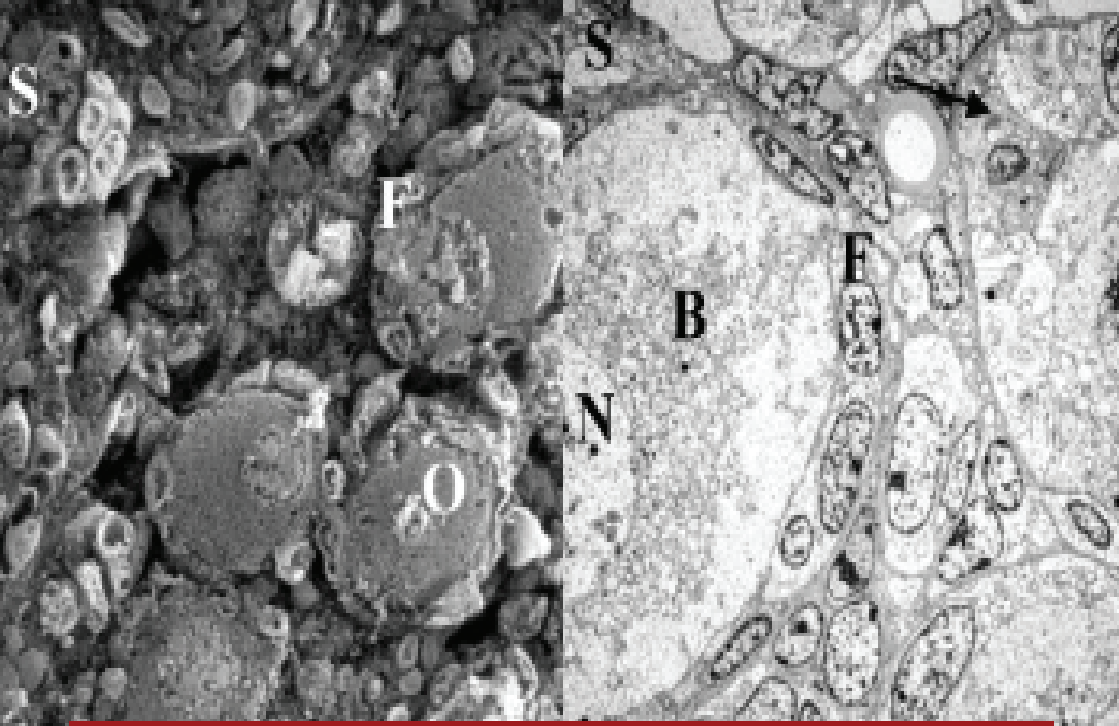

OVARIUM

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OVARIUM

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PREFACE

Ovarian follicules begins while the female fetus is in the uterus. In the fifth week of pregnancy, the fetus has an average of 450 to 1350 primordial germ cells in the ovary. Primitive germ cells undergo mitosis, and by the twentieth week of pregnancy, the female fetus has an average of 5 to 8 million germ cells. After mitosis is completed, germ cells undergo meiotic proliferation and arrest in meiotic prophase I, forming germ cell cysts. During the peripartum period, each germ disappears to form a primordial follicle containing an oocyte, a cell cyst, and a single layer of nutritive granulosa cells. The ovary is the most important part of the human reproductive mechanism and it is of great importance to understand the ovary better in this book we have written. I would like to thank my colleagues who contributed to the study.

CONTENTS

OVARIUM EMBRYOLOGY

The genotype of the embryo becomes 46, XX or 46, XY during fertilization [67]. Between the 1st and 6th weeks, genetically female or male embryos cannot be distinguished from each other in terms of phenotype [1]. By the seventh week, the embryo begins to change according to its sexual phenotype characteristics. This change process is controlled by the SRY gene. The SRY gene codes for the sex-determining region Y protein (also called testis determining factor [TDF]). When TDF protein is expressed in the embryo, the gonad differentiates into testis. In the absence of testosterone and Müllerian inhibitory factor (MIF), the embryo begins to differentiate into a female phenotype. By the 12th week, external genital characteristics become distinguishable as male or female phenotype, and this differentiation process is completed by the 20th week [1, 2].

In the early period of development, primordial germ cells appear among the endoderm cells on the wall of the yolk sac close to the allontois and progress along the dorsal side of the mesentery of the hindgut with ameboid movements, reaching the primitive gonads at the beginning of the 5th week, and settling in the genital ridges at the 6th week. Primordial germ cells have an inducing

effect on the formation of ovaries or testicles from primitive gonads; If these cells do not reach the genital ridges, gonad development does not occur. Primordial germ cells derived from the epiblast migrate along the primitive line and settle among the endoderm cells on the wall of the yolk sac close to the allontois in the 3rd week. In the fourth week, cells progress from the mesentery of the hindgut and reach the gonads at the beginning of the 5th week and the genital ridges at the 6th week [68]. If this migration is interrupted, gonads cannot develop. Shortly before and during the entry of primordial germ cells into the genital folds (primitive gonads), the epithelium of the genital folds proliferates and forms irregular cell cords called primitive sex cords, which progress to the mesenchyme. In male and female embryos, these cords maintain their connection to the surface epithelium for a while. Gonads at this stage are called undifferentiated gonads. In female gonads, primitive sex cords are arranged in irregular cell clusters. Cell cluster formations containing primitive germ cell groups are located mostly in the medullary region of the ovary. As these cell clusters disappear after a while, they are replaced by vascular stroma (ovarian medulla). The epithelium on the surface of the female gonad continues to proliferate and forms second generation cords called cortical cords in the 7th week. Starting from the fourth month, these cords continue to proliferate by

separating into isolated cell clusters. These cell clusters surround each oogonium with a layer of epithelial cells called follicular cells. These follicular cells together with the oogoniums form the primary follicle [4]. During these developmental stages, the medullary cords of the female gonad regress and the second generation of cortical cords forms [4, 5].

