard or wide cervix should be sampled by punch biopsy and endocervical curettage, even if cervical

cytology testing does not show evidence of neoplasia. Biopsy may cause bleeding in patients with large lesions. Therefore, hemostatic agents such as Monsel solution should be prepared at the biopsy site. Patients without a visible lesion (eg, symptomatic, abnormal cervical cytology) can undergo colposcopy with the aim of random 4-quadrant biopsy. If malignancy is suspected in patients in clinics where colposcopy is not available, guided biopsy can be performed with the help of visual inspection methods.

Other diagnostic methods: Imaging studies are not typically part of the diagnosis of cervical cancer, although some may be used for staging and evaluation of patients with known malignancies.

Differential diagnosis

The differential diagnosis of cervical cancer includes irregular or heavy vaginal bleeding, vaginal discharge, or other conditions that result in a visible cervical lesion. Postcoital bleeding, the most specific presentation of cervical cancer, can also result from cervicitis and other benign conditions. Benign tumor-like lesions that can mimic cervical cancer include nabothian cysts, mesonephric cysts, cervical ectropion, ulcers associated with sexually transmitted infections, reactive glandular changes from inflammation, and endometriosis.

Screening and prevention

Because of the epidemiology of HPV and its role in cervical cancer, it has led to the development of two main strategies for cervical cancer prevention and early detection: (Sung) HPV vaccination; and (Bosch)

screening for precancerous lesions. The World Health Organization (WHO) has called for a global initiative to eradicate cervical cancer as a public health problem by implementing the following 90%-70%-90% triple column intervention strategy before 2030 (World Health Organization. Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem. WHO; 2020. Accessed April 17):

- Vaccination: 90% of girls fully vaccinated with the HPV vaccine by the age of 15;
- Screening: 70% of women screened using a high-performance test by the age of 35, and again by the age of 45;
- Treatment: 90% of women with pre-cancer treated and 90% of women with invasive cancer managed.

The estimated worldwide cross-sectional prevalence of HPV among healthy women over the age of 30 is approximately 11.7%. The highest is in Sub-Saharan Africa, around 24%, and the country-specific prevalence ranges from 2% to 42% globally (Bruni L & ts/XWX.pdf). The prevalence of specific cross-sectional HPV peaks at 25% in women younger than 25 years, suggesting that the infection is predominantly sexually transmitted after sexual intercourse. Therefore, prophylactic HPV vaccination as a preventive strategy should target women before initiating sexual activity and should focus on girls aged 10-14 years. At the population level, there is evidence for the effectiveness of the HPV vaccine in terms of reduced prevalence of high-risk types of human papillomavirus, anogenital warts, and high-grade cervical abnormalities

(CIN2+) caused by vaccine strains among young women; it also provides some cross protection against non-vaccine types (Drolet).

Cervical cancer screening strategies have been used effectively to date and these screening methods are: traditional cytology (Pap smear); liquid-based cytology (LBC) and HPV testing in recent years; and visual inspection with acetic acid (VIA) in low-income countries. Although periodic Pap smear screening has resulted in a significant reduction in cervical cancer risk in high-income countries, it requires repeated testing to compensate for poor sensitivity and is not viable in poorly organized settings. Therefore, lack of coverage and quality assurance leads to suboptimal results (Sankaranarayanan R. (2014). Screening for cancer in low- and middle-income countries. Annals of global health). HPV-based screening has higher sensitivity and accuracy, lower variability, and better reproducibility compared to conventional or liquid-based screening. Along with the reduction of HPV infections in vaccinated populations, many healthcare systems are moving to primary HPV screening, which allows higher negative predictive value, longer screening intervals, and even a single lifetime screening in low-resource settings (Ronco; Sankaranarayanan).

Recent European guidelines strongly recommend primary HPV-based screening over standard cytology-based screening (Bosch). Observational screening with acetic acid is particularly suitable for the single-visit approach, and WHO has published guidelines for the application of the single-visit approach in public health settings (World Health Organization. WHO Guidelines for Screening and Treatment of

Cervical Precancerous Lesions for Prevention. WHO; 2013. Accessed April 16). Prior to the initiation of a cervical cancer screening program in a country, target age group, screening test and screening intervals, methods of reaching target women, management of screening positive women (triage and treatment or single visit approach), treatment modalities for CIN lesions (cryotherapy, thermal ablation, loop electrosurgery) Excision procedure (LEEP) and for common cervical cancers detected by screening, it is important to have policy and management guidelines that clearly state the criteria for the type of treatment (World Health Organization. WHO Guidelines for Screening and Treatment of Cervical Precancerous Lesions for Prevention. WHO; 2013. Accessed April 16; World Health Organization. WHO Guidelines for the Use of Thermal Ablation for Cervical Pre-Cancer Lesions. WHO; 2019. Accessed May 2).

Cervical cancer staging

Invasive cervical cancer spreads, usually locally, directly to the parametrium, vagina, uterus, and adjacent organs such as the bladder and rectum. However, it spreads along the lymphatic channels to regional lymph nodes, namely the obturator, external iliac, internal iliac, and subsequently iliac and para-aortic nodes. In addition, distant metastases such as the lungs, liver and skeletal system can also be seen by hematogenous route. Cervical cancer was clinically staged for cancer by FIGO in 1958, and the pathological (TNM) staging system was later used to document nodal and metastatic disease status. In 2018, the FIGO Committee on Gynecological Oncology again revised staging

as clinical, radiological, or pathological findings are available. The new staging system is shown in Table 2 (Bhatla).

Table 2. FIGO staging of cancer of the cervix uteri (2018)

Stage			Description
I			The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
	IA		Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤5 mma
		IA1	Measured stromal invasion ≤3 mm in depth
		IA2	Measured stromal invasion >3 and ≤5 mm in depth
	IB		Invasive carcinoma with measured deepest invasion >5 mm (greater than Stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter
		IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
		IB2	Invasive carcinoma >2 and ≤4 cm in greatest dimension
		IB3	Invasive carcinoma >4 cm in greatest dimension
II			The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic Wall
	IIA		Involvement limited to the upper two-thirds of the vagina without parametrial involvement
		IIA1	Invasive carcinoma ≤4 cm in greatest dimension
		IIA2	Invasive carcinoma >4 cm in greatest dimension
	IIB		With parametrial involvement but not up to the pelvic wall
III			The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes

	IIIA		The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
	IIIB		Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
	IIIC		Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases), irrespective of tumor size and extent (with r and p notations)
		IIIC1	Pelvic lymph node metastasis only
		IIIC2	Para-aortic lymph node metastasis
IV			The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
	IVA		Spread of the growth to adjacent pelvic organs
	IVB		Spread to distant organs

The revised FIGO staging is closely aligned with the latest TNM staging (Olawaiye). In this staging system, decisions are made according to imaging methods and pathology reports.

Diagnosis and evaluation

Microinvasive cervical cancer: The diagnosis of stages IA1 and IA2 is made by microscopic examination of the pathological specimen in the trachelectomy or hysterectomy specimen, either as a cone biopsy obtained by LEEP containing the entire lesion or by cold knife conization. The depth of invasion should not be more than 3 or 5 mm, respectively, from the epithelial floor. Boundaries should be reported

as negative for disease. If the margins of the cone biopsy are positive for invasive cancer, the patient will be Stage IB1 (Park).

Invasive cervical cancer: Punch biopsy, loop biopsy or conization may be required for diagnosis in visible lesions. Clinical evaluation of the case is the first step in staging. According to the new staging system, imaging methods such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) can be used to learn tumor size and lymph node status in order to investigate local or systemic spread. MRI is the best method for radiological evaluation of primary tumors larger than 10 mm (Patel-Lippmann). For the detection of nodal metastases larger than 10 mm, PET-CT shows better accuracy than CT and MRI, with false-negative results in 4-15% of cases (Havrilesky; Sakurai; Yang).

Management of cervical cancer

Treatment of cervical cancer is surgery or radiation therapy in the early stage, and radiotherapy and chemotherapy in the advanced stage.

Microinvasive carcinoma: As surgical treatment, it is suitable for the early stages (IA1, IA2) where cervical conization, trachelectomy, simple hysterectomy or radical hysterectomy can be selected according to the fertility status of the patient. Pelvic lymphadenectomy or sentinel lymph sampling is also recommended (Bouchard-Fortier; Coutant). If fertility-preserving surgery is performed, it is applied for 2 years with 3-month pap smear, followed by 3 years with 6-month follow-ups. If

the results are normal, they are followed up normally after 5 years (Marth).

Invasive cervical carcinoma: Surgical treatment is the preferred method for the treatment of stage IB1, IB2 and IIA1 lesions. It usually consists of pelvic lymphadenectomy and radical hysterectomy (Landoni). FIGO Stage IB1 is considered low risk by the following criteria: less than 50% cervical stromal invasion and no suspicious lymph nodes on imaging. The standard treatment is radical hysterectomy, but in these cases modified radical hysterectomy may be considered. Pelvic lymphadenectomy should always be included because of the high frequency of lymph node involvement (van Meurs; Webb). It can be applied in nerve-sparing surgery (Roh). A radical trachelectomy indicated for Stage IA2–IB1 tumors can be performed in young women seeking fertility preservation (Abu-Rustum). Trachelectomy can be performed by open abdominal, vaginal or minimally invasive means. In FIGO Stages IB2 and IIA1 cervical cancer, surgery or radiotherapy may be chosen as primary therapy, depending on other patient factors and local sources, as both have similar outcomes. Advantages of surgical treatment are (Sung) that it is possible to precisely determine the postoperative stage on the basis of histopathological findings, thus allowing individualization of postoperative treatment;(Bosch) that it is possible to treat cancers that are likely to be radiotherapy-resistant; and (IARC Working Group. Human Papillomaviruses: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer. Accessed May 2 & mono90.pdf) the

possibility of preserving ovarian function. The role of SLN mapping in cervical cancer is still experimental and more evidence is needed to incorporate it into routine practice. Tumors are larger in stage IB3 and IIA2 and there is a high probability of high risk factors such as positive lymph nodes, positive parameters or positive surgical margins that increase the risk of recurrence and require adjuvant radiation after surgery. Other risk factors that increase the risk of pelvic recurrence even if nodes are not included include: largest tumor diameter >4 cm, LVSI, and invasion of the outer third of the cervical stroma (Rotman; Sedlis). In such cases, adjuvant full pelvic irradiation reduces the rate of local failure and improves progression-free survival compared to patients treated with surgery alone (Sedlis). However, dual modality therapy increases the risk of major morbidity for the patient. Therefore, the method of treatment should be determined according to the availability of resources and factors related to the tumor and the patient. Concurrent platinum-based chemoradiation (CCRT) is the treatment of choice for Stage IB3 to IIA2 lesions. FIGO Stage IVA or recurrence, rarely, patients with Stage IVA disease may have only central disease without involvement up to the pelvic side wall or distant spread. In such cases or in such a recurrence, pelvic exenteration can be considered, but it usually has a poor prognosis (Benn; Estape; Morley).

Radiotherapy treatment management

Most patients in low-income countries present with locally advanced cervical cancer, in which surgery plays a limited role. In the last two decades, the development of sophisticated planning and

implementation techniques and the increase in computer technology and imaging have prompted the application of radiotherapy treatment, resulting in improved clinical outcomes and reduced toxicity (Dutta S; Harkenrider MM). Although the role of dual therapy modality is not recommended, it can also be used as adjuvant therapy to prevent local recurrence in operated patients and as palliative therapy to relieve distressing symptoms in patients with incurable advanced cancer.

Radiation therapy for early-stage disease (FIGO Stages IA, IB1, IB2, and IIA1): Although surgery is preferred in early stage disease, radiotherapy gives equally good results in terms of local control and survival in cases with contraindications to surgery or anesthesia. Treatment decision should be made on the basis of clinical, anatomical and social factors. Patients with microinvasive disease have been treated with intracavitary radiation therapy (ICRT) alone with good results if surgery is contraindicated due to medical problems.

FIGO Stages IB3 and IIA2: Although applicable, surgery is not recommended as first-line therapy, as 80% of Stage IB3 and IIA2 patients require postoperative radiotherapy or CCRT (Landoni). It is well known that the addition of adjuvant radiotherapy to surgery increases morbidity and thus impairs quality of life (Yeo RMC). In addition, combined modality therapy will unnecessarily overload surgical and radiation facilities that are already understaffed in low-resource countries. Therefore, CCRT is the standard of care for Stage IB3 and IIA2 disease. CCRT includes external radiotherapy and intracavitary brachytherapy (Small).

FIGO Stages IIB–IVA: CCRT is considered standard therapy for patients with locally advanced cervical cancer based on the results of large randomized trials testing the addition of chemotherapy to the pelvic region (Peters WA; Rose; Sardi). A weekly infusion of cisplatin (40 mg/m2 per week with appropriate hydration) for 5-6 cycles during external beam therapy is a commonly used concomitant chemotherapy regimen (18 randomized trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 26(35), 5802–5812.; Y. S. Kim, Shin, S. S., Nam, J. H., Kim, Y. T., Kim, Y. M., Kim, J. H., & Choi, E. K. (2008). Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy for locally advanced cervical cancer. Gynecologic oncology, 108(1), 195–200.). For patients unable to receive platinum chemotherapy, 5-fluorouracil-based regimens are an acceptable alternative (Y. S. Kim, Shin, S. S., Nam, J. H., Kim, Y. T., Kim, Y. M., Kim, J. H., & Choi, E. K. (2008). Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy for locally advanced cervical cancer. Gynecologic oncology, 108(1), 195–200.; Lanciano). Data on toxicity associated with concomitant chemotherapy and extended field irradiation are limited (Varia).

FIGO Stage IVB/ distant metastases: distant metastatic disease is rare and has been reported in approximately 2% of cases. A management plan should consider that the median survival time for distant metastatic

disease is approximately 7 months. Chemoradiotherapy may respond better than systemic chemotherapy, with overall and disease-free survival of 69% and 57%, respectively, reported in para-aortic and supraclavicular lymph node-positive patients (J. Y. Kim, Kim, J. Y., Kim, J. H., Yoon, M. S., Kim, J., & Kim, Y. S. (2012). Curative chemoradiotherapy in patients with stage IVB cervical cancer presenting with paraortic and left supraclavicular lymph node metastases. International journal of radiation oncology, biology, physics, 84(3), 741–747.). Currently, prophylactic extended field radiotherapy has no role in locally advanced cervical cancer (Varia). In the case of para-aortic nodes, concomitant chemotherapy with prophylactic extended-field radiotherapy should be used. Intensity modulated radiation therapy can be used to reduce toxicity in these patients. Despite limited response rates, cisplatin has been the standard chemotherapy used in the setting of distant metastatic disease. Cisplatin can be combined with taxanes, topotecan, 5-fluorouracil, gemcitabine or vinorelbine (Monk). The combination of carboplatin-paclitaxel has also been successful in these cases.

Radiotherapy therapy after incomplete surgery

Invasive cervical cancer may be found during pathological evaluation of a specimen from a simple hysterectomy for an apparently benign condition. Inadvertently, simple hysterectomy is considered inadequate surgery for invasive cervical carcinoma, and subsequent treatment is required for all these cases. In such a situation, extent of disease should be assessed by PET/CT scan, if available, or pelvic and abdominal CT

or MRI scan and chest imaging. The next treatment plan is evaluated according to histological and radiological findings.

Post-treatment follow-up

In a systematic review of 17 retrospective studies that followed women treated for cervical cancer, the median time to recurrence ranged from 7 to 36 months after primary treatment (Elit). Therefore, closer clinical follow-up in the first 2-3 years after treatment is important. Routine follow-up visits are recommended every 3-4 months for the first 2-3 years, then every 6 months for up to 5 years, and then annually for life. At each visit, history taking and clinical examination are performed to detect treatment complications and psychosexual morbidity, as well as to evaluate for recurrent disease. Routine imaging is not indicated. Women under the age of 50 who have lost ovarian function should be considered for menopausal hormone therapy.

Recurrent disease

Local recurrences may occur in the pelvic or para-aortic lymph nodes, the patient may develop distant metastases, or a combination of these. The risk of both pelvic and distant insufficiency increases in proportion to tumor volume. Most recurrences occur within 3 years and the prognosis is poor as most patients die from progressive disease and uremia is the most common terminal event (Eifel; Fagundes). The treatment plan depends on the patient's performance status, the location of the tumor, and the extent of treatment.

Palliative care

Symptom control is the foundation of palliative care and plays an important role in maintaining quality of life. Common symptoms and signs of advanced cervical cancer include pain, ureteral obstruction causing kidney failure, bleeding, foul-smelling vaginal discharge, lymphedema, and fistula. Patients need support from relevant clinical services, as well as psychosocial care and support for their families and caregivers. Short-term radiotherapy is very effective in relieving unpleasant symptoms.

Cervical cancer during pregnancy

A multidisciplinary team is required to effectively manage these patients. To respect the patient's wishes, the treatment plan should be discussed with the patient, and ideally with their spouse. Cervical cancer in pregnancy is treated in the same way as it is treated in non-pregnant patients. Patients are treated as soon as they reach 16-20 weeks of pregnancy. The treatment may be surgery or chemoradiotherapy, depending on the stage of the disease. Radiation often causes the conceptus to fall on its own. From the end of the second trimester, surgery and chemotherapy can be used while maintaining pregnancy in selected cases (Amant). When the diagnosis is made after 20 weeks of gestation, it has not been shown to have any adverse effect on prognosis compared to non-pregnant patients, and delaying definitive treatment is a valid option for Stages IA2 and IB1 and 1B2 (Duggan; Hunter). Timing of birth requires a balance between the health of the mother and fetus. In a tertiary center with appropriate neonatal care, delivery is

performed by classical cesarean section and radical hysterectomy, when the delivery is made at the latest 34 weeks of gestation. For more advanced disease, the effect of delay in treatment on survival is unknown. In women with locally advanced cervical cancer, neoadjuvant chemotherapy can be applied to prevent disease progression when a delay in treatment is planned (Boyd; Tewari). As a result, in the future, an appropriate combination of HPV vaccination and cervical cancer screening has an important role in eliminating cervical cancer.

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CHAPTER 17

SEX CORD-STROMAL TUMORS OF THE OVARY: A REVIEW

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1. INTRODUCTION

Sex cord-stromal tumors (SCSTs), can consist of cells from the sex cord, stromal cells, or both. Some of them are hormonally active tumors. It produces steroid hormones, especially androgens and estrogens, and may therefore show signs of virilization or estrogen excess(Busquets et al., 2010; Varras et al., 2011). They occur less frequently than tumors of epithelial cell and germ cell origin. Benign ovarian SCSTs account for <4 percent of ovarian benign neoplasms and malignant ovarian SCSTs account for <8 percent of ovarian malignant neoplasms. Unlike epithelial ovarian cancers, most patients with malignant SCST are diagnosed with early-stage disease(Quirk & Natarajan, 2005).

The tumor usually has a low-grade histology, lymph node metastases are rare, and the prognosis is often good. However, some tumors show an aggressive course and have fatal consequences(Abu-Rustum et al., 2006; Brown et al., 2009; Thrall et al., 2011). Many patients with SCST present with an adnexal mass or symptoms caused by hormones secreted by the tumor. The primary treatment is surgical excision. Chemotherapy is rarely necessary, as they often have only one ovary disease and have a low malignant potential.

2. EPIDEMIOLOGY

They are rare neoplasms that typically appear in the first two to thirty years of life. Adult granulosa cell tumors, which peak at 50-60 years of age, are the exception. Surveillance, Epidemiology, and End Results

(SEER) In the United States national cancer database, the incidence of SCST is 0.20 per 100,000 women. The mean diagnosis was 50 years old, 61 for epithelial ovarian cancer. 12 percent of patients were younger than 30 years old and 57 percent were between 30 and 59 years old. Interestingly, the risk of development was found to be 2 times higher in black women(Quirk & Natarajan, 2005). Being older than 40 years at last birth and less than 10 years since last birth has been associated with a reduction in SCST risk(Sköld et al., 2020). SCSTs typically arise from granulosa, theca, sertoli, and leydig cells and their surrounding fibroblasts.

There are no fully explained risk factors. While it is associated with hyperestrogenic conditions (obesity, etc.), smoking, oral contraceptive use, and parity-preserving were identified in a 2009 case-control study(Boyce et al., 2009). The etiology of SKSTs is still not well known. However, FOXL2 gene mutation has been detected in adult-type granulosa cell tumors. The FOXL2 mutation was found positive in 86 (97%) of 89 adult-type GCTs (granulosa cell tumors)(Shah et al., 2009).

3. CLINICAL PRESENTATION AND DIAGNOSIS

a) Symptoms And Physical Examination

Symptoms usually occur with the effect of abdominal and pelvic mass. Sometimes patients can be encountered due to imaging for another condition. It usually presents with secondary amonorrhea in adolescents. Patients diagnosed with hormonal complaints are more

likely to have early-stage disease(Schneider et al., 2003). In adult women, menstrual irregularities and postmenopausal bleeding are the most common symptoms. The classic onset of the disease is postmenopausal women who present with symptoms of androgen excess and an adnexal mass(Chan et al., 2005).

b) Laboratory

Testosterone and androstenedione may be elevated in women with virilization symptoms. A testosterone level of 150 g/dl and dehydroepiandrosterone sulfate (DHEAS) over 8000 g/L suggests the possibility of an androgen-secreting tumor(Carmina et al., 2006). But most patients are not tested for tumor markers preoperatively, even if there is a suspicion of SCSTs. Inhibin A and B, estradiol, alpha fetoprotein and steroid hormones are used as tumor markers.

c) Imaging And Diagnostic Procedures

Macroscopic appearances of SCSTs vary from small solid masses to large multicystic masses. Granulosa cell tumors often show semi-solid features on ultrasound. However, they are difficult to distinguish from epithelial ovarian tumors. The endometrial cavity may have thickened due to increased estrogen. Although CT or MRI are used, there is no perfect radiological method to diagnose these tumors (Jung et al., 2005).

d) Diagnostic Procedures

Ovarian masses thought to be and malignant should remove for definitive diagnosis. Surgery is essential not only for diagnosis, but also

for staging and treatment. The biopsy performed with imaging guidance has no diagnostic value. Observation with the help of laparoscopy or laparotomy does not benefit diagnosis. lSCSTs are distinguished from other ovarian tumors by inhibin immunohistochemistry evaluation(Cathro & Stoler, 2005). SCSTs should be considered if there is an adnexal mass and endocrine problem in the patient. FOXL2 mutation analysis can be helpful for diagnosis. However, more work is needed on this subject(Kommoss et al., 2014).

4. HISTOPATHOLOGY AND CLASSIFICATION

SCSTs originate from the ovarian sex cords and mesenchymal cells. The classification of SCSTs by the World Health Organization (WHO) is shown in the table(Table 1)(Vivien W Chen et al., 2003).

Table 1. Who Histologic Classification Of Sex-Cord-Stromal Tumors

SEX-CORD-STROMAL TUMORS	
1. Granulosa-stromal cell tumors	a) Granulosa-Stromal cell tumors
	• Adult type
	• Juvenile type
	b) Thecoma-Fibroma group
	• Thecoma
	• Fibroma
	• Sclerosing stromal tumor
2. Sertoli-stromal cell tumors, Androblastomas	• Well-differentiated, Sertoli-Leydig cell tumor of intermediate differentiation(Sertoli cell tumor)
	• Sertoli-Leydig cell tumor poorly differentiated (sarcomatoid), retiform
3. Sex cord tumor with annular tubules	
4. Gynandroblastoma	
5. Unclassified	

6. Steroid (lipid) cell tumors	• Stromal luteoma
	• Leydig cell tumor
	• Unclassified

The tumor's spreading properties and the possibility of distant metastasis vary by histological subtype, but lymph node metastasis is rarely encountered(Brown et al., 2009). As an example, in a retrospective study with 87 patients, no lymph node metastases were found(Thrall et al., 2011). Granulosa cell tumors are generally considered malignant as histologic. However, there are no definitive criteria for malignancy in other SCSTs. SCSTs have a low malignant potential and are typically unilateral. These tumors recur very rarely. If there is a recurrence, it is usually in the pelvis(Abu-Rustum et al., 2006). In a study showing the stage distribution at the time of diagnosis: Limited to the ovary (57%), spread to surrounding organs or tissues (15%), and distant metastases (22%)(Quirk & Natarajan, 2005).

A. Granulosa Cell Tumor

Granulosa cell tumors constitute more than 70% of SCSTs. They account for 2 to 5 percent of all ovarian malignant neoplasms and 90 percent of malignant SCSTs. There are two subtypes of this group of tumors. The adult type, the first of these, accounts for 95% of cases and the juvenile type only corresponds to a group of 5%.

1. Adult type granulosa cell tumor

It is usually diagnosed after the age of 30 with an average of 50 years of age. They present with menometrorrhagia and postmenopausal

bleeding, suggesting that the endometrium is exposed to excess estrogen. Conditions related to excess estrogen (adenocancer, endometrial hyperplasia, etc.) are observed in 25% of granulosa cell tumors. The granulosa cell tumor may range from 1 mm to 20 cm. The growing tumor may mimic ectopic pregnancy and ovarian torsion by causing pain and bleeding due to distention. If an adult-type granulosa cell tumor is encountered during surgery, inhibin B, a good tumor marker, can be checked. Because Inhibin B begins to rise months before the recurrence of the disease becomes clinical(Mom et al., 2007). In two studies conducted in 2009, mutations in FOXL2 were identified in 97 percent of adult granulosa cell tumors(Köbel et al., 2009; Shah et al., 2009). The macroscopic features of the tumor are very variable. But microscopic examination reveals pale and notched coffee bean-like granulosa cells. These cells can be arranged in small clusters around a central cavity. These arrangements, called "Call-Exner bodies", form a microfollicular pattern when present. Most granulosa cell tumors have a slow growth pattern. Estrogen effects are common, androgenic effects are also possible. The prognosis depends on the stage of the disease at diagnosis and the presence of residual disease after surgery(Gershenson et al., 2021). 5-year survival is above 90% in patients with stage 1 disease(Colombo et al., 2007). Recurrence usually occurs in the first 6 years. However, recurrence has been reported even after 30 years(East et al., 2005).

2. Juvenile granulosa cell tumor

The juvenile subtype has a macrofollicular and cystic histological structure. Call-Exner bodies and the appearance of coffee beans are rare. These tumors are usually seen in children and adolescents. The average age at diagnosis is 13 years. Ollier disease and Maffuci syndrome can be associated with these tumors(Young et al., 1984; Yuan et al., 2004). Menstrual irregularities and amenorrhea are common in these patients. Peripheral puberty-precox is seen in girls with breast enlargement, development of pubic hair and development of other secondary sex characteristics(Kalfa et al., 2005). These tumors can reach large sizes and the mean diameter at the time of diagnosis is around 12 cm. The prognosis is very good. 5-year survival is around 95%, almost all tumors are seen unilaterally and are in stage 1 at the time of diagnosis. Late recurrence is not typically seen. Relapses are seen in the first 3 years(Frausto et al., 2004).

B. Thecoma-Fibroma Group

1. Thecoma

Tekoma occurs in postmenopausal women. It can be yellow and very large in size (30-40cm). They are unilateral and acid is not frequent. There may be signs and symptoms of excess estrogen. Endometrial hyperplasia and carcinoma are present in about 15% and 20-25% of cases(Aboud, 1997). Patients usually present with abnormal vaginal bleeding and a pelvic mass. Thecomas are considered clinically benign and surgical excision is curative.

2. Fibroma

Fibromas usually occur in postmenopausal women (mean age 48). Fibromas are the most common of benign SCSTs and are all made up of fibroblasts(Chechia et al., 2008). Fibromas are hormonally inactive tumors. The surface is hard and white-colored tumors. On ultrasound, it is observed as a unilateral mass with calcific or cystic degeneration. Ascites is present in 10-15% of patients and in 1% of pleural effusion. Its treatment is surgical excision, like benign masses.

3. Sclerosing stromal tumor

They are very rare tumors. The average age of onset is 21. They are clinically benign and unilateral tumors. Menstrual irregularities and pelvic pain are the most common symptoms. It is hormonally inactive. Histologically, there are edematous cellular areas, increased vascularity, and marked areas of sclerosis.

C. Sertoli-Stromal Cell Tumors

1. Sertoli Cell Tumors

Sertoli cell tumors are very rare. Although it is usually seen in women of reproductive age, it can occur in a wide spectrum from children as young as 2 years old and postmenopausal women. On ultrasound, it can be unilateral and solid. About half of patients produce hormones. Most commonly, it produces estrogen. It is clinically benign. Up to 80% of patients are stage 1 at the time of diagnosis. Cytological atypia, increased mitotic activity and tumor necrosis increase the risk of recurrence(Oliva et al., 2005).

2. Sertoli – Leyding Cell Tumors

Sertoli-leydig cell tumors constitute 5-10% of SCST of the ovary(Zhang et al., 2007). Although these tumors can be seen in very young and very old patients, more than 90% are seen in women of reproductive age. These tumors are hormonally active tumors. They secrete more androgens, and with this, some hyperandrogenemic findings such as virilization, temporal baldness and clitoris enlargement develop in patients(Young et al., 1984). In addition, the increased serum testosterone / androstenedione ratio facilitates the diagnosis. Tumor sizes average 13 cm. They may contain mostly solid and partially cystic areas. It has four subtypes: well differentiated, moderately differentiated, poorly differentiated, and retiform. Well-differentiated tumors are all clinically benign(V. W. Chen et al., 2003; Young, 2005). Up to 20 percent of Sertoli Leydig cell tumors are malignant. The prognosis in these malignant tumors depends on the stage of the disease and the degree of differentiation of the tumor. 5-year survival in stage 1 patients is 92%(Zaloudek & Norris, 1984). The prognosis in advanced stage patients is very poor.

D. Sex Cord Tumor With Annular Tubules

Annular tubule sex cord tumors are clinically divided into two groups: sporadic and associated with Peutz-Jeghers syndrome. The average age of onset is 36. They are usually large and unilateral tumors. Almost all patients have signs/symptoms of excess estrogen. Malignancy may develop in 20% of cases(Young et al., 1982).

In the subtype associated with Peutz-Jeghers syndrome, the mean age is 27 years. This group is seen in patients younger than the sporadic group. They are usually small (<3cm) tumors. They are detected on ultrasound bilaterally, multifocally and calcified. Almost all patients have signs/symptoms of excess estrogen. Most are benign tumors.

E. Gynandroblastoma

These tumors are the rarest type of ovarian SCSTs. The average age of onset is 30(Martin-Jimenez et al., 1994). These tumors contain scattered granulosa cells and certoli cell tubules. Ginandrablastomas have a very low malignant potential and only one death related to this tumor has been reported in the literature. These tumors are associated with androgen and estrogen production. However, estrogen production is less common(Martin-Jimenez et al., 1994).

F. Steroid (Lipid) Cell Tumors

These tumors are thought to originate from adrenal cortical debris around the ovary. These tumors consist of cells similar to steroid hormone secreting cells and are classified according to the histological structures of these cells. Although the average age of onset is 20, it can be seen at any age.

Stromal luteomas are benign tumors that develop from the stroma of the ovaries. It occurs in postmenopausal women and has estrogenic effects.

Leydig cell tumors are benign. They occur in postmenopausal women. Reinke crystals are found in the cytosol of tumor cells. Leydig cells secrete testosterone, which has androgenic effects.

Steroid cell tumors Not Otherwise Specified(NOS), are the most common subgroup of steroid cell tumors. Unlike the other two groups, they are seen in young women. They are andogenic secretory tumors. Steroid cell (NOS) tumors are considered clinically malignant and have a very poor prognosis(Oliva et al., 2005).

G. Unclassified

Unclassifiable tumors account for less than 5% of SCSTs. These tumors typically lack granulosa and Sertoli cell differentiation. Interestingly, these tumors occur especially during pregnancy(Young, 2005). Their hormonal activities and prognosis are variable.

5. TREATMENT

a. Surgey

These tumors are resistant to Chemotherapy and Radiotherapy. Therefore, the main method of treatment is surgery. However, since these tumors occur mainly in women of reproductive age, the surgeon should consider the patient's future expectation of fertility when planning surgery. Total abdominal hysterectomy + bilateral salpingoophorectomy (TAH+BSO) is the appropriate treatment for advanced age and patients who do not want to have children. But, unilateral salpingooopherectomy (USO) may be an option for tumors that are confined to the ovary and have not spread to the surrounding

organs, with expectation of fertility(Zanagnolo et al., 2004). Endometrial sampling should be performed before the operation in hormone-active tumors such as granulosa cell tumor and Thecoma. Ovarian mass excision and surgical staging can be performed with laparoscopy(Kriplani et al., 2001). Standard ovarian cancer surgery should be modified in SCSTs. Washing the pelvis, observing the abdomen, peritoneal biopsies and omentectomy are still important. However, pelvic-paraaortic lymph node dissection is a controversial issue nowadays. Although lymphadenectomy prolongs survival in epithelial ovarian cancer, it has no effect on survival in sex cord stromal tumors(Chan et al., 2007). While staging surgery is required for some SCSTs, staging surgery is not required for some tumor types.(Table 2.)