There are approximately 5,000,000 oogoniums in the 5th month of fetal life. Starting from the third month, oogoniums begin to enter the prophase phase of the first meiosis and wait in the diplotene phase. This pause continues until puberty. These cells are surrounded by flat follicular cells and are called primary oocytes. By the seventh month, most of the oogoniums have transformed into primary oocytes. However, most of the primary oocytes undergo resorption and atresia and their numbers decrease, and there are approximately 600,000-800,000 primary oocytes at birth (Junqueira and Carneiro 2006). The many germ cells are lost and the female emerges with one to two million primordial follicles. Then it reaches adulthood, an average of 350,000 to 550,000 primordial follicles remain. After the first menstrual period, approximately 1000 follicles are lost per month. The rate of follicular loss increases after the age of 35 [2].

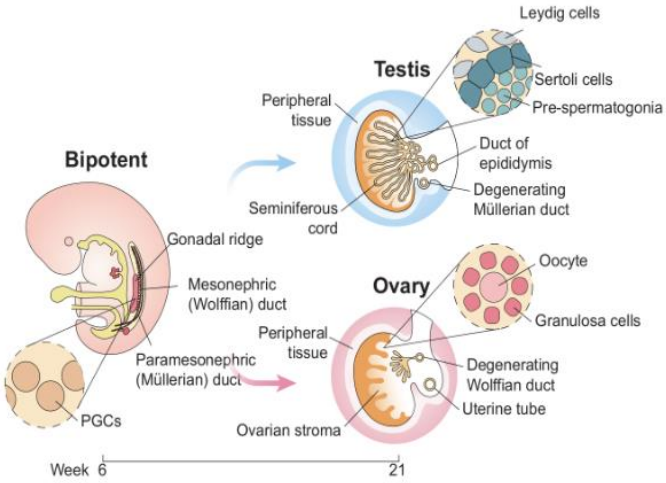

Figure 1. Human-mouse compatible single-cell atlases of gonadal and extragonadal tissues [3].

OVARIUM ANATOMY

The ovary is responsible for the production of the female sex cell, the ovum, and hormones such as progesterone and estrogen. In the pelvis minor, there is a place called fossa ovarica. iliaca interna et a. They are located in the depression between the iliaca externa [6].

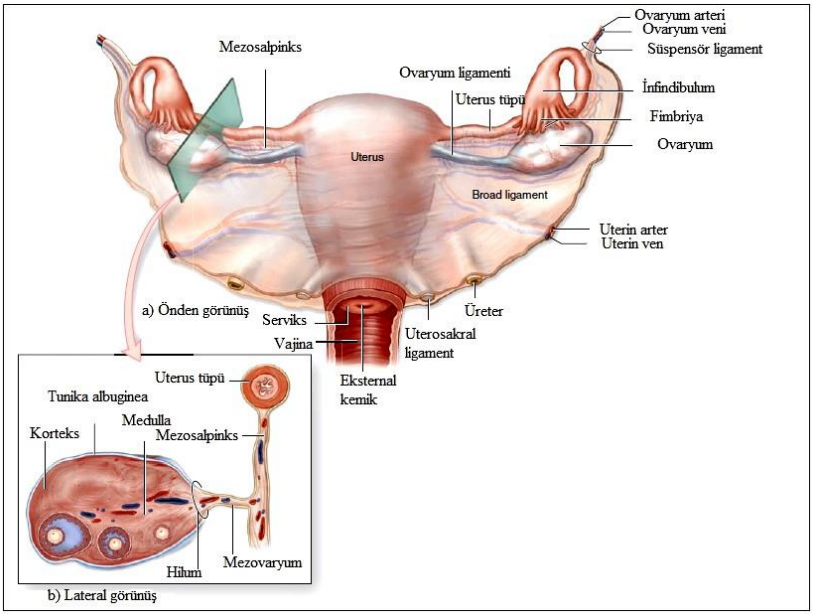

Figure 2. Location and structure of the ovary in humans [7].

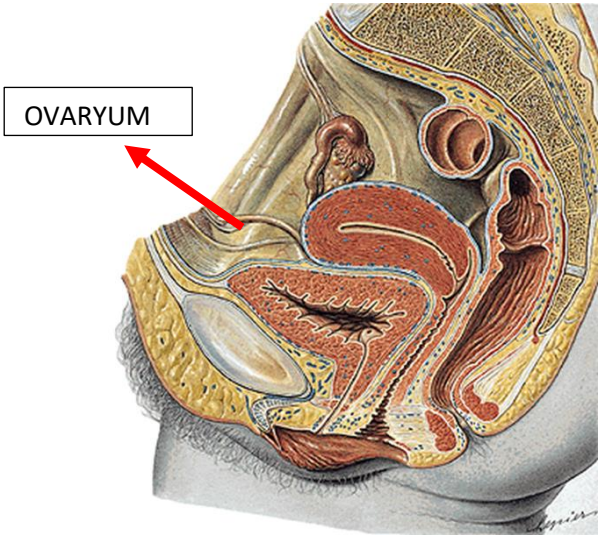

Figure 3. Layout of the ovarıum [8].

The outer surface of the ovaries, which are pinkish gray in color, is smooth before puberty, but becomes rough after puberty due to ovulation. The pea-sized ovaries are 2 cm wide, 4 cm long, 1 cm thick and weigh approximately 5 grams.

The ovary has two sides, facies medialis and facies lateralis, two ends, extremitas uterina and extremitas tubaria, and two edges, margo liber and margo mesovaricus. Tortoiseshell ligament extending between the end of the ovary facing the uterus (extremitas uterina) and the upper outer corner of the uterus. It is called ovary proprium. Since the peritoneum surrounds the vessels feeding the ovary (a.v. ovarica), it has taken the form of a ligament [6]. This ligament (lig. ovari suspensorium) plays a suspending role on the ovary. Thanks to this ligament, the position of the ovary changes along with the uterus in a pregnant woman. Tunica albuginea is a layer rich in collagen fibres. Under the tunica albuginea is the main tissue of the ovary. This tissue is divided into two parts called outer cortex ovarii and inner medulla ovarii. Inside the cortex ovarii, there is connective tissue filling the space between them and follicles with varying degrees of development.