Table 2. Staging management in sex-cord stromal tumors

STAGING REQUIRED	**NO STAGE REQUIRED**
• Granulosa cell tumor (adult, juvenile, fibrosarcoma)	• Theoma
• Sertoli Leydig cell tumor (moderate, poorly differentiated)	• Fibroma
• Annular tubuli sex cord stromal tumor (sporadic)	• Sclerosing stromal tumor
• Steroid cell tumor	• Gynandroblastoma
	• Sertoli-Leydig cell tumor (well differentiated)
	• Annular tubuli sex-cord stromal tumor (PJS-associated subtype)

Patients with stage 1 SCST do not need any additional treatment after surgery. The prognosis is very good. Post-surgical follow-up is performed with physical examination, laboratory, pelvic ultrasound and other imaging methods.

b. Chemotherapy

Stage 1 patients are mostly treated with surgery. However, chemotherapy may be required in some patients with a high mitotic index, understaging, and tumor rupture. Appropriate chemotherapy in these patients is platinum-based chemotherapy(Schneider et al., 2003). Chemotherapy after surgery is a mandatory treatment in stage II and IV patients. A five-day chemotherapy regimen based on bleomycin, etoposide, and cisplatin (BEP) is used as first-line chemotherapy(Gershenson et al., 1996).

c. Radiotheraphy

The efficacy of radiotherapy in SCSTs of the ovary is limited. In a study conducted in 1999, it was shown that irradiation of the entire abdomen with radiotherapy prolongs survival(Wolf et al., 1999). However, the main complementary treatment after the operation is chemotherapy.

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CHAPTER 18

GESTATIONAL TROPHOBLASTIC DISEASE

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1. INTRODUCTION

Gestational trophoblastic disease (GTD) comprises a heterogeneous group of related lesions arising from abnormal proliferation of trophoblast of the placenta. Differential diagnosis on clinical grounds may be difficult in a patient with an elevated serum beta-human chorionic gonadotropin (hCG) therefore, histology is necessary for definitive diagnosis.

Gestational trophoblastic disease (GTD) – This category is comprised of benign, non-neoplastic lesions, including placental site nodule, exaggerated placental site, and hydatidiform mole.

Gestational trophoblastic neoplasia (GTN) – Gestational neoplasms include: choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor, and invasive mole (Shih, Seidman, et al, 1999); (Shih, Kurman, 2001).

1.1.1. Placental site nodule — It found in uterine curettages, cervical biopsies, or hysterectomy specimens most commonly in reproductive-age patients. The intermediate trophoblastic cells of PSNs are likely derived from the migratory intermediate (extravillous) trophoblasts of the placenta, similar to the trophoblast in the chorion laeve and chorionic plate. In about half of cases, PSNs are discovered as an incidental finding in abortion or hysterectomy specimens. PSNs express the intermediate trophoblastic markers of migratory trophoblast, and therefore show strong diffuse staining for PLAP, but only focal staining for hPL and Mel-CAM (CD146) (Shih, Seidman, et al, 1999); (Shih, Kurman, 2001).).

1.1. 2. Exaggerated placental site — The exaggerated placental site (EPS) is characterized by an extensive infiltration of the endometrium

and myometrium by implantation site intermediate (extravillous) trophoblastic cells that occur in clusters or as single cells (Shih, Seidman, et al, 1999). It may represent an extreme physiological process rather than a true lesion. The associated placenta is usually normal. The absence of mitotic activity and its relationship with chorionic villi is an important clue in the diagnosis, especially between EPS and placental trophoblastic tumor. They show strong positivity for human placental lactogen (hPL) and Mel-CAM (CD146) and focal positivity for placental alkaline phosphatase (PLAP).

1.1.3. Hydatıdıform mole – Molar pregnancy originate in the placenta and have the potential to locally invade the uterus and metastasize. The tumor arises from gestational rather than maternal tissue (Berkowitz, Goldstein, 2013). Molar pregnancies, although benign, they have the potential to develop into a malignancy. Hydatidiform mole is divided into two as partial and complete (Vassilakos, Riotton, et al, 1977).

Table 1. Pathologic and Genetic Features of Hydatidiform Mole

	Complete	**Partial**

Fetal or embryonic tissue	Absent	Present
Hydatidiform swelling of chorionic villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Trophoblastic stromal inclusions	Absent	Present
Karyotype	46XX; 46XY; all chromosomes are paternal in origin	69XXY; 69XYY; 69XXX; extra set of chromosomes is paternal in origin
Immunochemistry*	p57-negative	p57-positive
Risk of gestational trophoblastic neoplasia	15 to 20%	1 to 5%

* p57 is expressed only on the maternal allele.

Adapted from: Berkowitz RS, Goldstein DP. The management of molar pregnancy and gestational trophoblastic tumors. In: Knapp RC, Berkowitz RS, eds. Gynecologic oncology.

1.1.3.1 Complete hydatidiform mole — It often has a diploid chromosome structure, 46XX. It occurs as a result of abnormal fertilization of an empty ovum. Both pairs of chromosomes are of paternal origin.

1.1.3.2 Partial hydatidiform mole — Partial moles are triploid, usually resulting from fertilization of an apparently normal ovum by two sperm or occasionally by a diploid sperm, and may therefore be

69XXX, 69XXY, or 69XYY (Vassilakos, Riotton, et al, 1977); (Szulman, Surti, 1978).

1.2. Epidemiology And Risk Factors

Middle Eastern, Latin American and Asian nations report high rates (23 to 1299 per 100,000 pregnancies) (Altieri, Franceschi, et al, 2003). The incidence of complete mole is nearly1 per 1000 pregnancies In the United Kingdom (Newlands, Paradinas, et al, 1999). The main risk factors for hydatidiform mole are extremes of maternal age and a history of previous mole (Altieri, Franceschi, et al, 2003); (Messerli, Lilienfeld, et al, 1985).

1.3. Clinical Features

Patients with hydatidiform mole typically present with missed menstrual periods, a positive pregnancy test, and signs and symptoms consistent with early pregnancy or early pregnancy complications (bleeding, pelvic discomfort, hyperemesis gravidarum) (Berkowitz, Goldstein, 1996); (Zalel, Dgani, 1997). Molar pregnancy may be suspected based on unusually high human chorionic gonadotropin (hCG) levels. The diagnosis of hydatidiform mole may be missed If the products of conception are not examined histologically. The availability of both ultrasonography and sensitive quantitative measurement of serum hCG has led to earlier diagnosis of complete mole (Sebire, 2005); (Braga, Moraes, et al, 2016). Vaginal bleeding, hyperemesis gravidarum, an enlarged uterus, and pelvic pressure or pain are common presenting symptoms. Vaginal bleeding is common which results from separation of the molar villi from the underlying decidua. Pelvic pressure or pain is nonspecific symptoms in molar

pregnancy due to the enlarging uterus or enlarged cystic ovaries. Hyperemesis gravidarum was present in approximately 8 percent of patients in one study (Soto-Wright, Bernstein, et al, 1995) and may develop earlier than in a nonmolar pregnancy and/or be more severe. Sequelae associated with the high hCG levels include theca lutein cysts, hyperthyroidism, and early onset of preeclampsia are less common. hCG levels are typically far lower in partial mole so partial mole is less likely to be associated with sequelae of hCG stimulation (Szulman, Surti, 1982); (Czernobilsky, Barash, et al, 1982).

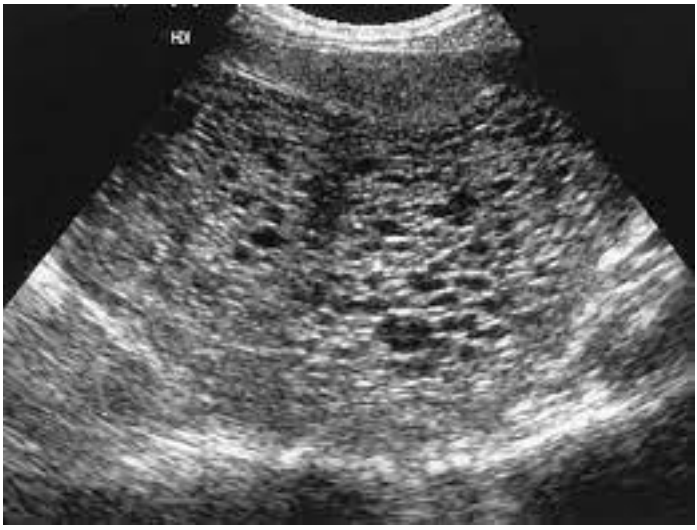
1.4.Diagnostic Evaluation

The possibility of hydatidiform mole should be considered in any reproductive-age female with abnormal vaginal bleeding. A quantitative serum human chorionic gonadotropin (hCG) level should be obtained and, if elevated, ultrasound examination should be performed. A complete pelvic examination should be performed. On bimanual examination, the uterus may be larger than the expected gestational age and bilateral adnexal masses may be present if ovarian theca lutein cysts have developed due to hCG stimulation.

In laboratory, the serum hCG concentration in patients with hydatidiform mole is usually higher than that observed with intrauterine or ectopic pregnancies of the same gestational age. If the hCG level is high (>100,000 mIU/mL) and the ultrasound shows an apparently normal singleton gestation, the ultrasound and hCG should be repeated in one week to exclude the possible presence of a twin conception with normal fetus and coexistent molar pregnancy. Further testing depends on the likelihood of complications and the clinical assessment should include: complete blood count, renal and

liver function tests, urine protein, and thyroid function tests are for hyperthyroidism and preeclampsia. If molar pregnancy is suspected, a transvaginal ultrasound should be performed. There is no an embryo or fetus and amniotic fluid on ultrasonography for complet mole. Central heterogeneous mass with numerous discrete anechoic spaces has classically been described as a "snowstorm or Swiss cheese pattern" on ultrasounds (image 1) (Goff, 2021).

Image 1. Sonogram of a Complete Hydatidiform Mole



The fetus is absent, and the hydropic vesicle changes of the trophoblast have the typical grapelike appearance (Lazarus E., Hulka C., et al, 1999).

For partial mole based on ultrasound findings a fetus may be identified, but is often growth restricted, amniotic fluid is present, but the volume may be reduced, placenta with one or more abnormal findings ("Swiss cheese pattern"), increased transverse diameter of

the gestational sac. Theca lutein cysts are usually absent (Fine, Bundy, et al, 1989); Naumoff, Szulman, et al, 1982). When patients present with hydatidiform mole, a chest radiograph is needed only if the patient has pulmonary symptoms such as dyspnea or chest pain. Suction evacuation of the uterus is both diagnostic and therapeutic for molar pregnancy (Goff, 2021).

1.5. Diagnosis

Hydatidiform mole is a histologic diagnosis. Complete and partial mole are differentiated based on histopathology, karyotype (complete moles are diploid; partial are triploid), and whether a fetus is present (fetus is only present in partial mole) (Van de Kaa, Schijf, et al, 1997); (Niemann, Hansen, et al, 2007). The differential diagnosis for hydatidiform mole includes nonmolar pregnancy, spontaneous abortion with hydropic change, and other etiologies of an enlarged uterus, hyperthyroidism, or ovarian theca lutein cysts (Goff, 2021).

1.6. Treatment

Uterine evacuation consists of mechanical dilation of the cervix, followed by suction aspiration (regardless of uterine size), and then sharp curettage to help assure complete evacuation of molar tissue. At the same time of anesthesia induction, an oxytocin infusion is begun. This promotes myometrial contraction and reduces blood loss. Bleeding is typically more than normal. Rh D negative patients should be given anti-D immunoglobulin after curettage. Sometimes hysterectomy or uterine artery embolization may be needed for emergency management of acute hemorrhage (Tse, Chan, et al,

2007). Non-curettage methods may be considered in selected cases. Hysterectomy may be considered in cases that have completed their fertility. The ovaries may be left in situ since ovarian metastases are rarely encountered. Theca lutein cysts usually regress slowly over two to four months following evacuation as hCG levels decline. Ovarian theca lutein cysts can be aspirated to reduce the volume and patient discomfort (Goff, 2021-b).

1.7. Postoperative Monitoring

Postoperative human chorionic gonadotropin (hCG) monitoring is performed to detect development of gestational trophoblastic neoplasia. Patients with hydatidiform mole must be advised to use reliable contraception (hormonal contraception or barrier methods) during the entire period of postoperative hCG monitoring (Dantas, Maesta, et al, 2017). A new pregnancy during this time would make it impossible to interpret hCG results. Insertion of an intrauterine device (IUD) is not recommended due to the theoretical risk of perforation, infection, and bleeding for patients.

After surgical treatment of hydatidiform mole, measurements of serum hCG levels are performed weekly in all patients until undetectable. The hCG level is expected to gradually decrease by more than 10 percent over a three-week period. The weekly follow-up until the hcg values become unmeasurable is done monthly for 6 months after a negative value, and then it is stopped. The important thing is to evaluate the possibility of gestational trophoblastic neoplasia if the hCG levels increase or persist during the period of monitoring. After a complete mole, approximately 15 to 17 percent

of patients develop gestational trophoblastic neoplasia and after a partial mole, 1 to 4.5 percent of patients develop GTN (Albright, Shorter, et al, 2020). Uterine size greater than gestational age, serum hCG levels >100,000 milli-international units/mL and ovarian theca lutein cysts >6 cm in diameter are a marker for high risk of development of GTN. Older age (>40 years) is another high-risk factor for development of GTN (Goff, 2021-c).

2. GESTATIONAL TROPHOBLASTIC NEOPLASIA

Gestational trophoblastic neoplasia (GTN) refers to a group of malignant neoplasms that consist of abnormal proliferation of trophoblastic tissue. Gestational neoplasms include: choriocarcinoma, placental site trophoblastic tumor (PSTT), epithelioid trophoblastic tumor (ETT), and invasive mole.

In the absence of tissue for a definitive histopathologic diagnosis, disease diagnosed as a result of persistent elevation of hCG after evacuation of a molar pregnancy is termed GTN.

2.1. Histopathological classification

2.1.1. Invasive Mole: Almost all develop after molar pregnancy and are characterized by the presence of edematous chorionic villi with trophoblastic proliferation invading the myometrium. Although locally aggressive, it has a low tendency to metastasize, unlike choriocarcinoma. Metastases of invasive moles spread hematogenously; the lungs and vagina are the most common sites (Ngan, Seckl, et al, 2018).

2.1.2. Choriocarcinoma: Choriocarcinoma occurs cytotrophoblasts and syncytiotrophoblasts without villi. Choriocarcinoma can follow any type of pregnancy, after a non molar pregnancy, choriocarcinoma is the most common type of GTN. The most aggressive histologic type of GTN is choriocarcinoma. Metastases often develop early and become hematogenous. It often presents with bleeding from a metastatic site (Lurain, 2010).

2.1.3. Placental site trophoblastic tumor: Placental site trophoblastic tumors are develop from extravillous, intermediate trophoblasts. The main difference from invasive mole or choriocarcinoma is that it secretes very low levels of hCG (Zhao, Lv, et al, 2016). hCG levels in these patients are usually <1000 milli-international units/mL. Hysterectomy is preferred for treatment because these are locally invasive tumors and are often resistant to chemotherapy.

2.1.4. Epithelioid trophoblastic tumor: It develops from neoplastic transformation of chorionic-type extravillous trophoblasts (Shih and Kurman, 1998). The clinical behavior of ETT is similar to PSTT. Primary treatment is hysterectomy.

2.2. Clinical presentation

High hCG level and non-reset hCG level after treated molar pregnancy suggest the development of GTN. Abnormal uterine bleeding, pelvic pain due to ovarian cysts and enlarged uterus may be clinical manifestations.

When the diagnosis of GTN is made, patients must be evaluated for extent of disease. All patients should have a chest radiograph and pelvic examination to identify possible lung and vaginal

involvement. In general, the sites of GTN metastases include lung, vagina, the brain, liver, kidney, gastrointestinal tract and spleen.