Medulla ovarii contains loose connective tissue, vessels and nerves. The ovaries are attached to the ligamentum latum uteri by the mesovarium, which is a peritoneal fold. The suspension ligament contains the vessels that nourish the ovary and extends to the upper part of the ovary. Between the two leaves of the mesovarium are arteries, veins, nerves and lymphatics that reach the hilum ovarii [8].

OVARIUM HISTOLOGY

Ovaries are considered internal secretory glands due to the secretion and synthesis of steroid hormones, and external secretory glands due to the production of germ cells. Its surface is covered with cuboidal epithelium or simple columnar epithelium called germinal epithelium. In the lower part of the germinal epithelium, there is a dense irregular tight connective tissue called tunica albuginea. Underneath this is the cortex containing ovarian follicles. Follicles are embedded in connective tissue in the cortex [9]. Flat spindle-shaped cells in the stroma region are called fibroblasts. The medulla region is located in the inner most part of the ovary and contains a rich vascular bed in loose connective tissue. While primordial follicles are seen in the cortex region before puberty, there are primary, secondary and

tertiary follicles after puberty. In addition to these follicles, atretic follicles and corpus luteum are seen in sexual adulthood. A healthy adult young woman has approximately 410,000 follicles in her ovaries. In the reproductive age, only 450-500 of them reach the tertiary follicle stage. The rest undergo atresia and degenerate. Within a few years after menopause, all remaining oocytes degenerate and disappear [10, 11].

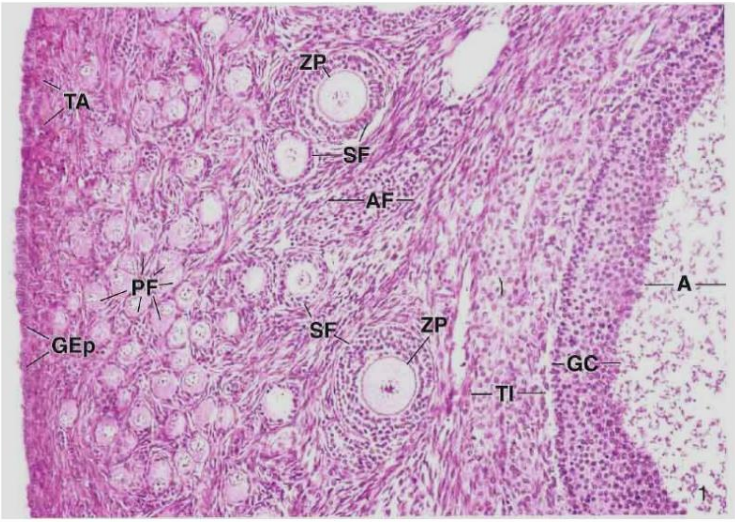

Figure 4. H&E staining of the ovary GEp: germinal epithelium. A: antrum ZP: zona pellucida, TA: Tunica albuginea, SF: secondary follicles PF: primordial follicles [12].

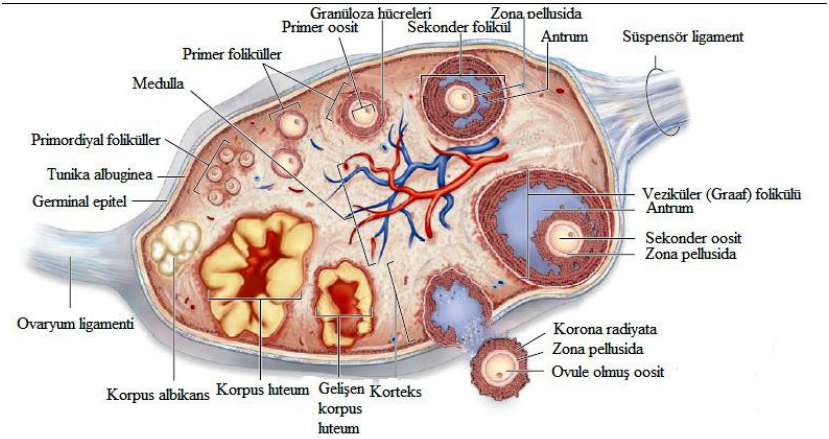

Figure 5. Ovary schematic drawing [12].

Primordial Follicle

It is located under the tunica albuginea and forms the majority of the follicles. Oocytes are round cells with a large vesicular nucleus or prominent multiple nucleoli, with an average diameter of 30 μm. They are primordial follicles that represent the first stage of follicular development. In female individuals, pyrimordial gamete cells divide by mitosis in the 25th week, forming an average of 7 million oogonia. Squamous epithelial cells surrounding the oogium in a single layer form primordial follicles. The majority of primary oocytes that have entered meiosis cannot form primary follicles and undergo atresia and disappear [10].

Primary Follicle

The flat cells of the primordial follicles develop and first become cuboidal and then prismatic cells. Primary follicle cells become single-layered cuboidal cells. As the immature oocyte develops, it secretes glycoproteins and glycosaminoglycans into its environment. The structure called zona pellucida is the region that is strongly stained positively with PAS. Zona pellucida appears when the oocyte reaches a diameter of approximately 50-80µ. The cells surrounding the oocyte divide and turn into a multilayered epithelium called stratum granulosum. Primary follicles containing single-layer columnar or multilayer columnar epithelium are of different sizes. Unilaminar primary follicle contains a single-layered epithelium. The follicle containing a multilayered epithelium is called multilaminar primary follicle or stratum granulosum.

Gap junction type connections between granulosa cells are common. The theca follicle forms a tight tissue called stroma around the follicle. There is a transparent basement membrane between the theca and stratum granulosum. Theca follicle consists of the theca interna, the inner layer rich in blood vessels; The outer layer is called theca externa, which is rich in smooth

muscle cells and collagen fibers. Cells in the theca interna that secrete steroids; collagen fibers, fibroblasts and small blood vessels. Following steroid secretion and stimulation by LH, androgens, the precursors of estrogens, are synthesized. After the hormone androstenedione, which has a steroid structure, is secreted from the theca interna cells, the effect of FSH is converted to estrogen by aromatase, an enzyme produced from granulosa cells. Estrogen is distributed throughout the body via veins. As the primary follicle develops, the oocyte also matures [9].

Secondary Follicle

The stratum granulosum increases to a layer of 7-13 cells and turns into a multilayered columnar epithelium. Gaps filled with transparent fluid occur between the cells. The cavities merge to form a large cavity called the antrum. This follicle is now called antral follicle or secondary follicle. The antrum contains follicular fluid rich in hyaluronic acid. Oocyte diameter reaches 250 μm. As the follicle develops, as the fluid increases, the antrum expands and the oocyte surrounded by granulosa cells is pushed to one side of the follicle. Secondary follicle acquires the characteristics of tertiary follicle over time. Granulosa cells surrounding the oocyte

form a bump called cumulus oophorus that extends towards the follicle lumen. The granulosa cells surrounding the ovum are called corona radiata. The size of the follicles is under the influence of inhibitory factors produced by granulosa cells secreted into the antrum fluid [11].

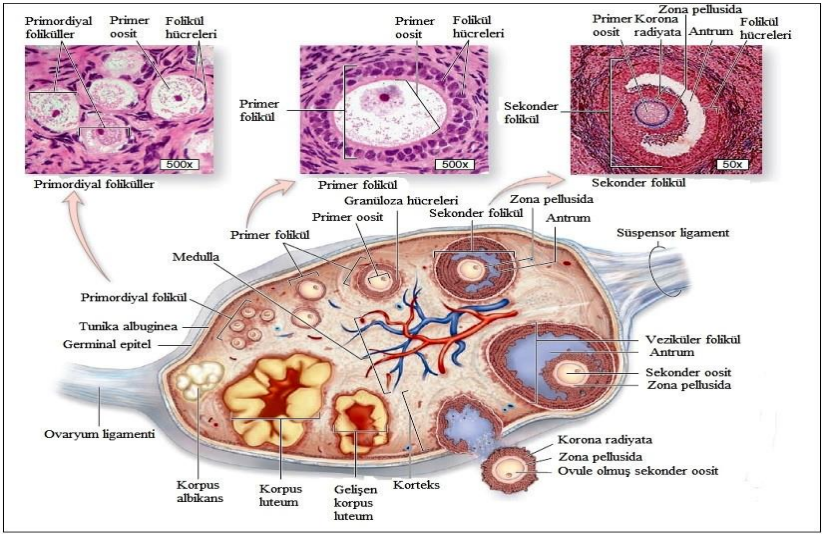

Figure 6. Morphological image of primary, primordial and secondary follicles in follicular development [12].

Tertiary Follicle (Graaf Follicle)

The first maturity division continues as follicle growth continues and ends just before ovulation. The oocyte inside the graafian follicle is now a secondary oocyte. The graafian follicle, which contains follicular fluid, has a large antrum. The corona radiata

and oocyte, separated from the cumulus oophorus, float freely within the follicle. The follicle, which reaches 10 mm, swells towards the surface of the ovary. Its connections with the granulosa cells loosen and the oocyte prepares for expulsion [9,12].

Structure and Functions of the Corpus Luteum

Granulosa lutein cells are large (approximately 30 μm in diameter) cells with a vesicular nucleus and pale staining. There are abundant lipid drops in their cytoplasm and these cells begin to produce progesterone [5]. Theca cells, the other group in the corpus luteum, are smaller than granulosa cells and have a heterochromatic-looking nucleus. These cells continue to secrete estrogen as they did before ovulation. These hormones secreted from the corpus luteum have very important functions in preparing the uterine wall for pregnancy. If the ovulated oocyte is not fertilized by any sperm, the corpus luteum degenerates on average nine days after the oocyte is expelled. This structure is called menstrual corpus luteum. Degeneration occurs in the corpus luteum, whose cells shrink and their vascularization decreases, and the cells begin to die by apoptosis. As these processes progress, hyalinization begins to be observed in the

expanding connective tissue and the corpus luteum gradually turns into corpus albicans, a white scar structure. If the ovulated oocyte undergoes fertilization during this period, the corpus luteum continues to exist and develops further, thanks to the hCG secreted by the syncitrotrophoblasts, forming the gestational corpus luteum. These luteal cells continue to produce progesterone until the end of the 4th month, even though the placenta begins to produce hormones in the 2nd month. After this time, this task is completely taken over by the placenta. At the end of this period, the gestational corpus luteum is replaced by the corpus albicans. However, this structure is larger than the corpus albicans, which originates from the menstrual corpus luteum [5].

Follicular atresia

Follicular atresia occurring in the ovary is a process that continues regularly, starting from the embryonic period [13]. Follicles at different stages of atresia can be observed in any section taken from the ovary after puberty. The first changes observed in this process are the nuclei of follicle cells becoming pyknotic and their cytoplasm dispersing. In the following process, the follicle is invaded by macrophages and other connective tissue cells.

Afterwards, the oocyte degenerates and leaves behind a distinct zona pellucida structure. During this process, the follicle may fold inward or collapse, but it generally does not lose its thickness and staining properties. If found in the cross-sectional area, deformed zona pellucida structures provide reliable data in determining the atretic follicle. In case of atresia in large follicles that are nearing the end of the maturation process, theca interna cells remain as epithelioid cells that form clusters in the ovarian cortex. These cells together are defined as interstitial glands and continue to secrete steroid hormones [14].