Dyspnea, chest pain, cough, or hemoptysis may occur due to lung metastases. Vaginal metastases are typically present with vaginal bleeding or purulent vaginal discharge (Yingna, Yang, et al, 2002); (Cagayan, 2010). It most commonly located in the suburethral area or fornices. Central nervous system involvement may be asymptomatic initially, but as the disease progresses, patients develop neurologic signs and symptoms. Jaundice, epigastric, or back pain may occur in patients with liver metastases and should not be biopsied because of risk of hemorrhage.

2.3. Diagnosis

GTN is a clinical diagnosis and unlike other solid tumors, a tissue diagnosis is not required prior to treatment.

The diagnosis of postmolar GTN is based International Federation of Gynecology and Obstetrics criteria (Kohorn, 2001); (Ngan, Bender, et al, 2003):

1- Weekly hCG levels plateau (remain within ±10 percent of the previous result) over a three-week period

2- hCG level increases >10 percent across three values recorded over a two-week duration

Serum hCG monitoring is not routinely performed after nonmolar pregnancies. For this reason, women who develop GTN after a

nonmolar pregnancy typically undergo evaluation with serum hCG and ultrasound only after they become symptomatic.

2.4. Staging And Risk Assessment

GTN is typically staged using a combination of the International Federation of Gynecology and Obstetrics (FIGO) staging system and the World Health Organization (WHO) Prognostic Scoring System. This system predicts the development of resistance to single-agent chemotherapy (methotrexate (MTX) or actinomycin D (ActD) over eight risk factors.

Table 2. FIGO Staging of Gestational Trophoblastic Neoplasia (GTN) and Modified WHO Prognostic Scoring System as Adapted by FIGO

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina)
Stage III	GTN extends to the lungs, with or without genital tract involvement
Stage IV	All other metastatic sites

Table 3. Risk Factor and Scores of Gestational Trophoblastic Neoplasia

Risk factor	Score			
	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval (months)*	4	4 to 6	7 to 12	>12
Pretreatment serum hCG (mIU/mL)	<103	103 to 104	104 to 105	>105
Largest tumor (including uterus)	<3 cm	3 to 4 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases	–	1 to 4	5 to 8	>8
Prior failed chemotherapy	–	–	Single drug	≥2 drugs

FIGO: International Federation of Gynecology and Obstetrics; WHO: World Health Organization; hCG: human chorionic gonadotropin; GI: gastrointestinal.

* Interval (in months) between end of antecedent pregnancy and start of chemotherapy (Berkowitz, Goldstein, 2009).

A score of 0 to 6 indicates a low risk of resistance to single-agent chemotherapy, while a score above 7 requires combination chemotherapy. A score ≥12 is considered as ultra high risk and particularly associated with nonmolar antecedent pregnancy, brain metastases, and failed prior multiagent chemotherapy.

All patients with FIGO stage I GTN are low risk, and >90 percent achieve remission with single-agent chemotherapy. However, patients with FIGO stage IV disease have high risk scores. Therefore, the need for multi-agent chemotherapy is included in the primary treatment. This system applies primarily to FIGO stages II and III.

This is not applicable to patients with placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT).

2.5. Treatment

Treatment is planned as low-risk disease and high-risk disease. Low-risk disease is defined as stage II or III GTN with a WHO risk score <7 or FIGO stage I GTN. High-risk disease is defined as stages II and III with risk score >6 or stage IV disease.

Most patients with low-risk GTN are cured with single-agent chemotherapy, using either methotrexate (MTX) or dactinomycin (ActD) (Horowitz, Eskander, et al, 2021). Patients with low-risk GTN have an overall excellent prognosis with survival rates approaching 100 percent after treatment. Different regimens can be used in treatment. One of them MTX is dosed as 1 mg/kg intramuscular (IM) or intravenous (IV) injection and administered on days 1, 3, 5 and 7.

Folinic acid is given after each dose of MTX in this regimen. In another regimen, 50 mg/m2 weekly MTX, HCG levels are repeated until undetectable. Dactinomycin is usually given to patients who cannot be treated with MTX, have MTX resistance, or cannot be given due to toxicity. After the success of the treatment is achieved, the hCG value

should be followed for 1 year, monthly. It is recommended that pregnancy be considered at the end of this one year.

High-risk patients may develop resistance to single-agent chemotherapy. For this reason, multi-agent chemotherapy is used. Preferred regimen for these patients is etoposide, methotrexate (MTX), plus actinomycin D (ActD) alternating with cyclophosphamide and vincristine (EMA-CO). Treatment should be continued until the hCG level becomes undetectable and remains undetectable for three consecutive weeks.

Placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT) are relatively resistant to chemotherapy, patients with nonmetastatic PSTT and ETT are generally treated with hysterectomy or combination with chemotherapy.

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CHAPTER 19

EPITHELIAL CANCERS OF THE OVARY, TUBAL UTERINE AND PERITONEUM

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INTRODCTION

Ovarian cancer is the second most common gynecological malignancy in developed countries and the third most common gynecological malignancy in developing countries. Ovarian cancer is the second most common gynecological malignancy in the United States and one of the most common causes of gynecological cancer deaths. 95% of ovarian cancers originate from epithelium. The remaining ovarian cancer types originate from sex cord and germ cells. 90% of ovarian cancer originates from coelomic epithelium or mesothelium. (Scully et al. 1998). The most common type of epithelial ovarian cancer is high-grade serous cancers. graded serous cancers are called epithelial ovarian cancer together with peritoneal and tubal cancers. Each year, 230,000 people are diagnosed with epithelial ovarian cancer and 150,000 people are expected to die. It is the 7th most common cancer among female cancers and the 8th most common cancer causing death.

Histology and pathogenesis

Histological types of epithelial ovarian cancer are as follows. High-grade serous carcinoma, low-grade serous carcinoma, endometrioid, clear cell carcinoma, mucinous carcinoma. Serous carcinoma is the most common type and constitutes 75% of epithelial ovarian cancers Scully et al. 1998).Serous, clear cell and endometrioid ovarian cancers are thought to be caused by fallopian tube, inclusion cysts, endometriosis and endosalphingiosis. Epithelial ovarian, fallopian tube and peritoneal cancers are divided into 5 subtypes as pathological,

genetic and immunohistochemical. 75-80% of epithelial ovarian, fallopian and peritoneal cancers The other types are serous cancers. Other types; endometrioid (10%), clear cell (5%), mucinous (5%), transitional and undifferentiated cancers make up less than 1% (Scully et al. 1998).

High grade serous carcinom

High-grade serous carcinomas have typical slit-like fenestrations under the microscope. In some areas, they may have a papillary, cribriform, and glandular appearance similar to the tubal epithelium. BRCA 1 mutation was detected in these carcinomas. . High-grade serous carcinomas are the most common type of ovarian cancer. They constitute 70-80% of all ovarian cancer cases. . High-grade serous cancers are usually detected in advanced stages at stage 3 and stage 4. Their prognosis is generally poor. High-grade serous carcinomas can be seen as masses larger than microscopic sizes . Tumors may have a flat outer surface and have papillary protrusions. Areas of hemorrhage and necrosis may be found. Invasion of the cell stroma is detected in high-grade serous carcinomas. Psammoma bodies are found. In high-grade serous carcinoma cells, marked atypia at a magnification of 10 and mitosis of 12 and above are evident. Mitoses below 12 mitosis are consistent with low-grade serous carcinoma. p53 mutation was detected in the vast majority of carcinomas. BRCA 1, BRCA2, PTEN, PI3CA mutations were detected in high-grade serous carcinomas.

Low grade serous carcinoma

It is less common than high-grade serous carcinomas. It constitutes less than 5% of all ovarian cancers. (Gersherson DM et al.2006). Low-grade serous carcinomas are usually slow-growing tumors and are advanced stage when detected. They have a poor prognosis and are platinum-resistant tumors. The next stage of tumors is low-grade serous carcinomas. Cellular atypia 12 or less atypical cells were detected in the 10 magnification field.

Endometrioid carcinoma

Endometrioid carcinoma accounts for 10% of all ovarian cancers. It is most commonly seen between the ages of 40-55. (Seidman JD ,2003). The prognosis of endometrioid carcinomas is good and they are usually detected at an early stage and have a high response rate to chemotherapy. Endometrioid tumors are generally thought to originate from endometriosis. Endometrioid ovarian carcinoma can be associated with endometrioid whole endometrial cancer. Endometrial biopsy is required in such patients.

Clear cell carcinoma

It constitutes 5% of all ovarian cancers. They are often detected at an early stage (stage 1 – stage 2). If detected in the late stage, the prognosis is poor. If clear cell carcinoma is detected in the late stage, it is usually fatal. This is due to its resistance to chemotherapy. KRAS, PTEN, PIK3CA, ARID1A mutations have been reported .

Mucinous carcinoma

They are seen in 5% of all ovarian cancers (Scully et al., 1998). Ovarian mucinous carcinomas are usually detected at an early stage. Primary mucinous carcinomas consist of borderline mucinous carcinoma of the ovary (Lee KR et al. 2000). Ovarian mucinous neoplasms can reach very large sizes. They can reach and are usually unilateral. Mucinous tumors that are bilateral in the ovary are usually tumors that metastasize from gastrointestinal tumors.

Risk factors in epitelial ovary carcers

The incidence of epithelial ovarian cancer increases with increasing age. Early menarche and late menopause increases the risk of ovarian cancer. With the effect of genes such as BRCA1, RAD51C, RAD51D, the risk of ovarian cancer increases with first degree consanguinity.

Lynch syndrome is primarily associated with an increased risk of colon and endometrial cancer. Compared to the general population, 38% of patients with Lynch syndrome have an increased incidence of ovarian cancer. Endometriosis increases the risk of endometrioid ovarian cancer. It has been determined that the risk of ovarian cancer is increased, albeit at a slight rate, secondary to radiotherapy treatment given to rectal cancer.

Among the ovarian cancer protective factors; bilateral salpingoophorectomy, oral contraceptive use, hysterectomy, tubal ligation, breastfeeding and parity count.

Clinical appearance in epitelial cancers

Epithelial ovarian cancer patients may present to the clinic in various ways. The first of these is ascites. Ascites can be detected in the abdomen and pleural space. Acid; It may occur from the fluid released from the tumor cells in the peritoneum and from the obstruction of the fluid circulation by the tumor cells in the diaphragm. Paracentesis made from ascitic fluid can be used for diagnosis before neoadjuvant chemotherapy.

Pleural effusion can be detected in the pleura like ascites in the abdomen. A cytological diagnosis of the patient can be made by performing thoracentesis.

A mass in the intestines is a metastatic finding of ovarian carcinoma. Patients with an intestinal mass may present to the clinic with nausea, vomiting and ileus.

Venous thromboembolism was found to be 3 times higher than the normal population.(White RH et al. 2005)

Patients can apply to the clinic with pelvic and abdominal symptoms. These are; bloating and abdominal distension, dysuria, difficulty eating, early satiety, pelvic and abdominal pain.

Patients may present with postmenopausal bleeding. First of all, endometrial biopsy should be performed to evaluate the patients for endometrial pathologies.

Fallopian tube carcinoma may present with the pathognomonic triad of pelvic pain, pelvic mass, clear or bloody vaginal discharge. This condition is called hydrops tuba profluens. (SINHA AC, 1959)

Rare symptoms such as cervical and inguinal lymphadenopathy, paraneoplastic syndromes and rectal bleeding are seen.

It can be detected incidentally in post-operative pathologies. If atypical glandular cells are detected in cervical cytology, ovarian cancer should come to mind after cervical and endometrial pathologies are excluded

Diagnostic approach in epitelial ovary cancer

Physical examination and imaging studies are required to diagnose epithelial cancers. Pelvic mass and ascites may be detected in physical examination. Pelvic ultrasound should be performed first in imaging. Malignant features of the pelvic mass can be detected in pelvic imaging. Irregularly thick septal cyst, hypoechoic solid mass in the cyst, diffuse acid in the abdomen, Increased blood supply on Doppler ultrasound and papillary protrusions in the cyst are malignant pelvic ultrasound findings.

Laboratory tests should be done during the diagnosis phase, physical examination and imaging studies. The most important of these is the ca125 test. In epithelial ovarian cancer, the ca125 value is found to be

increased by 80% (Prat J, 2014). The Ca125 test is used in the diagnosis phase and in the follow-up of recurrence.

Since epithelial ovarian cancer applies to the clinic in advanced stages in imaging studies, distant metastasis is investigated using thorax and pelvic tomography. This is used to determine whether the patient is advanced stage and whether he is a candidate for surgery. Patients with advanced stage may be candidates for neoadjuvant chemotherapy if they are not suitable for surgery. Ultrasound of ovarian cancer and pleural and omental biopsy using tomography; Diagnosis is made by taking cytology materials with paracentesis and thoracentesis. Ovarian biopsy is not recommended. Because tumor cells can be transplanted into the abdomen during ovarian biopsy, and it carries the disease to an advanced stage and adversely affects the prognosis.

Diagnosis of epithelial cancers is by histological diagnosis. Except for the above-mentioned method for diagnosis, cytoreduction can be performed surgically and pathological biopsy can be obtained.

In the early stage, staging surgery is performed before the disease spreads to the abdomen, and the patient is staged. If it is a center where cytoreductive surgery can be performed in the advanced stage, optimal cytoreduction should be performed. BRCA1 and BRCA2 genetic evaluation tests are recommended for epithelial cancers with histological diagnosis.

Surgical staging of epitelial cancers

Epithelial ovarian cancers are surgically staged according to the TNM (tumor, lymph node, metastasis) classification by the 2017 American Joint Cancer Committee and the International Federation of Obstetrics and Gynecology

A common surgical staging system is used for ovarian, fallopian tube and peritoneal cancers. Staging is done surgically. Hysterectomy and bilateral salpingo-oophorectomy, peritoneal cytology (washing and ascitic fluid), biopsy from abnormal peritoneal areas, visual inspection of all peritoneal surfaces, upper abdominal liver palpation and intestinal mesentery examination, pelvic and paraaortic lymph node dissection, infracolic or infragastric omentectomy should be performed.

Midline incision should be made as a surgical incision. Phannentiel incision should not be chosen as the incision. If it is selected, Maylard and Cherney incisions should be used to increase visibility. Fertility-sparing surgery can be performed in stage 1A patients who want to preserve their fertility in young people. In these patients, salphingoopherectomy on the side of the tumor, peritoneal biopsy from multiple abnormal areas, peritoneal washing fluid and pelvic-paraaortic lymph node dissection should be performed.

Operative technique, open laparotomic method is the classical method. In addition, laparoscopic and robotic surgery can be performed. The laparoscopic operation depends on the experience and skill of the surgeon. Visualization may be difficult when the operation is performed laparoscopically. There may be metastasis at the port sites. In large

ovarian masses, due to capsule rupture during surgery As a result, the spread of the tumor into the abdomen may occur.

The primary site should be determined during the surgery and should be stated in the operation note. This does not determine the prognosis and treatment modality. First of all, the presence of STIC (serous intraepithelial carcinoma) in the fallopian tube should be determined microscopically and macroscopically. If it is absent macroscopically or microscopically, peritoneum should be considered as primary. Peritoneal tumors are not detected at an early stage. If a tumor is detected in the peritoneum, it is considered as stage 3.

Posterior exenteration or radical oophorectomy can be performed in patients with invasion and obstruction in the sigmoid colon. In patients with metastasis in the upper abdomen, posterior approach is not recommended as it will not provide cure and increase postoperative morbidity.

Making lymph nodes in advanced ovarian carcinoma has no effect on the prognosis and is not recommended. There is a 0.7% risk of lymph node metastasis in mucinous ovarian carcinoma. Therefore, lymphadenectomy is not routinely recommended. (Hoogendam JP et al. 2016). If mucinous ovarian carcinoma is considered during surgery, routine appendectomy recommended. (Rosendahl M et al.2017)

According to Figo and AJCC's 2017 TNM classification system, epithelial ovarian cancer is divided into stages as follows.

STAGE 1A: Tumor limited to an ovary (capsule intact) and fallopian tube, no tumor on the ovary and fallopian tube surface; no malignant cells in ascites and washing fluid.

STAGE 1B: Tumor limited to both ovaries (capsule intact) and fallopian tube, no tumor on ovary and fallopian tube surface; no malignant cells in ascites and washing fluid.