OVARIUM PHYSIOLOGY

Various factors are needed for the growth of oocytes and follicles. The most important of these factors are FSH, growth factors; growth factors such as epidermal growth factor (EGF), insulin-like growth factor I (IGF-I) and calcium ions [14]. In addition, control of follicle sizes is provided by inhibitory factors such as oocyte maturation inhibitor (OMI), which is produced by granulosa cells and released into the antrum fluid [69]. In addition, it is known that angiogenesis also plays an active role in follicular development [69]. The granulosa layer is avascular until the moment of ovulation, because although there are two capillary

networks in the theca interna and externa layers, these vessels cannot cross the basement membrane [9, 14]. Since ovulated follicles contain a more widespread vascular network than other antral follicles, it has been revealed that they remain active in greater amounts of gonadotropin. In short, the level of vascularization is also important in determining which follicle will ovulate [9]. Vascular endothelial growth factor (VEGF) is the most important molecule controlling the vascularization of follicles. While this factor strongly stimulates the proliferation and migration of endothelial cells, it also increases vascular permeability. The main source of VEGF in the ovary is the granulosa cells, as well as the vessels in the theca cell layer.

It is also produced in endothelial cells. As the follicle develops, the concentration of this molecule in the follicular fluid increases. The most important factor in determining which follicle will participate in ovulation is the level of VEGF in the follicular fluid. In addition to this factor, another potent endothelial cell mitogen found in the ovary is fibroblast growth factor-2. This factor, which is especially high in developed follicles, is found mainly in pericytes and endothelial cells in the theca cell layer. While primary oocytes are found in tertiary follicles in the early period, secondary oocytes are found in these follicles in the period close

to ovulation [9-14]. Although primary oocytes located in primordial follicles begin their first meiotic division in the embryo, this process is arrested in the diplotene phase of meiotic prophase. Since the first meiotic prophase is not completed until just before ovulation, primary oocytes remain in the first meiotic prophase for 12-50 years. As development in the follicle continues, the oocyte also develops and completes the first meiotic division (reduction division) just before ovulation. Although each daughter cell of the primary oocyte has the same amount of chromatin material, one of the daughter cells receives a greater amount of cytoplasm and becomes the secondary oocyte. The diameter of the secondary oocyte reaches an average of 150 micron meters. The other daughter cell, called the first polar body, receives a very small amount of cytoplasm [14].

Although it enters the second meiotic division 6-12 hours before ovulation, this division is not completed and it pauses in the metaphase phase 3 hours before ovulation. This division is completed only when the secondary oocyte is penetrated by a spermatozoon. Following this event, the secondary oocyte completes the second meiotic division and a mature ovum with a maternal pronucleus with a set of 23 chromosomes is formed. The other cell resulting from this division is called the second polar

body [14]. The initial development of follicles participating in this cycle is under the control of FSH. [9]. During this process, changes are also observed in the theca layer. Theca interna cells transform into cells that can produce steroids by storing lipids in their cytoplasm. Androgens secreted from these cells with LH stimulation are then converted to estrogens. Some of the androgens are converted into estrogens, which stimulate the proliferation of granulosa cells via FSH stimulation in the nongranular endoplasmic reticulum [9].

Hormones that play a role in ovulation include:

During each menstrual cycle, the ovary undergoes two-phase cyclic changes. These phases are divided into two: follicular phase and luteal phase. Ovulation occurs between these two phases [15].

Follicular Phase

The follicular phase begins with the development of a small number of primary follicles, numbering between 10 and 20, under the control of FSH and LH. 5-7 days of the menstrual cycle. On these days, the dominant follicles are selected. FSH on days 8-10 of the cycle. It is the main hormone that controls follicle growth. FSH stimulates the granulosa and theca cells to secrete steroid

hormones, mainly estrogens, into the follicle lumen. In this process, there is a feedback between estrogen production in the dominant follicle and FSH release from the pituitary gland.

As estrogen production here increases, FSH production in the pituitary is also suppressed. As the process continues, the estrogen produced accumulates in the follicle lumen, eventually reaching a level that eliminates the follicles' dependence on FSH to continue development and growth.

In the late follicular phase before ovulation, progesterone levels begin to increase under the influence of LH. With the concentration of estrogen in the blood, the adenohypophysis is now suppressed from producing more FSH. The change that induces ovulation is a sudden LH surge accompanied by small increases in FSH. Ovulation occurs on average 34-36 hours after the LH surge begins, or 10-12 hours after the LH peak occurs [15, 16].

Luteal Phase

Immediately after ovulation, the ruptured follicle undergoes rapid morphological changes in the granulosa and theca cells and forms the corpus luteum, which initiates the luteal phase.

The resulting corpus luteum secretes high amounts of progesterone and estrogen. If the oocyte is penetrated by a spermatozoon, the secretory phase necessary to prepare the endometrium for implantation is entered with the activity of these two hormones, especially progesterone [17, 18]. It is thought that the development and continuity of the corpus luteum throughout the menstrual cycle is under the control of LH. Without fertilization, the corpus luteum degenerates within a few days due to decreased hormone levels. If fertilization occurs, the corpus luteum is preserved and continues its function of producing estrogens and progesterone. The hCG hormone, which is initially released by syncytiotrophoblasts, is produced by the placenta in the future. HCG stimulates the corpus luteum and is responsible for the continuity of this structure throughout pregnancy [19].

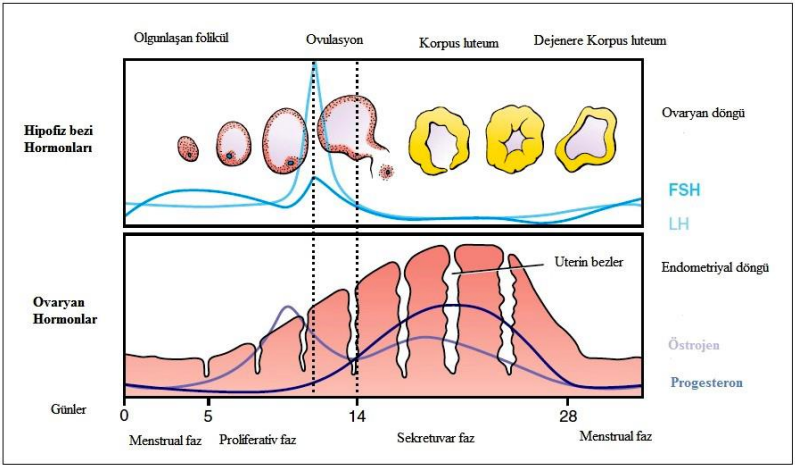

Figure 7. Effects of FSH and LH hormones on the ovary [20].

Ovulation

In the middle of the genital cycle (day 14), which occurs regularly with puberty, the oocyte in the mature follicle is expelled from the ovary under the influence of FSH and LH. At this stage, the follicular fluid of one of the mature follicles increases suddenly and forms a protrusion towards the surface of the ovary somewhere on the follicle wall. In a short time, the macula pellucida or follicular stigma, an oval and avascular spot, appears on the surface of the ovary at the level of this protrusion. With the rise of LH, the stigma swells in the form of a balloon and ruptures (14). The increase in gonadotropin (LH/FSH) is a physiological

trigger that stimulates ovulation of preovulatory follicles. Ovulation usually occurs 12-24 hours after the LH surge.

When the LH surge reaches its highest level, the primary oocyte completes the first meiotic division either just before or during ovulation. Two oocytes of unequal size, each carrying 23 pairs of chromosomes and 2n amount of DNA, are formed. The first cell is the secondary oocyte, which is quite large and rich in cytoplasm. The secondary oocyte immediately enters the second meiosis but finishes its division while being fertilized by sperm. The second cell is the first polar body, which is very small, devoid of cytoplasm, and has no function. Shortly after the secondary oocyte is formed, it is located between the cell membrane and the zona pellucida. While the secondary oocyte is thrown into the peritoneal cavity from the ruptured area, along with some granulosa cells and follicular fluid, it is taken into the tubes by the fimbria structures of the uterine tubes. The rupture of a mature graafian follicle and the transfer of the secondary oocyte it contains into the uterine tubes is called ovulation. Expulsion of the oocyte is a result of increased intra-follicular pressure and possibly contraction of the smooth muscles in the theca externa due to prostaglandin stimulation.

Ovulation is a periodic event that repeats every 28 days, from puberty to menopause, and occurs approximately in the middle of the 28-day period between two menstruations. Generally, one secondary oocyte is released with ovulation in each cycle. However, several ovulations may occur at the same time. This causes twin or multiple pregnancy. Usually both ovaries ovulate alternately [20].

Luteal phase

Shortly after ovulation, the walls of the theca follicle contract and fold. Under the influence of LH, it turns into a glandular structure known as corpus luteum (yellow body) that secretes progesterone and a small amount of estrogen. These hormones, especially progesterone, cause the endometrial glands to secrete and prepare the endometrium for the implantation of the blastocyst. If the oocyte is fertilized; The corpus luteum expands to form the pregnancy corpus luteum and increases hormone production. In the event of pregnancy, human chorionic gonadotrophin hormone (hCG), secreted by the syncytiotrophoblasts of the chorion, prevents the degradation of the corpus luteum. The syncytiotrophoblast is rich in LH. The gestational corpus luteum is functionally active during the first 20 weeks of pregnancy. The placenta then secretes estrogen and progesterone, which are

necessary for the continuation of pregnancy. If the oocyte is not fertilized; Regression and degeneration of the corpus luteum is observed 10-12 days after ovulation. The corpus luteum in this state is called menstrual corpus luteum. The corpus luteum subsequently turns into white scar tissue on the ovary, called corpus albicans or atretic corpus luteum [19, 20].

ELECTRON MICROSCOPIC STRUCTURE OF THE OVARIUM

The free surface of the human ovary is covered with a single layer of cells. This layer forms the ovarian surface epithelium and is the continuation of the peritoneal mesothelium. The ovarian surface epithelium originates embryologically from the coelomic epithelium, and this epithelium also forms the Müllerian ducts, that is, the epithelium of the fallopian tubes, the endometrium, the uterine cervix and the upper part of the vagina. During follicle rupture, ovarian surface epithelial cells secrete lysosomal enzymes to destroy the connective tissues that form the follicle wall and are subsequently ruptured. They also participate in the healing process of ovarian follicles after ovulation. As a result, epithelial inclusion lumens are formed by invaginations of the surface epithelium into the cortical stroma, and larger epithelial lumens are recognized as inclusion cysts. Surface epithelial cells

of the human ovary are characterized by dome-shaped tips in scanning electron microscopy (SEM). They are also covered with numerous, often branching microvilli [21].

Figure 8. Scanning and transmission electron micrographs of human ovarian surface epithelial cells. The dome-shaped hills are covered with numerous branching microvilli [21].