Stage 1C: Tumor confined to one or both ovaries or fallopian tubes with any of the following:

STAGE1C1: Shedding during surgery

STAGE1C2: Capsule is perforated before surgery or tumor has tumor surface involvement of fallopian and ovarian tumors.

STAGE1C3: Malignant cells in ascites or peritoneal washings

STAGE2A:Implants on the uterus and fallopian and ovaries

STAGE 2B: Implants in other pelvic tissues

STAGE 3A: Histologically confirmed retroperitoneal lymph node positivity

STAGE 3A1i: Lymph node metastasis up to 10 mm in greatest dimension

STAGE3A1ii: Metastasis to the len node greater than 10 mm in greatest dimension

STAGE 3A2: Extrapelvic peritoneal involvement with or without positive lymph nodes

STAGE 3B: Macroscopic peritoneal metastasis less than 2 cm in size, with or without retroperitoneal lymph node positive

STAGE 3C: Macroscopic peritoneal metastasis greater than 2 cm with or without retroperitoneal lymph node positivity (liver and spleen capsule involvement, no spleen and liver parenchyma)

STAGE 4A: Positive pleural cytology

STAGE 4B: Liver and spleen parenchymal metastasis; metastasis to extra-abdominal organs (inguinal lymph node metastasis and lymph node metastasis outside the abdominal cavity), intestinal transmural involvement.

Fertility preserving surgery staging

It can be performed in ovarian cancers with low malignant potential or non-epithelial and in stage 1a epithelial ovarian cancer. Unilateral salpingoophorectomy, pelvic paraaortic dissection, omentectomy, multiple peritoneal biopsy, peritoneal washing fluid, endometrial biopsy, and upper abdomen, intestinal mesentery examination are performed routinely. biopsy is not performed. Less than 1% may have metastasis to the contralateral ovary. Biopsy is not routinely performed. Complementary surgery should be recommended and performed after the completion of fertility or after the age of 35.

Treatment in epitelial tumors

If treatment is possible in epithelial ovarian carcinoma, cytoreductive surgery should be performed and adjuvant therapy should be performed after surgery. There are risk factors to determine adjuvant therapy. These risk factors are: Histologically clear cell type, the tumor being in grade 3 histology, and the surgical stage being stage 2 and stage 1c. These high-risk features are used as criteria to determine the suitability of adjuvant therapy in clinical studies in women with early-stage disease and to apply adjuvant therapy outside of clinical trials (Chan JK et al, 2010). Five-year disease-free survival rates for women with these characteristics range from 40 to 80 percent (Ahmet FY et al., 1996). This is at least 90 percent among women with well-differentiated (grade 1) tumors confined to the ovary (stage IA or IB). Compared to a five-year survival rate of

It is controversial whether women with stage 2 ovarian cancer should be considered a high-risk disease and whether adjuvant therapy should be recommended. The benefit of adjuvant chemotherapy in patients with early stage EOC has also been demonstrated in two meta-analyses:

- The first included 13 studies conducted between 1965 and 2004, but only eight of these studies were performed in stage I ovarian cancer only (Elite L et al 2004)

Combined results for chemotherapy for women with stage I ovarian cancer showed a benefit in terms of recurrence-free survival (relative

risk [RR] 0.70, 95% CI 0.58-0.86) and overall survival (RR 0.74, 95% CI) for adjuvant therapy. 0.58-0.94).

- Five-year overall survival was improved with the use of adjuvant platinum-based therapy (hazard ratio [HR] 0.67, 95% CI 0.50-0.90).

- Secondly, five randomized studies with 1,277 women between 1990 and 2003 were included in the analysis (Winter Roach et al2012). Again, adjuvant chemotherapy was associated with benefit in both progression-free survival (HR 0.67, 95% CI 0.52-0.84) and overall survival (HR 0.71, 95% CI 0.53-0.93).

- For women without gross residuals after surgery, chemotherapy did not appear to improve overall survival compared to observation (HR 1.22, 95% CI 0.63-2.37). By comparison, for women whose disease was not completely resected, chemotherapy resulted in superior survival compared to observation (HR 0.63, 95% CI 0.46-0.85).
- Women with high-risk tumors had a survival advantage (HR 0.48, 95% CI 0.32-0.72) with the use of adjuvant chemotherapy by observation. Those with low-risk tumors did not benefit from chemotherapy (HR 0.95, 95% CI 0.54-1.66).

A subsequent publication of the Adjuvant Chemotherapy in Ovarian Neoplasms (ACTION) study questioned the usefulness of adjuvant chemotherapy in early-stage disease following complete surgical

staging (Trimbos B et al 2010). The ACTION study included 448 women with early EOC and high-risk traits, and post-surgical care was randomly assigned to adjuvant platinum-based chemotherapy versus observation (Trimbos JB et al, 2003). Although surgical treatment was not mandated by the protocol, the study included strict definitions of optimal and suboptimal staging. After a median follow-up of ten years, adjuvant chemotherapy resulted in the following outcomes compared with observation:

Significant improvement in relapse-free survival (RFS, 62 percent vs. 70 percent, HR 0.64, 95% CI 0.46-0.89) and a trend for an improvement in cancer-specific survival (CSS, 76 versus 82 percent, HR 0.73 percent) 95 CI 0.48-1.13).

For women undergoing full surgical staging, neither in RFS (78 vs 72, HR 0.73, 95% CI 0.38-1.42) nor in CSS (85 vs 89, HR 1.58, 95% CI 0.61). -4.08) there was no significant improvement. . However, in women with incomplete surgical staging, both RFS (65 vs 56 percent, HR 0.60, 95% CI 0.41-0.87) and CSS (80 percent vs. 69, HR 0.58, 95% CI 0.35-) there was a significant improvement. 0.95).

Overall, available evidence supports the use of adjuvant chemotherapy in patients with early-stage ovarian cancer with high-risk features. In contrast, patients with no risk factors do not seem to benefit from chemotherapy. Further prospective clinical trials are needed to determine whether patients with one or more of these high-risk features who have undergone optimal surgical staging should omit adjuvant

chemotherapy, but strong evidence of no benefit from chemotherapy will be needed to reject treatment. The goal of treatment in this population is treatment

For women with resected and wholly stage 1, stage IA, or IB disease, observation alone rather than adjuvant therapy is recommended. For women with high-risk disease (stage IC or II defined as high-grade or clear cell cancers of any stage), adjuvant chemotherapy is recommended. We also recommend the use of adjuvant chemotherapy in women with stage 2 tumors, although it is recognized that in the absence of other risk factors, surveillance may be an acceptable alternative for this subset of patients.

Chemotherapy should be started within 21-35 days in patients who are determined to be high risk after adjuvant treatment primary debulking surgery. Carboplatin and paclitaxel chemotherapy is recommended as an adjuvant treatment regimen. The chemotherapy protocol is applied as carboplatin and paclitaxel throughout the lower cycle. At least three cycles of chemotherapy are performed. Depending on the patient's toxicity and tolerance, it can be extended up to 6 cycles.

Although the efficacy of chemotherapy in serous ovarian carcinomas has an effect on the tumor, it cannot prevent recurrence.

Intravenous or intraperitoneal chemotherapy can be given in patients who underwent optimal cytoreductive surgery (tumor less than 1 cm in primary surgery). PARP inhibitors are used as maintenance therapy in plantine-sensitive tumors. Intravenous and intraperitoneal therapy was

found to be more effective than intravenous chemotherapy alone in patients with optimal cytoreductive surgery.(Tewari D et al.2015)

In the GOG 252 study, there was no difference in terms of treatment between the patients who received bevacizimab treatment and IV chemotherapy and those who received intravenous chemotherapy and intraperitoneal chemotherapy.

The most commonly used intravenous/intraperitoneal (IV/IP) regimen comes from GOG 172 and consists of six cycles. IV paclitaxel (135 mg/m2 in 24 hours) on day 1, IP cisplatin (100 mg/m2 in one liter of normal saline) on day 2, paclitaxel IP (60 mg/m2) on day 8

It is promising to perform HIPEC in advanced epithelial ovarian carcinomas. It is not recommended to apply HIPEC in the first stage and researches are continuing.

Neoadjuvant chemotherapy - We recommend neoadjuvant chemotherapy for women with advanced EOC who are poor candidates for an aggressive initial surgical cytoreduction, or for those with extensive disease that may prevent pre-optimal cytoreduction (<1 cm residual disease). (Wright AA et al,2016). Examples of disease that may be best managed with neoadjuvant therapy because of failure to achieve optimal cytoreduction include tumors containing porta hepatis, metastasizing to the liver or lungs, or causing massive ascites.

Warmed intraperitoneal (IP) therapy (HIPEC) during intermittent volume reduction surgery following neoadjuvant chemotherapy has been evaluated and appears promising but requires further evaluation.

Neoadjuvant therapy is a chemotherapy protocol applied to reduce the extent of the tumor and make it suitable for surgery for patients who are not suitable for surgery, have extensive metastases, and are not candidates for primary surgery due to medical comorbidities. Neoadjuvant chemotherapy is administered in 3 cycles and evaluated with imaging results. If there is improvement in imaging, patients are candidates for surgery. and medical treatment is continued. There was no difference in survival between surgery after neoadjuvant chemotherapy and adjuvant chemotherapy after primary surgery.

In the postoperative evaluation, the patient's complete physical examination, chest, pelvic and upper abdomen tomography are requested. If the patient has a previously requested ca125 value, current values are requested and the response to treatment is evaluated. Those that respond to treatment are called platinum-sensitive tumors. Those that do not respond to treatment are called plantin-resistant tumors. is evaluated.

Most ovarian carcinomas will recur after treatment. Tumors that recur in the first 6 months despite surgical treatment and subsequent platinum therapy are platinum-resistant tumors. Tumors that recur after 6 months are platinum-sensitive tumors. surgical cytoreduction is performed. It is recommended to add bevacizumab to the carboplatin and paclitaxel

regimen in platinum-sensitive tumors. It is recommended to add a PARP inhibitor in patients who cannot tolerate bevacizumab treatment. It is recommended to add a PARP inhibitor in the post-treatment care. If the patient has symptoms, ca125 and necessary imaging methods are recommended. monthly, every 6 months for the next 3 years, annual checks after 5 years are recommended.

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CHAPTER 20

NON-EPITHELIAL OVARIAN TUMORS: A REVIEW

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1. INTRODUCTION

Ovarian cancer is the most deadliest gynecologic malignancy. Survival rates of ovarian cancer are low due to diagnosis at late stages and chemotherapy resistance. Non-epithelial ovarian cancers are extremely challenging uncommon malignancies. Each require special management. Most non-epithelial ovarian tumours arise from specific cells of the ovary. New studies provided evidence that primary ovarian tumors originate in other pelvic organs and secondary ovarian tumors involve the ovary. Ovarian borderline tumors are epithelial origin, grow slowly and are less life-threatening than most ovarian cancers.

This article reviews incidence, pathology, therapeutic interventions, survival and prognostic factors of non-epithelial ovarian cancers.

Women internal reproductive organ cancer generally goes undiscovered until unfolded among the abdomen and pelvis. At this late stage, treat of this organ cancer is challenging (Lee, 2021). Ovarian cancer is the most deadliest gynecologic malignancy. Early detection efforts and therapeutic approaches to degrease mortality is mostly unsuccessful due to poorly understood origin and pathogenesis of epithelial ovarian cancer. Studies reveal that epithelial ovarian cancer is not a single disease but composes of different group of tumors based on morphological and molecular genetic proerties. New studies provided evidence that primary ovarian tumors originate in other pelvic organs and secondary ovarian tumors involve the ovary. It was proposed that serous tumors arise from the implantation of epithelium (benign or malignant) from the fallopian tube. Endometrioid and clear

cell tumors were associated with endometriosis as the precursor of these tumors. As generally, endometriosis develops from endometrial tissue by retrograde menstruation, it is logic to assume that these ovarian neoplasms is sourced from endometrium. New data suggest that mucinous and Brenner tumors arise from transitional-type epithelial nests at the tubal-mesothelial junction by a process of metaplasia. These new concepts may allow new approaches to screen, treat and prevent or reduce the mortality of these diseases (Kurman & Shih, 2010).

Non-epithelial ovarian cancers are extremely challenging uncommon malignancies. These tumours represent 10-15% of all ovarian cancers. They occur at all age groups from children to old women. Each require special management. Eetiology and molecular origins of each non-epithelial ovarian cancer sub-group is still poorly understood (Boussios et al., 2016). Some of the ovarian tumors are benign and never spread outside the ovary. Malignant or borderline ovarian tumors can metastasize and can be fatal. Types of benign epithelial tumors include serous cystadenomas, mucinous cystadenomas, and Brenner tumors. Ovarian borderline tumors are epithelial origin, typically present in young patients and less aggressive than malignant tumors. Borderline tumors affect younger women than typical ovarian cancers. These tumors grow slowly and are less life-threatening than most ovarian cancers (Flicek et al., 2021).

Non-epithelial ovarian tumours represent 10% of all ovarian cancers. Most non-epithelial ovarian tumours arise from specific cells of the ovary (germ cells, theca cells, stromal fibroblasts, granulosa cells, and

steroid cells); The symptoms of non-epithelial ovarian cancers are a subacute pelvic pain, feeling pelvic pressure due to pelvic mass and menstrual irregularities. Diagnostic works should contain pelvic ultrasound, abdomino-pelvic CT, chest X-ray and PET in germ cell tumours [III, B]. At young patients, full blood count, serum human chorionic gonadotropin, alpha-foetoprotein and lactate dehydrogenase levels, and liver and renal function tests should applied (Ray-Coquard et al., 2018). The WHO classification of germ cell tumours has two main groups. 1) Malignant germ cell tumours (GCTs) which include Dysgerminoma, Yolk sac tumour, Embryonal carcinoma, Non-gestational choriocarcinoma, Mature teratoma, Immature teratoma Mixed germ cell tumour. 2) Sex cord stromal tumours (SCSTs) which include Fibroma, Cellular fibroma, Thecoma, Luteinized thecoma associated with sclerosing peritonisis, Fibrosarcoma, Sclerosing stromal tumour, Signet-ring stromal tumour, Microcystic stromal tumour, Leydig cell tumour, Steroid cell tumour, Steroid cell tumour, malignant, Adult granulosa cell tumour, Juvenile granulosa cell tumour, Sertoli cell tumours, Sex cord tumour with annular tubules, Sertoli–Leydig cell tumours, Sex cord-stromal tumours not otherwise specified (Young, 2014)

Survival rates of ovarian cancer are low due to diagnosis at late stages and platinum chemotherapy resistance sourced disease recurrence. High-grade serous ovarian cancer is the most common ovarian cancer subtype. This is treated with surgery and chemotherapy with paclitaxel/carboplatin combination. First response rates are 60–80%, but majority of patients become platinum-resistant with following

relapses. Researches on individual biomarkers of platinum resistance was revealed different targets for new treatments. There exist also epigenetic, DNA repair, genome and immune changes characterised in platinum-resistant high-grade serous ovarian cancer which may be targeted with therapies (van Zyl et al., 2018). Improvements in outcome for advanced-stage ovarian cancer patients are low due to intrinsic and acquired chemoresistance and tumor heterogeneity at diversified anatomical sites in relation with disease progression. Molecules and cellular pathways which mediate chemoresistance is different for histological types of ovarian carcinoma (Davidson, 2016).

2. Genes & Markers

PTEN is a tumour suppressor gene. Its loss of function is observed in heritable and sporadic cancers. Its involvement in different biological processes cover maintenance of genomic stability, cell survival, migration, proliferation and metabolism. Improved understanding of PTEN activity and regulation is emerged as an interest in cancer research (Nero et al., 2019). Granulosa-cell tumors are the most frequent malignant ovarian sex cord–stromal tumor type. Its pathogenesis is unknown, histopathological diagnosis may be a challenge, and there isn't any curative treatment different than surgery. Shah et al., (2009) conducted a whole-transcriptome sequencing for four Granulosa-cell tumors. They identified a single, recurrent somatic mutation in FOXL2 which was exsisting in nearly all morphologically identified adult-type granulosa-cell tumors. Mutant FOXL2 was determined as a potential effector for the pathogenesis of adult-type

Granulosa-cell tumors (Shah et al., 2009). In sex cord-stromal tumors and germ cell tumors, tumorigenesis is a result of multiple genetic alterations pushing a normal cell into malignant state. A single point missense mutation (C134W) was determined in FOXL2 gene in nearly 95% of adult-type granulosa cell tumors, which suggest a significant role for FOXL2 in these tumors (Van Nieuwenhuysen et al., 2013). FOXL2 mutation was determined in adult granulosa cell tumours. DICER1 mutations were described predominantly in Sertoli–Leydig cell tumours. Opposite to FOXL2 mutations in adult granulosa cell tumours, DICER1 mutations in Sertoli–Leydig cell tumours may be better for prognosis than diagnosis. Identification of genetic alterations in sex cord–stromal tumours are promising therapeutic options (Goulvent et al., 2016). For ovarian sex cord-stromal tumors immunostaining and molecular analysis for Forkhead box L2 (FOXL2) was developed in pathology (Maillet et al., 2014).

Many studies showed that miRNAs are differentially expressed in epithelial ovarian cancer and act as oncogenes or tumor suppressor genes. Cancer cells secrete exosomes containing miRNAs, that exert diversified effects on the tumor microenvironment components (cancer-associated fibroblasts, adipocytes and macrophages). Also cancer cells receive exosomes from these cells. Due to cell-to-cell communication, epithelial ovarian cancer transforms into a much more aggressive phenotype and get resistance to multiple drugs. Some circulating miRNAs are protected from RNase degradation in the peripheral blood and have potentials as non-invasive biomarkers. Combination of different circulating miRNAs enhance cancer

screening accuracy. It was revealed that specific miRNA signatures in non-epithelial ovarian tumors and many miRNAs contribute to carcinogenic pathways alterations. miRNAs play a significant role in ovarian cancer progression and in the near future, miRNAs will be expected to be practical biomarkers. Also, miRNAs are potential therapeutic targets and agents. There are active clinical trials on miRNA replacement therapies currently (Yoshida et al., 2020). Chang et al., (2018) characterized miRNA expression profiles of nine ovarian germ cell tumors (two malignant and seven benign) and three sex cord stromal tumours using small RNA sequencing. Significant miRNA expression variations were observed among three tumor groups.

Neuron-restrictive silencer factor can be upregulated or downregulated according to the type of tumor. Neuron-restrictive silencer factor significantly gets upregulated in ovarian cancer cells and tissues and negatively related with patient survivals. Knockout of neuron-restrictive silencer factor inhibit proliferation of ovarian cancer cells. Neuron-restrictive silencer factor may influence G1/S transition of cell cycle via regulating the transcription of Hippo pathway. Neuron-restrictive silencer factor may be a valuable early detection marker of ovarian cancers and inhibiting their expression can be an effective method for the treatment of ovarian cancers (Deng et al., 2018).

3. Metastasis

Increased incidence of uterine and breast malignancies are observed among patients diagnosed with granulosa cell tumors (Nasioudis et al., 2019). Cancer metastasis and therapy resistance are main unsolved

challenges. They cover nearly all cancer-related deaths. Both therapy resistance and metastasis are supported by 1) epithelial plasticity, 2) reversible phenotypic transitions between epithelial and mesenchymal phenotypes, including epithelial-mesenchymal transition (EMT) 3) mesenchymal-epithelial transition (MET). Epithelial-mesenchymal transition and mesenchymal-epithelial transition are binary processes. Here, cells detach from primary tumor as individual units with many traits of a mesenchymal cell and then convert back to being epithelial. But, new studies showed that cells may metastasize in alternative ways. They can detach as clusters, and/or occupy one or more stable hybrid epithelial/mesenchymal (E/M) phenotypes that can be the end point of a transition. Such hybrid E/M cells can integrate various epithelial and mesenchymal traits and markers, facilitating collective cell migration. Hybrid E/M cells can possess higher tumor-initiation and metastatic potential compared to cells on epithelial-mesenchymal transition spectrum (Jolly et al., 2019).

Activation of Notch1 induces epithelial–mesenchymal transition in epithelial ovarian cancer cells. This is prooved by downregulation of E-cadherin and cytokeratins, upregulation of Slug and Snail, and morphological changes. Interestingly, activation of Notch1 increases “Transforming growth factor beta/Small mothers against decapentaplegic” (TGFβ/Smad) signaling by upregulating the expression of transforming growth factor beta and transforming growth factor beta type 1 receptor. Inhibition of Notch by DAPT (a γ-secretase inhibitor) decreases transforming growth factor beta-induced phosphorylation of receptor “Small mothers against decapentaplegic”

at late timepoints. Results suggest that Notch activation plays a role in sustaining transforming growth factor beta/Smad signaling in epithelial ovarian cancer cells. Notch and transforming growth factor beta form a reciprocal positive regulatory loop and cooperatively regulate epithelial–mesenchymal transition and promote epithelial ovarian cancer cell motility and migration (Zhou et al., 2016).

Myeloid-derived suppressor cells are immune cells populations which negatively regulate immune responses. This may promote tumor invasion and metastasis. Tumor may actively reshape the immune-microenvironment for progression. “Karyopherin alpha 2” is a candidate oncogene in ovarian cancer which is tightly related to Myeloid-derived suppressor cell density. There is a positive position feedback between “Karyopherin alpha 2” expressed and Myeloid-derived suppressor cells density. This may contribute to the poor prognosis of patients. Explaining the molecular mechanisms for the KPNA2 regulation of ovarian cancer via suppressing immune system may produce new strategies for molecular targeted therapy combining biological therapy for ovarian cancer (Huang et al., 2017).

Hormonal therapies are generally applied to metastatic granulosa cell tumours patients, based on high response rates in small retrospective studies. Aromatase inhibitors have high response rates and an accepted treatment option (Banerjee et al., 2021).

A role for cancer cell epithelial-to-mesenchymal transition in cancer is well established. Additional to cancer cell epithelial-to-mesenchymal transition, ovarian cancer cell metastasis relies on epigenomic

mesenchymal-to-epithelial transition in host mesenchymal stem cells. These reprogrammed mesenchymal stem cells, termed “carcinoma-associated mesenchymal stem cells”, acquire pro-tumorigenic functions and directly bind cancer cells to serve as a metastatic driver/chaperone. Cancer cells induce this epigenomic mesenchymal-to-epithelial transition characterized by enhancer-enriched DNA hypermethylation, altered chromatin accessibility, and differential histone modifications. This phenomenon appears clinically relevant, as “carcinoma-associated mesenchymal stem cells” mesenchymal-to-epithelial transition is highly correlated with patient survival. Mechanistically, mirroring mesenchymal-to-epithelial transition observed in development, mesenchymal-to-epithelial transition in “carcinoma-associated mesenchymal stem cells” is mediated by “Wilms tumor 1” gene and “enhancer of zeste homolog 2” gene. Importantly, “enhancer of zeste homolog 2” gene inhibitors, which are clinically available, significantly inhibited “carcinoma associated mesenchymal stem cells mediated metastasis” in mouse models of ovarian cancer (Fan et al., 2020).

4. Programmed cell death

High PD-L1 (programmed death ligand 1) expression is associated with worse oncological outcomes in type I epithelial ovarian cancers (Nhokaew et al., 2019). Recently, “programmed cell death protein 1” (PD1) blocking and “anti-programmed death-ligand 1” agents were approved for the treatment of various human malignancies. As well as cancer cell expression of “programmed death ligand 1”, a high “Soluble Programmed Death Ligand-1” level characterizes a subset of patients

with ovarian cancer. The value of this latter feature as a biomarker for the administration of anti-PD-L1/PD1 therapy needs further evaluation. Micro-RNAs, such as miR34a and miR200, may have a role in the efficacy of immunotherapy (Koukourakis et al., 2018).

5. Chemotherapy

Most of the advanced ovarian germ cell cancer patients are treated by cisplatin-based chemotherapy. Instead of adequate first-line treatment, nearly 1/3 of patients relapse and almost 1/2 develop cisplatin-resistant disease. Treatment of cisplatin-resistant disease is challenging and prognosis remains poor (De Giorgi et al., 2019). Epithelial ovarian cancer is responsive to cisplatin and carboplatin. These two are DNA damaging agents as first line therapy. However, patients relapse with a tumor resistant to subsequent treatment with platinum containing drugs. Several mechanisms are associated with the development of acquired drug resistance (Damia & Broggini, 2019). Bleomycin-induced pneumonitis is commonly occur in sex cord stromal tumours patients and lacks effective treatment. Prevention lies in limiting cumulative bleomycin dose, monitoring pulmonary function during treatment, discontinuing bleomycin at the onset of pulmonary symptoms or if pulmonary function is impaired, and avoiding bleomycin in older patients (Delanoy et al., 2015).

In epithelial ovarian cancer, stromal tumour infiltrating lymphocytes levels are prognostic at diagnosis and after neoadjuvant chemotherapy. Tumour infiltrating lymphocytes and “programmed death ligand 1” expression increase following neoadjuvant chemotherapy. Evaluation

of immune parameters in the post-neoadjuvant chemotherapy tumour may help select patients for immunotherapy trials (Mesnage et al., 2017). Sex cord stromal tumors are typically detected at an early stage, and may recur in a period of 30 years after initial treatment. 70% of the patients present with stage I tumors. As a result, surgery is the most important therapeutic way. There are no data on any type of postoperative adjuvant treatment for stage IA or IB Sex cord stromal tumors patients. Platinum-based chemotherapy is currently used for patients with advanced stage sex cord stromal tumors or recurrent disease (Ray-Coquard et al., 2014).

The Wnt/β-catenin signaling pathway which is regulating stemness in a broad spectrum of stem cell niches including the ovary, play an important role in ovarian cancer. Wnt activity correlates with grade, epithelial to mesenchymal transition, chemotherapy resistance, and poor prognosis in ovarian cancer (Teeuwssen & Fodde, 2019).

Instead of improvements in treatment modalities lead to a longer survival period, patients death rates with solid tumors is not changed in the last decades. Emerging studies identified many physical barriers limiting the therapeutic performance of cancer therapeutic agents such as chemotherapeutic agents, monoclonal antibodies, gene therapeutics and anti-tumor immune cells. Most solid tumors origin from epithelial and, although malignant cells are de-differentiated, they maintain intercellular junctions, which is an important feature of epithelial cells, in primary tumor and in metastatic lesions. Nests of malignant epithelial tumor cells are shielded by layers of extracellular matrix proteins

(collagen, fibronectin, elastin, laminin) whereby tumor vasculature rarely penetrates into the tumor nests. Malignant tumor cells protect themselves from immune responses of host and from anti-cancer therapeutics by building physical barriers preventing intratumoral penetration to contact malignant cells. Production of cytokines and chemokines attract fibroblasts and myeloid cells into the tumor, differentiate them into tumor growth support cells and produce extracellular matrix proteins shielding malignant tumor cells nests. Although malignant cells show a high level of de-differentiation, they maintain epithelial junctions sealing the paracellular space between tumor cells to block access to tumor antigens or target receptors. Tumor extracellular matrix and epithelial junctions are major basic mechanisms building cancer treatment resistance. Due to their importance for the tumor, they are weak chain to be used at cancer therapy. Removing these barriers may directly affect tumor cells negatively or simplify anti-tumor immune responses and drug treatment for higher intratumoral penetration and access to target cells. Some experimental approaches focused on transient degradation or downregulation of extracellular matrix proteins by injection of extracellular matrix-degrading enzymes in tumor or their intratumoral expression after viral- based or stem cell-based gene transfer. Recombinant epithelial junction opener used in combination with Doxil chemotherapy in ovarian cancer patients is an ongoing study. Other approach is to overcome physical barriers in tumors by indirectly decrease tumor-associated extracellular matrix by killing tumor stromal cells that produce extracellular matrix proteins (tumor-associated

fibroblasts or macrophages). Extracellular matrix production and epithelial junctions can also be targeted through influencing signaling pathways in tumor cells, specifically pathways involved in the regulation of EMT/MET and hypoxia. There is an increasing approaches to enhance the efficacy of classical cancer therapeutics and overcome treatment resistance (Choi et al., 2013).

Prognosis of epithelial ovarian cancer is a combination of late diagnosis and increasing resistance to chemotherapy and targeted therapy. Organoids, a novel in vitro 3D cell culture derived from stem cells of various organs and tissues, could provide an interesting in vitro preclinical platform to address these issues and could be the next step for personalized medicine (Sander Dumont et al., 2019).

6. CONCLUSIONS

Survival rates of ovarian cancer are low due to diagnosis at late stages and chemotherapy resistance. Non-epithelial ovarian cancers are extremely challenging uncommon malignancies. Most non-epithelial ovarian tumours arise from specific cells of the ovary. New studies provided evidence that primary ovarian tumors originate in other pelvic organs and secondary ovarian tumors involve the ovary. Therapeutic performance of cancer therapeutic agents such as chemotherapeutic agents, monoclonal antibodies, gene therapeutics and anti-tumor immune cells are not very successful for non-epithelial ovarian cancers. There is an increasing approaches to enhance the efficacy of classical cancer therapeutics and overcome treatment resistance. Molecules and cellular pathways are targets for novel approaches. Accelerating

research on miRNA might improve the prognosis of patients with ovarian cancers.

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CHAPTER 21

GYNECOLOGIC INFECTIONS

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They are divided into sexually transmitted and non-transmitted. Sexually transmitted infections are an important public health problem.

1. VAGINITIS

Vaginitis is the general name for vaginal disorders caused by infection, inflammation or changes in the normal vaginal flora. Some of symptoms are vaginal discharge, odor, pruritus, and/or discomfort. In normally estrogenized premenopausal women, the non-keratinized stratified squamous epithelium of the vagina is rich in glycogen. The substrate of Döderlein lactobacillus is glycogen from shed cells and converts glucose to lactic acid, creating an acidic vaginal environment (pH 4.0 to 4.5). This acidity helps maintain normal vaginal flora and inhibits the growth of pathogenic organisms. Sexually transmitted diseases, antibiotics, foreign body, estrogen level, use of hygienic products, pregnancy, sexual activity and choice of contraceptives may lead to disruption of the normal ecosystem. Bacterial vaginosis, Candida vulvovaginitis, and trichomonas account for more than 90 percent of infections (Sobel, 1999) Noninfectious etiologies include atrophic vaginitis, foreign body, irritants, allergens and some systemic medical disorders (eg, systemic lupus) (Sobel, 2021).

1.1. Bacterial vaginosis:

Bacterial vaginosis is a polymicrobial clinical syndrome. It is the disruption of the normal flora as a result of loss of lactobacilli and overgrowth of mainly anaerobic bacteria. The absence of inflammation is the basis for the term "vaginosis" rather than "vaginitis". The main

bacteria detected in women with bacterial vaginosis are Gardnerella vaginalis, Prevotella spp., Porphyromonas spp., Bacteroides spp., Peptostreptococcus spp., Mycoplasma hominis and Ureaplasma urealyticum. Sexual activity, sexually transmitted infections, vaginal douching and cigarette smoking are some risk factors for BV. Gram staining of vaginal discharge is the gold standard for the diagnosis of bacterial vaginosis (Nugent et al., 1992). Diagnosis of bacterial vaginosis requires Amsel criteria (at least three criteria must be present) (Workowski and Bolan, 2015). These criteria are:

1-Homogeneous, thin, white discharge that smoothly coats the vaginal walls
2-Vaginal pH >4.5
3-Positive whiff-amine test
4-Clue cells

Vaginal culture is not useful in the diagnosis of bacterial vaginosis. If microscopy is not available, physical examination, pH testing, olfactory-amine testing are recommended to diagnose bacterial vaginosis. Metronidazole, clindamycin, tinidazole or secnidazole can be used for treatment. There is no need for sexual partner treatment (Sobel and Michell, 2020).

1.2. Trichomoniasis:

Trichomoniasis is a genitourinary infection with the protozoan Trichomonas vaginalis. It is the most common nonviral sexually transmitted disease worldwide. Men are less affected than women.

Trichomoniasis is almost always sexually transmitted (CDC, 2017). T. vaginalis has been associated with an adverse reproductive health outcomes. The risk of contracting T. vaginalis infection can be reduced by using condoms and limiting the number of sexual partners. Common signs and symptoms of acute infection include burning, pruritus, dysuria, frequency, lower abdominal pain, or purulent, malodorous, thin discharge associated with dyspareunia [5] (CDC, 2017). Physical examination often reveals erythema of the vulva and vaginal mucosa, green-yellow, frothy, foul-smelling discharge, and punctate bleeding in the vagina and cervix (ie strawberry cervix). Diagnosis of Trichomonas vaginalis is based on a positive culture, positive nucleic acid amplification test or positive rapid antigen test (ACOG, 2020). Nucleic acid amplification test is the gold standard for the diagnosis. Metronidazole, tinidazole or secnidazole can be used for treatment. Treatment is indicated for both symptomatic and asymptomatic patients. Treatment of sex partners is necessary. Patients should be screened for other sexually transmitted infections.Patients should be instructed to abstain from sexual intercourse until they and their partners have completed treatment and are asymptomatic, which usually lasts about one week (Sobel and Michell, 2020).