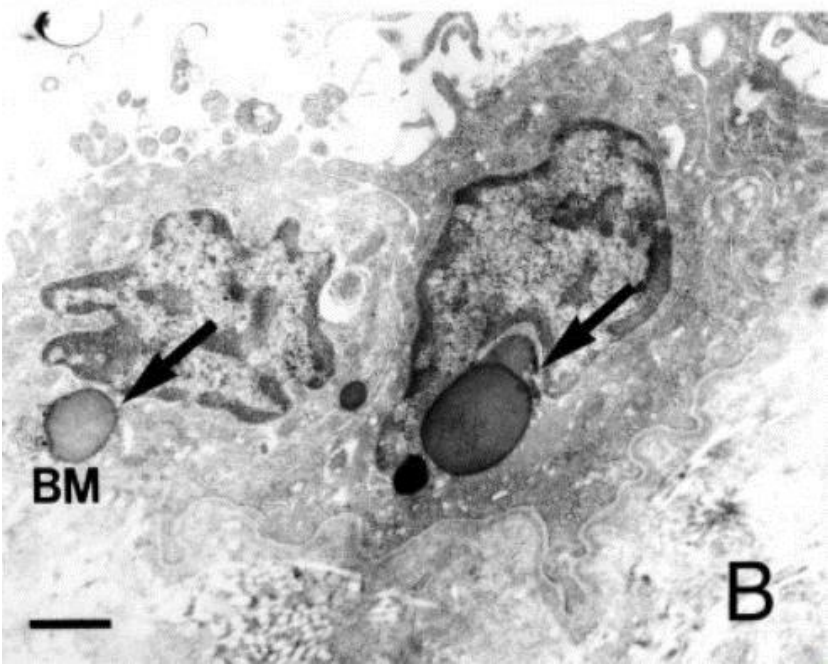

Figure 9. There are many microvilli on the surface cells of the ovary. The lateral plasma membranes of ovarian surface cells are reinforced by luminal junction complexes and a basement membrane (BM) separates the cells from the underlying stroma [21].

Primordial Follicle

Primordial follicles 16-20 days after fertilization. It begins to form in the human fetus in weeks. Because most do not undergo significant morphological changes until sexual maturity, they are generally considered to be in a "dormant" state. The primordial follicle is a round structure (55-75 μm in diameter) consisting of a diplotene oocyte (30-40 μm in diameter) surrounded by a single

layer of flattened follicle cells. It is covered by a delicate basal lamina that separates the follicle from the surrounding ovarian stroma [22].

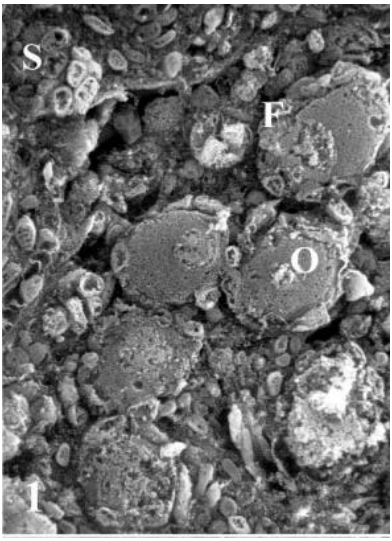

Figure 10. Term (39 weeks) fetal human ovary. Some primitive and primary follicles located in the cortical stroma of the gonad (S). A single layer of flat or cuboidal follicular cells (F) surrounding an oocyte (O). SEM-ODO method;3900 [22].

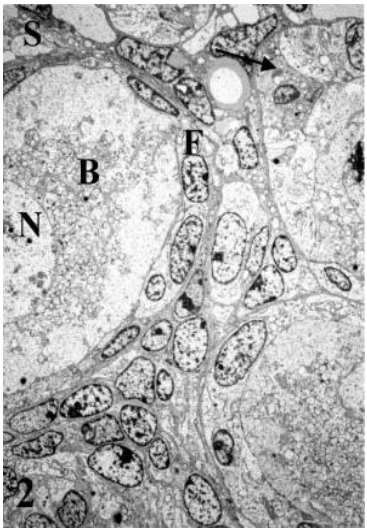

Figure 11. Fetal human ovary (18 weeks). Primordial follicles in corticalovarian stroma (S). A single layer of flat follicular cells (F) surrounding the oocyte. N: oocyte nucleus. In a follicle, polyhedral shaped follicular cells (arrow), this type of follicle corresponds to the “early-to-mid follicle stage”. The 'Balbiani vitelline body' (B) is evident in the perinuclear region. TEM;33,000 [22].

In the resting phase, the oocyte is spherical or oval in shape and has a large, round or oval vesicular nucleus, usually located eccentrically. Nuclear chromatin often appears finely dispersed. However, residual chromosomes may be visible in the form of fibril condensations in the nucleoplasm. Additionally, one or more dense reticular nucleoli are often observed in the nucleoplasm. Numerous organelles can often be seen in the ooplasm, characteristically concentrated close to the nucleus. This corresponds to the "paranuclear complex," the ultrastructural counterpart of Balbiani's vitelline body [22].

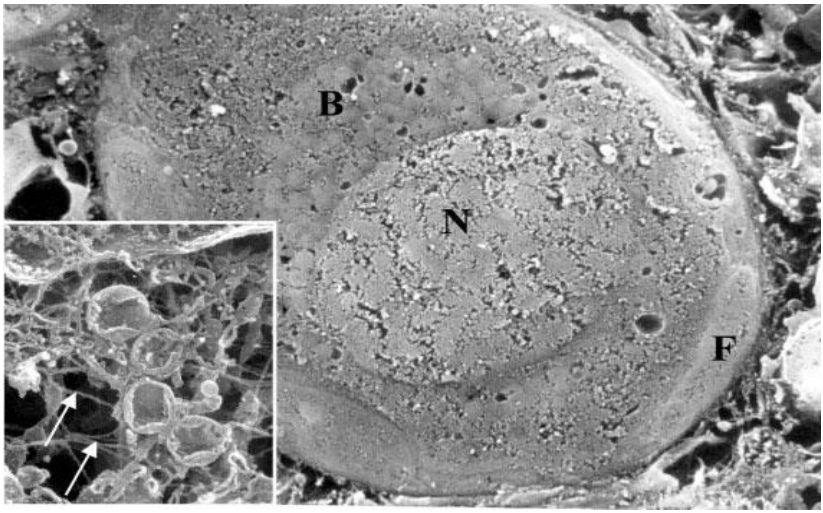

Figure 12. Fetal human ovary (18 weeks). Primordial follicle. A large oocyte with an oval nucleus (N) surrounded by a single layer of flat follicular cells (F). B:Balbiani vitelline body. Microtubular network (arrows) intertwined with different components of the "Balbiani vitelline body" [22].