1.3. Candida vulvovaginitis:

Vulvovaginal candidiasis is one of the most common causes of vulvovaginal itching and discharge. Vulvovaginal candidiasis accounts for approximately one-third of vaginitis cases (Workowski, Bolan, 2015). Candida albicans and candida glabrata are responsible for almost

all cases. It is not accepted a sexually transmitted disease. The risk factors are diabetes mellitus, using antibiotic, increased estrogen levels (pregnancy and postmenopausal estrogen therapy), immunosuppression and genetic. Discharge one of symptoms is classically white, thick, adherent to the vaginal sidewalls, and clumpy (curd-like or cottage cheese-like) with no or minimal odor. Evaluation of vaginal pH and microscopy are appropriate for diagnosis. The vaginal pH is normal and pathogenic yeast is seen on microscopy. With uncomplicated Candida vaginitis, culture is not required for diagnosis if yeast is seen under the microscope, but culture is necessary in refractory and recurrent disease. Treatment is indicated for relief of symptoms, and asymptomatic carriers do not require treatment. Fluconazole and ibrexafungerp are used for uncomplicated infection. Uncomplicated infection means less than 4 episodes in a year, mild to moderate signs, healthy person who is not immunosuppressed and infection with Candida albicans. Complicated infection means more than 3 episodes in a year, severe signs, pregnancy, poorly controlled diabetes, immunosuppression and infection with other candida species. Fluconazole, ibrexafungerp, vaginal boric acid, nystatin and intravaginal clotrimazole, miconazole or terconazole can be used for complicated infection. And complicated infection requires longer treatment. Treatment of sexual partners is not recommended (Sobel and Michell, 2020).

1.4. Desquamative inflammatory vaginitis:

It is a clinical syndrome that causes intense purulent discharge. Besides, there may be dyspareunia, vaginal/introital pain, burning, pruritus complaints. Vaginal pH is measured as >4.5 in these patients. Intravaginal clindamycin or glucocorticoids can be used for treatment (Sobel, 1994).

1.5. Atrophic vaginitis:

Vaginal atrophy typically occurs in menopausal patients, but can also occur in women of any age with low estrogenic stimulation of the urogenital tissues. On physical examination, it can be seen that the external genitalia have atrophy and loss vaginal rugae. Some symptoms of atrophic vaginitis are vulvovaginal dryness, burning, irritation and dyspareunia (Portman and Gass, 2014). Vaginal estrogen is used to treat atrophic vaginitis (Bachman and Pinkerton, 2022).

2. CERVICITIS

Cervicitis means to inflammation of the uterine cervix. The same microorganisms that cause vaginitis can cause inflammation of the ectocervical epithelium. Acute cervicitis is usually due to infection, while chronic cervicitis usually has a non-infectious causes. While the most common causes are Chlamydia trachomatis and Neisseria gonorrhoeae, other causes include Herpes simplex virus, Mycoplasma genitalium and Trichomonas vaginalis (Workowski et al., 2021). Non-infectious causes are usually mechanical or chemical irritation. It is

diagnosed clinically. It is diagnosed with yellow or green mucopurulent endocervical discharge (Brunham et al., 1984). The first aim of treatment is to prevent upper genital tract infection. The second aim of treatment is relief of symptoms. Because of Chlamydia trachomatis and Neisseria gonorrhoeae are the most common infectious etiologies of cervicitis, empirical treatment should be applied for them. Doxycycline 100 mg orally twice a day for seven days is preferred for Chlamydia. A single dose of ceftriaxone is sufficient for gonorrhea. Sexual partners of patients should be treated at the same time (Powell and Nyirjesy, 2021).

3. PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) refers to acute infection of the upper genital tract. The upper genital tract includes the uterus, fallopian tubes, and ovaries. The endocervical canal acts as a barrier protecting the normally sterile upper genital tract. Sexually transmitted pathogens can disrupt this barrier. While Neisseria gonorrhoeae and Chlamydia trachomatis are generally the causative microorganisms, PID is generally considered polymicrobial [16-18] (Lis et al., 2015); (Forslin et al., 1978). The risk factors are sex, multiple partners, age, partner who has got STI and PID history. Risk of developing PID for IUD user limited to the first three weeks after IUD insertion. Barrier methods protect against PID (Eschenbach et al., 1977). Traditionally, the diagnosis of PID is made with pelvic pain, painful cervical movements, adnexal tenderness, and high fever. PID should be suspected in any young or sexually active female patient who presents with pelvic

discomfort (Ross, 2020). Since the clinical symptoms are mild in many PID patients, delay in diagnosis and treatment may cause sequelae in the genital organs (Hillis et al., 1977). Pelvic imaging (transvaginal ultrasound, CT, or MRI) may show fluid-filled tubes/ovarian ducts or a tubo-ovarian complex. Also, laparoscopy and endometrial biopsy can help confirm the diagnosis. PID can be treated on an outpatient basis, but if severe clinical illness ,tubo-ovarian abscess, pregnancy, unresponsiveness to oral medications, inability to take oral medications and need for surgical intervention are present need for hospitalization and parenteral antibiotics [21] (Workowski et al., 2021). Antibiotic therapy options depend on whether the patient is initially hospitalized or managed as an outpatient. You can see the PID treatment for outpatient and inpatient treatment in table 1 (Soper, 2010).

Table 1. Treatment of PID

Outpatient therapy
Cefoxitin (2 g intramuscularly) with probenecid (1 g orally) or
Ceftriaxone (250 mg intramuscular) or
Equivalent cephalosporin
+
Doxycycline (100 mg orally twice daily for 14 days) or

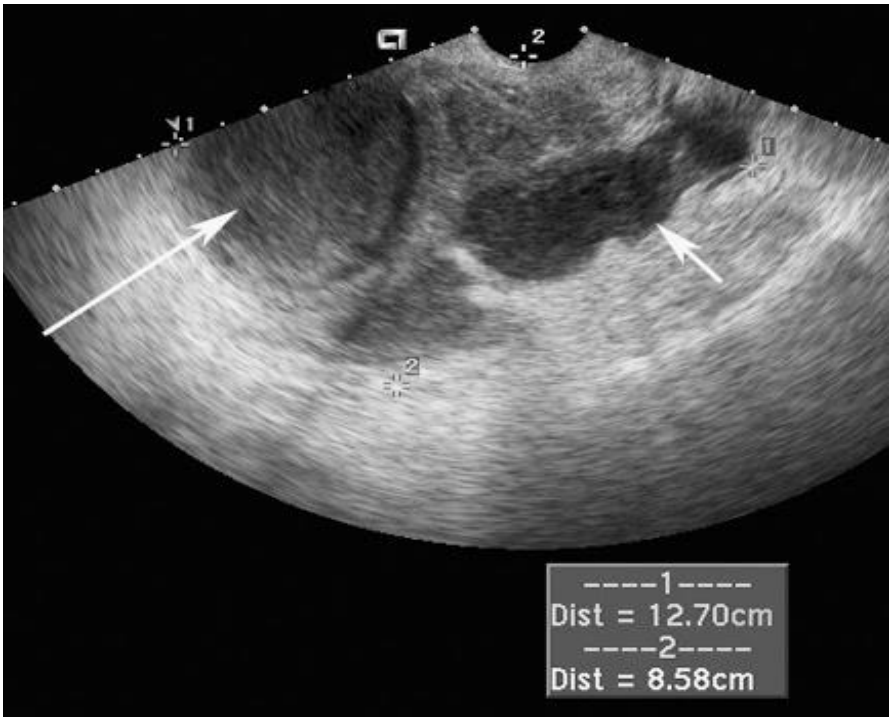
Azithromycin (500 mg daily for 7 days, then 250 mg for another 7 days)

Inpatient therapy

Regime A
Cefoxitin (2 g intravenously every six hours) or
Cefotetan (2 g intravenously every 12 hours)
+
Doxycycline (100 mg orally or intravenously every 12 hours)
Regime B
Clindamycin (900 mg intravenously every eight hours)
+
Ceftriaxone (1-2 g intravenously every 12 hours) or
Gentamicin (3 to 5 mg/kg intravenously daily or 2 mg/kg intravenously once followed by 1.5 mg/kg every eight hours).

4. TUBO-OVARIAN ABSCESS

It is the last stage of acute PID, usually produces a palpable pelvic mass on physical examination and potentially life-threatening condition. Once patients are diagnosed with PID, further evaluation for tubo-ovarian abscess (TOA) is required. Pelvic ultrasonography or pelvic computed tomography (CT) are the most useful and common imaging modalities. Ultrasound is also useful for excluding other genital tract pathology. Computed tomography may also be used, particularly when pathology associated with the gastrointestinal tract must be excluded (eg, appendicitis, abscess associated with inflammatory bowel disease).



Imagine 1. Tubo-Ovarian Abscess

Transvaginal ultrasound image of the left adnexa showing a tubo-ovarian abscess. A complex solid and cystic mass is identified. The tubo-ovarian abscess is seen as a complex cyst and fluid-filled tube (Beigi, 2022).

Treatment options for TOA include antibiotic therapy, drainage procedures, invasive surgery, or a combination of these interventions. 75% of women with tubal ovarian abscess respond to antibiotic therapy alone. Medical treatment failure indicates the need for abscess drainage (Reed et al., 1991). Patients suspected of having a ruptured TOA or who present with signs of sepsis require surgical exploration (Beigi, 2021).

5. GENITAL ULCERS

The most of genital ulcers are caused by sexually transmitted infections, although there are noninfectious causes. Sexually transmitted pathogens are Herpes simplex virus types I and II, Treponema pallidum, Chlamydia trachomatis, Haemophilus ducreyi and Klebsiella granulomatis. Other rare Noninfectious etiologies of genital ulcers include fixed drug reactions, Behçet syndrome, neoplasms, Crohn's disease, and trauma (Sehgal et al., 2014); (Davis-Kankanamge, 2016). Diagnosis based on history and physical examination alone is often incorrect. Although the history and physical examination can give important clues to the diagnosis, it is important that diagnostic testing must be done to confirm the infectious agent. However, instead of waiting for diagnostic test results, empirical treatment is usually started (Tuddenham and Ghanem, 2020).

5.1.Herpes simplex virus

Both herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) can cause genital herpes. Herpes simplex virus (HSV) infection are divided into three 1- primary, 2- non-primary and 3- recurrent. The clinical symptoms of genital herpes simplex virus (HSV) vary accordingly. In primary infection can be severe genital ulcers, dysuria, fever and tender local inguinal lymphadenopathy. In non-primary infection, symptoms are usually not severe because of antibodies to HSV. Recurrent infection is typically less severe than primary or non primary infections. Vesicles grouped together with small ulcers are almost always specific to genital herpes, especially if there is a similar history in the past. A clinical diagnosis of genital herpes should be confirmed with laboratory testing [26]. Viral culture, polymerase chain reaction (PCR), direct fluorescence antibody, and type-specific serologic tests can confirm the diagnosis of HSV infection. The most sensitive test is PCR. Acyclovir (400 mg three times daily or 200 mg five times daily), famciclovir (250 mg three times daily) and valacyclovir (1000 mg twice daily) can be used for treatment for 7 to 10 days (Workowski and Bolan, 2015).

5.2. Syphilis

The microorganism that causes syphilis is Treponema pallidum. Syphilis is divided into three as early syphilis, late syphilis and neurosyphilis. Early syphilis has two stages primary syphilis and secondary syphilis. The lesion of primary syphilis, the chancre, begins

as a painless papule and ulcerates. The chancre heals spontaneously, even without treatment. Within weeks to a few months after the chancre develops, approximately 25 percent of individuals with untreated infection develop a systemic illness that represents secondary syphilis (Clark and Danbolt, 1964). Patients with secondary syphilis may develop systemic symptoms including fever, headache, malaise, anorexia, sore throat, myalgias, and weight loss. Condylomata lata is also seen. Approximately 25 to 40 percent of patients with untreated syphilis can develop late syphilis (Rosahn, 1947).There are two serologic tests for syphilis to diagnose: nontreponemal tests and treponemal-specific tests. Nontreponemal tests are rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL). Treponemal tests are Fluorescent treponemal antibody absorption (FTA-ABS) and Microhemagglutination test for antibodies to T. pallidum (MHA-TP). The diagnosis is confirmed with the treponemal test, while the initial screening is performed with the nontreponemal test. The preferred regimen for early syphilis is penicillin G benzathine (2.4 million units intramuscularly once), but for late syphilis it is once a week for three weeks.

5.3. Lymphogranuloma venereum

The causative agent in genital ulcer disease is L1, L2, and L3 biovars of Chlamydia trachomatis (Workowski et al., 2021). Lymphogranuloma venereum (LGV) has got three stages: primary infection, secondary infection and late LGV. First a genital ulcer or a mucosal inflammatory reaction appear. Two to six weeks later after

these lesions the characteristic groove sign occurs which is an inflammatory reaction. Complications include chronic colorectal fistulas and strictures if left untreated in the late LGV. Diagnosis of Chlamydia trachomatis is based on nucleic acid amplification testing (NAAT), culture, antigen detection, and genetic probes. Routine screening with NAAT should be offered to sexually active patients at high risk of infection because of chlamydial infections are asymptomatic. The main goal of treatment is to prevent complications. In addition, azithromycin (1 g orally once a week for three weeks) is an alternative (Workowski et al., 2021); (de Vries et al., 2019). People who diagnosed with C. trachomatis should be screened for sexually transmitted infection and sexual partners should be examined and treated.

5.4. Chancroid

The causative microorganism is Haemophilus ducreyi. The most common sites for chancroid are the labia, vaginal introitus, and perianal areas in women. Ulcers, lymphadenopathy and fluctuant bubos are seen in this disease. Presence of 1-3 very painful ulcers accompanied by tender inguinal lymphadenopathy is compatible with chancroid. Culture and NAAT tests are available to diagnose H. ducreyi. Azithromycin 1 g orally in a single dose or ceftriaxone 250 mg IM in a single dose preferred for treatment. Ciprofloxacin and erythromycin may be alternative regimens for patients who cannot take azithromycin or ceftriaxone (O'Farrell and Lazaro, 2014); (Workowski et al, 2021). Sex partners of patients with chancroid should be treated if they have had

sexual contact with the patient within 10 days of symptom presentation (Workowski et al, 2021).

6. ANOGENITAL WARTS

External genital warts are a symptom of Human papillomavirus (HPV) infection (Beutner et al., 1998). HPV types 6 and 11 are detected in most cases of condylomata acuminata, also known as anogenital warts. Anogenital warts are almost always transmitted through sexual contact and are most common in young adults (Hoy et al., 2009). External genital warts usually appear in anogenital areas, such as the vulva, groin, perineum, perianal skin, or mucosal surfaces (Lynde et al., 2013). Malignant degeneration of anogenital warts is unlikely, but malignant transformation can occur in immunocompromised individuals. (Gormley and Kovarik, 2012); (Paul et al., 2015). Findings that suggest CA are single or multiple soft, smooth or papillated papules or plaques. There are two treatment options, medical treatment and surgical treatment. Medical treatment includes podophyllotoxin, imiquimod, sinecatechins, fluorouracil, interferon, trichloroacetic acid and bichloracetic acid. Surgical treatment consists cryoablation, laser ablation, electrocautery, the cavitron ultrasonic aspirator (CUSA) technique and excision. Although treatment can eradicate the warts, disease recurrence occurs in 20 to 30 percent of patients overall.

7. HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

Human immunodeficiency virus (HIV) most often enters the host through the anogenital mucosa. The viral envelope protein,

glycoprotein (GP)-120, binds to the CD4 molecule. Half of the HIV population is women (UNAIDS, 2017). Heterosexual contact is the most common reported risk factor for women, having overtaken injection drug use (CDC, 2011). HIV infection creates a wide spectrum from asymptomatic patient to Acquired Immunodeficiency Syndrome. HIV testing should be performed in patients with clinical signs and symptoms and in patients with potential exposure to HIV. Infection is most commonly diagnosed with HIV antibody tests. Tests to diagnose HIV infection detect antibodies, antigens, and HIV RNA. In the initial evaluation of the disease, screening for tuberculosis and sexually transmitted diseases should be performed. The decision regarding the initiation of antiretroviral therapy is made according to HIV RNA, CD+ cell count, laboratory parameters and the clinical condition of the patient. The goals of antiretroviral therapy are to suppress viral load as much and as long as possible, to prevent transmission, and to reduce morbidity and mortality. The use of dual nucleoside regimens in addition to protease inhibitor or mononucleoside reverse transcriptase inhibitor provides better and longer-lasting clinical benefit than monotherapy.

8. ACUTE SIMPLE CYSTITIS

Women with acute cystitis have suprapubic pain in addition to urinary system symptoms such as dysuria and frequent urination, urinary urgency (Bent et al., 2002). Hematuria is also often observed. The risk factors are sexual intercourse, use of diaphragms and spermicides, history of urinary tract infections (Hooton et al., 1996); (Scholes et al.,

2005). The most common bacteria isolated from the urine of young women with acute cystitis is Escherichia coli (Stamm et al., 1982). The pathogenesis of urinary tract infection in women begins with the invasion of the vaginal entrance by uropathogens from the fecal flora. For those with suspected acute simple cystitis with classic symptoms, no additional testing is required to make the diagnosis. Urine culture and susceptibility testing are also often unnecessary in women with acute simple cystitis, but should be performed if there is a risk of a resistant organism. The preferred agents for empiric therapy are nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin (Gupta et al., 2011).

9. RECURRENT SIMPLE CYSTITIS

Recurrent urinary tract infection refers to ≥2 infections in six months or ≥3 infections in one year. There are typical symptoms that include dysuria, urinary frequency, urgency, and suprapubic pain. Risk factors are frequent sexual intercourse, use of spermicides, and mechanical and/or physiologic factors that impede bladder emptying (Hooton et al., 1996). In the presence of these symptoms, the diagnosis of recurrent cystitis is evident and testing is unnecessary to establish the diagnosis. In some special cases, urine culture can be performed like antimicrobial resistance or severe infection. Behavioral approaches such as increasing fluid intake are recommended for prevention. It can be treated with vaginal estrogens in postmenopausal women and, in selected cases, antibiotics.

10. ACUTE PYELONEPHRITIS

The clinical spectrum of acute pyelonephritis in young women ranges from cystitis-like with mild flank pain to gram-negative septicemia. Escherichia coli is responsible for more than 80% of these cases (Stamm et al., 1982). Symptoms and signs of pyelonephritis classically include fever, chills, flank pain, costovertebral angle tenderness, and nausea/vomiting (Fairley et al., 1971). A urine culture should be performed from all women with suspected pyelonephritis. In the absence of nausea, vomiting and severe illness, outpatient oral therapy can be given. Trimethoprim-sulfamethoxazole and fluoroquinolones are used in outpatient regimens. In inpatient treatment parenteral levofloxacin, ceftriaxone, ampicillin and gentamicin or aztreonam are used. If fever and flank pain persist 48-72 hours after the start of treatment, ultrasound or computed tomography can be performed to exclude renal abscess or urethral obstruction. A follow-up culture should be performed two weeks after completion of treatment (Gupta et al, 2011).

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CHAPTER 22

ENDOMETRIOSIS

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INTRODUCTION

Endometriosis is defined as the presence of endometrial tissue outside the uterine cavity. In another definition, it is necessary to show that normal physiology is affected and to observe cellular activation.. It causes consequences such as chronic pain, dysmenorrhea, dyspareunia, infertility. Women are affected in terms of physical, mental and social well-being in the most productive period of their lives, and this disease affects their relationships, social activities, fertility, physical and sexual functioning possibly negatively affecting making career choices or advancing in a chosen career .About 10 percent of women of reproductive age have endometriosis, and the true prevalence is not known precisely because of the difficulty in diagnosis (Shafrir et al., 2018); (Soliman et al., 2018). Nulliparity has been shown to be associated with conditions such as early menarche, late menopause, short menstrual cycles, severe menstrual bleeding, and low body mass index (Ballard et. Al., 2008); (Hediger et al., 2005); (Sinaii et al., 2008); (Treloar et al., 2010); (Giudice , 2010). In a prospective study, increased consumption of long-chain omega-3 fatty acids was associated with a reduced risk of endometriosis (Missmer et al., 2010)

PATHOLOGY

Endometrial lesions may appear as superficial petechiae on the peritoneum. Endometriosis implants often contain fibrous tissue, blood, and cysts. Destruction of red blood cells by inflammatory cells results in the formation of pigmented histiocytes and hemosiderin-laden

macrophages; old lesions are observed as more pigmented (Jansen et al., 1986).

At more advanced stage, the lesion turn a dark brown, black-dark blue appearance that reaches 5-10mm in diameter. A cystic structure called endometrioma occurs as a result of endometriotic lesions in the ovary and bleeding from the endometrial tissue. Deep infiltrative endometriosis is defined as a solid endometriosis mass located more than 5 mm deep into the peritoneum. Deep infiltrative endometriozis is usually found in the retrovaginal septum, rectum, retrosigmoid colon, bladder, ureter, and other pelvic fibromuscular structures (Woodward et al., 2001).

PATHOGENESIS

Although many theories have been proposed about the pathophysiology of endometriosis, it is actually thought that the combination of these theories is responsible. The theory of retrograde menstruation is that during the menstrual cycle, endometrial cells pass through the fallopian tubes and become implanted in the pelvis (Sampson, 1927). The increase in the frequency of endometriosis in outflow tract obstructions such as vaginal septum and cervical stenosis supports this theory. However, the rare occurrence of endometriosis foci in the lungs and brain reveals that the theory alone cannot explain endometriosis. At the same time, while 90% of women have retrograde menstruation, the fact that most of them do not develop endometriosis indicates that other factors should be investigated (Halme et al., 1984) One of them is

genetic studies. In a meta-analysis of 8 genome-related studies, 6 sites related to endometriosis were found (Rahmioglu et al., 2014)

Increased production of inflammatory and pain mediators is thought to play a role in endometriosis-associated pelvic pain.

It has also been found to be associated with neurological dysfunction associated with implants (Anaf et al., 2000); (Wang et al., 2009).

Other theories of endometriosis formation are coelomic epithelial metaplasia, mullerian rests, lymphatic or vascular dissemination (Burney et al., 2012); (Javert, 1952); (Peter, 1942).

CLINICAL MANIFESTATIONS

Clinical findings such as pelvic pain, dysmenorrhea, dyspareunia, infertility, and ovarian mass are frequently observed in endometriosis. Endometriosis may diagnosed incidentally during radiological imaging or surgery. Patients with peritoneal or deep infiltrative endometriosis often present with dyspareunia. Although nonspecific urinary symptoms are seen in patients with bladder endometriosis, ureteral endometriosis may be asymptomatic or associated with colic flank pain or gross hematuria (Berlanda et al., 2009) Symptoms vary according to anatomical location, women with intestinal endometriosis may present with diarrhea, constipation, intestinal cramps, and women with deeply infiltrating endometriosis implants in the posterior cul-de-sac and rectovaginal septum typically present with dyspareunia and painful defecation (Ballard et al., 2009); (Fauconnier et al., 2002); (Porpora et al., 1999). Women with abdominal wall endometriosis may complain

of cyclic pain. In women with thoracic endometriosis, pneumothorax or hematorax may present with hemoptysis (Horton et al., 2008); (Hwang et al., 2015).

DIAGNOSIS

The definitive diagnosis of endometriosis is made by the histological evaluation of the intraoperative biopsy. Surgical evaluation may be performed in patients with severe symptoms unresponsive to treatment. A presumptive diagnosis can be made with the combination of the patient's symptoms, signs, and imaging modalities. Evaluation of serum microRNA markers is another diagnostic method (Papari et al., 2020)

Other diagnostic evaluations of endometriosis include ultrasonographic imaging of endometrioma, observational focus in the posterior vaginal fornix and biopsy of rectovaginal lesions, evaluation and biopsy of detrusor lesions by cystoscopy, and confirmation of physical examination findings of rectovaginal endometriosis with imaging methods. Endometriosis is surgically staged according to the revised American Society for Reproductive Medicine scoring system.

Stage I – Minimal disease is characterized by isolated implants and no significant adhesions.

Stage II – Mild endometriosis consists of superficial implants that are less than 5 cm in aggregate and are scattered on the peritoneum and ovaries. No significant adhesions are present.

Stage III – Moderate disease exhibits multiple implants, both superficial and deeply invasive. Peritubal and periovarian adhesions may be evident.

Stage IV – Severe disease is characterized by multiple superficial and deep implants, including large ovarian endometriomas. Filmy and dense adhesions are usually present.

American Society for Reproductive Medicine revised classification of endometriosis

Patient's name _____ Date _____

Stage I (minimal) _____ 1 to 5 Laparoscopy _____

Stage II (mild) _____ 6 to 15 Laparotomy _____

Stage III (moderate) _____ 16 to 40 Photography _____

Stage IV (severe) _____ >40 Recommended treatment _____

Total _____ Prognosis _____

Peritoneum	Endometriosis	<1 cm	1 to 3 cm	>3 cm
	Superficial	1	2	4
	Deep	2	4	6
Ovary	R superficial	1	2	4
	Deep	4	16	20
	L superficial	1	2	4
	Deep	4	16	20
	Posterior cul-de-sac obliteration	Partial		Complete
		4		40
Ovary	Adhesions	<1/3 enclosure	1/3 to 2/3 enclosure	>2/3 enclosure
	R filmy	1	2	4
	Dense	4	8	16
	L filmy	1	2	4
	Dense	4	8	16
Tube	R filmy	1	2	4
	Dense	4*	8*	16
	L filmy	1	2	4
	Dense	4*	8*	16

* If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16. Denote appearance of superficial implant types as red ([R], red-pink, flamelike, vesicular blobs, clear vesicles), white ([W], opacifications, peritoneal defects, yellow-brown), or black ([B], black, hemosiderin deposits, blue). Denote percent of total described as R__ percent, W__ percent, and B __ percent. Total should equal 100 percent.

Original figure modified for this publication. American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997; 67:817. Illustration used with the permission of Elsevier Inc. All rights reserved.

TREATMENT

Treatment of endometriosis should be individualized according to the patient's symptoms, desire for pregnancy, and the stage of the disease.

Medical treatment is not effective for infertility, endometrioma treatment, or complications of deep infiltrative endometriosis. Treatment should be planned after other causes of pelvic pain have been excluded.

The agents used in the treatment are nonsteroidal analgesics, hormonal contraceptives, gonadotropin-releasing hormone (GnRH) analogs, and aromatase inhibitors (AI). There is no information showing superiority of one of these treatments over the other or the combination of treatments.

Nonsteroidal anti-inflammatory drugs

There are 3 most commonly suggested mechanisms for the occurrence of pain in endometriosis.

Production of substances such as growth factors and cytokines from activated macrophages and other cells associated with functional endometriotic implants; direct or indirect effects of bleeding from endometriotic implants; and irritation or invasion of the pelvic floor nerves or direct invasion of these nerves, particularly by infiltrative endometriotic implants in the cul-de-sac.

In addition, prostaglandin levels were increased in the peritoneal fluids of infertile women with endometriosis. This suggests that

prostaglandins that cause pain and tubal dysfunction can be synthesized by abnormal endometriotic cells and released into the peritoneal fluid (Haney, 1992). It may be preferred as first-line therapy in patients with mild symptoms. It can also be used in combination with oral contraceptives.

Estrogen-progestin contraceptives

Endometriosis-related pain can be treated with combined (estrogen and progestin) contraceptives . It has benefits such as being well tolerated, easy to use, and providing contraception. These drugs are known to reduce menstrual bleeding by reducing gonadotropin secretio. Estrogen-progestin contraceptives are thought to reduce endometriosis disease activity and pain by suppressing ovarian function (Hickey et al., 2014)

Progestins

Progesterone inhibits the release of LH and thus suppresses ovarian steroidogenesis . After that progestins first cause decidualization followed by atrophy. This is believed to be progestogens effect of upon the estrogen receptors of the endometrium. Additionally it is thought to that suppression of matrix metalloproteinases is another mechanism of progestins (Olive et al., 2003).

Medroxyprogesterone acetate (MPA) has been used orally for the treatment of endometriosis at doses ranging from 20 to 100 mg per day. There is also a depot formulation used at a dose of 150 mg every 3

months. However, if the patient is planning pregnancy, it would be better to avoid the use of depot MPA.

Norethindrone acetate can be prescribed as 5 mg daily, but the dose can be changed to 2.5 to 15 mg daily depending on side effects.

Dienogest is the regime can be used 2 mg oral pill daily or in combination with estradiol valerate.

The levonorgestrel intrauterine device (Lng-IUD) successfully reduces pelvic pain associated with endometriosis and significantly reduces the risk of dysmenorrhea recurrence after laparoscopic surgery for symptomatic endometriosis (Vercellini et al, 2003).

Gonadotropin-releasing hormone agonists/antagonists

Agonist analogs

Gonadotropin-releasing hormone (GnRH) agonists most commonly used for the treatment of endometriosis-related pain include nafarelin, leuprolide, buserelin, goserelin, and triptorelin.

GnRH analogs bind to the pituitary gland and thereby cause desensitization of pituitary GnRH receptors. Receptors desensitization refers to the decreased estrogen levels.

Amenorrhea and endometrial atrophy are a result of treatment with GnRH analogues and cause a reduction in dysmenorrhea, dyspareunia and pelvic pain.

When prescribed, leuprolide acetate 3.75 mg intramuscular injection given monthly, leuprolide acetate 11.25 mg intramuscular injection given every three months, goserelin 3.6 mg subcutaneous injection given monthly or 10.8 mg every three months and intranasal nafarelin acetate 200 mcg given two times in a day.

It prevents long-term therapy because of the adverse effects of the hypoestrogenic state, including hot flashes, vaginal dryness, decreased libido, mood swings, headache, and decreased bone density. The addition of concomitant medications during treatment with GnRH analogues, a strategy known as add-back therapy, may decrease the side effects. According to Practice Committee of the American Society for Reproductive Medicine the addback treatment is typically with oral norethindrone acetate or a combination of estrogen and progestin .

Antagonist

GnRH antagonists suppress pituitary gonadotropin hormone production and create a hypoestrogenic state (Bedaiwy et al., 2017)

Unlike GnRH agonists, GnRH antagonists do not have an initial potentiating effect on gonadotropin release and thus immediately suppress gonadotropins and sex steroid hormones.

GnRH antagonists are new agents used in the treatment of endometriosis. Clinical data on this drug are still being collected.

Danazol

Danazol acts as an estrogen antagonist on endometriotic tissue. By suppressing ovarian-derived estrogen production, the development and

continuity of ectopic endometrial implants are reduced (Dickey et al., 1984). It has androgenic side effects as acne, muscle cramps, edema, weight gain, spotting, hirsutism, and voice deepening. The use of Danazol may be limited by its side effect profile.

Aromatase inhibitors

Aromatase inhibitors have off-label use in the treatment of endometriosis, and data are limited.

A commonly used regimen of oral anastrozole 1 mg once daily or oral letrozole 2.5 mg once daily. These agents appear to regulate local estrogen formation and are also known to inhibit estrogen production in the ovaries, brain and periphery (Attar et al., 2006).

Surgical treatment

In patients who do not benefit from medical treatment, surgical treatment approach can be considered and also histological diagnosis can be provided with surgery. Surgical intervention reduces pain by destroying the endometriotic implants and allows assessment of pelvic cysts. Surgical treatment may include ablation or resection of endometriosis lesions, hysterectomy with or without oophorectomy, resection of endometriosis, or removal of all visible implants during surgery. In endometriosis surgery, in addition to the standard surgical risks, the risk of injury, possible decrease in ovarian reserve and adhesion formation can be listed.

Nerve transection

Laparoscopic uterosacral nerve ablation (LUNA) and presacral neurectomy can be listed as nerve cutting procedures. European Society of Human Reproduction and Embryology point out that presacral neurectomy has been shown to be beneficial in endometriosis-induced dysmenorrhoea, but information on long-term outcomes is limited. Limited data suggest that LUNA is not effective.

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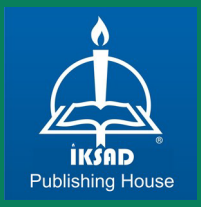

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