Primary Follicle

The follicle harvested from the resting follicle pool to enter the growth phase is often called an early growing or primary follicle. The diameter of the primary follicle is approximately 60-70 μm and contains an oocyte that gradually increases in size, reaching a diameter of approximately 50 μm. The primary follicle preserves the general morphological characteristics of the primordial follicle. Thus, the follicular cells are still arranged in a single row surrounding the oocyte, but they now appear polyhedral or cuboidal in shape rather than flat. In parallel, from the early stages of follicular development, surrounding stromal cells begin to accumulate concentrically around the follicular basal lamina and form theca follicles. When observed by TEM, the oocyte in the primary follicle has a large, eccentrically located vesicular nucleus with a prominent nucleolus. As the follicle grows, the oocyte shows some changes: the organelles gradually become more dispersed in the ooplasm; The Golgi undergoes fragmentation and begins to form and assemble granules in the cortex of the oocyte. These then become typical "cortical granules". At this stage, deposition of the ZP matrix gradually begins in the form of irregular patches of dense, homogeneous material in areas in close contact with the oolemma and

surrounding follicle cells. Follicular cells retain the general morphological features observed in resting follicles. They are still arranged in a single row, but gradually increase in size and actively multiply. Thus, most of it becomes cubic or polyhedral [22].

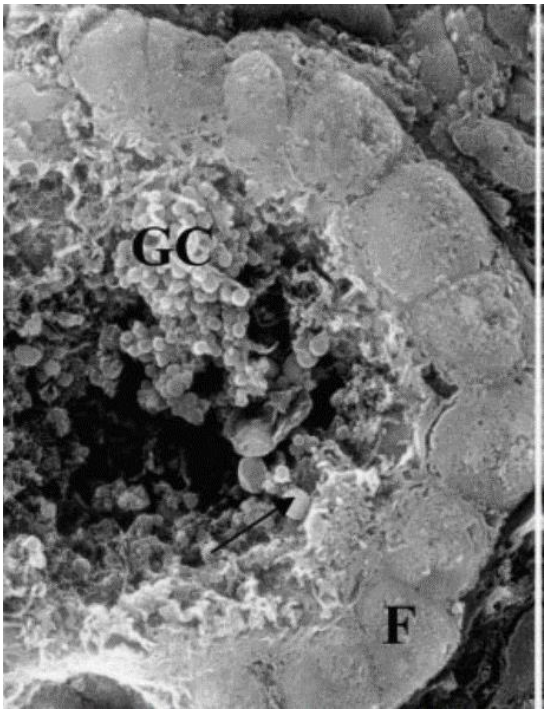

Figure 13. Adult human ovary: ruptured primary follicle. Monolayer of cuboidal and polyhedral follicle cells (F) around the oocyte. The cytoplasm was partially chemically dissolved and the nucleus mechanically removed. Mitochondria appear as regular spherical structures (arrow).GC: Vesicles of the Golgi complex [22].

Secondary Follicle

The oocyte gradually grows (approximately 80 μm in diameter), the number of multilayered follicle cells increases, a complete ZP formation and the organization of two theca layers are observed. The stromal cells now align to form a complete theca follicle, consisting of a concentric layer of specialized stromal cells around the follicular basal lamina. Theca follicles are divided into two compartments: an inner layer (theca interna), rich in endocrine cells and vascularized by capillaries, and an outer layer (theca externa), consisting mainly of typical connective tissue components and partly smooth muscle cells. As revealed by TEM and conventional SEM observations in the secondary oocyte, follicular growth causes significant changes in the ooplasm. Mitochondria, Golgi complexes, ER, lysosomes, ribosomes and peroxisomes become increasingly numerous and dispersed throughout the ooplasm, leaving the perinuclear position. The nucleus grows. The secondary oocyte is characterized by the presence of numerous very short microvilli on its surface. By SEM and TEM, follicular cells appear mostly polyhedral. At this stage of development, they are arranged in several concentric layers of cells around the oocyte and begin to form the so-called stratum granulosum. Granulosa cells are characterized by an

irregular nucleus containing one or more nucleoli. Granulosa cells secrete a fluid, usually called "antrum fluid", which accumulates in a small number of small intercellular lacunae scattered among the granulosa layer.

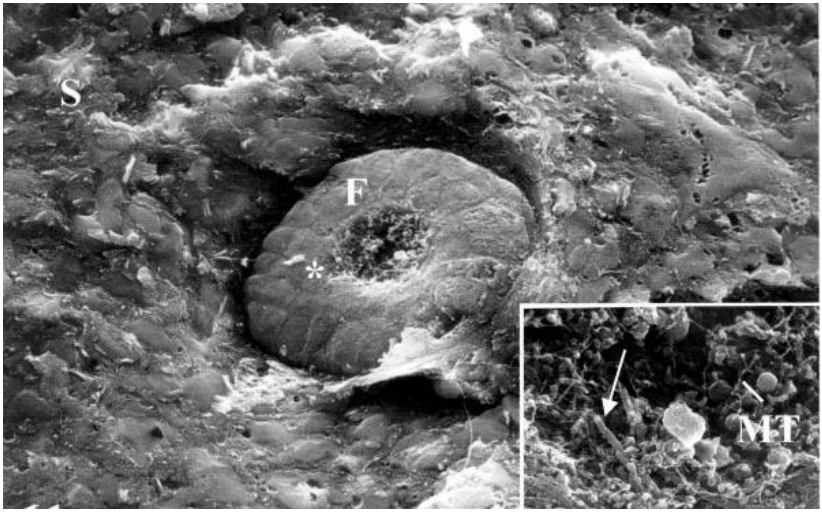

Figure 14. Adult human ovary: secondary follicle ruptured. Follicular cells (F) are cuboidal and form two layers (stars) proliferating in the same areas S: ovarian stroma. Long and tortuous follicular microvilli (arrow). MT:microtubules [22].

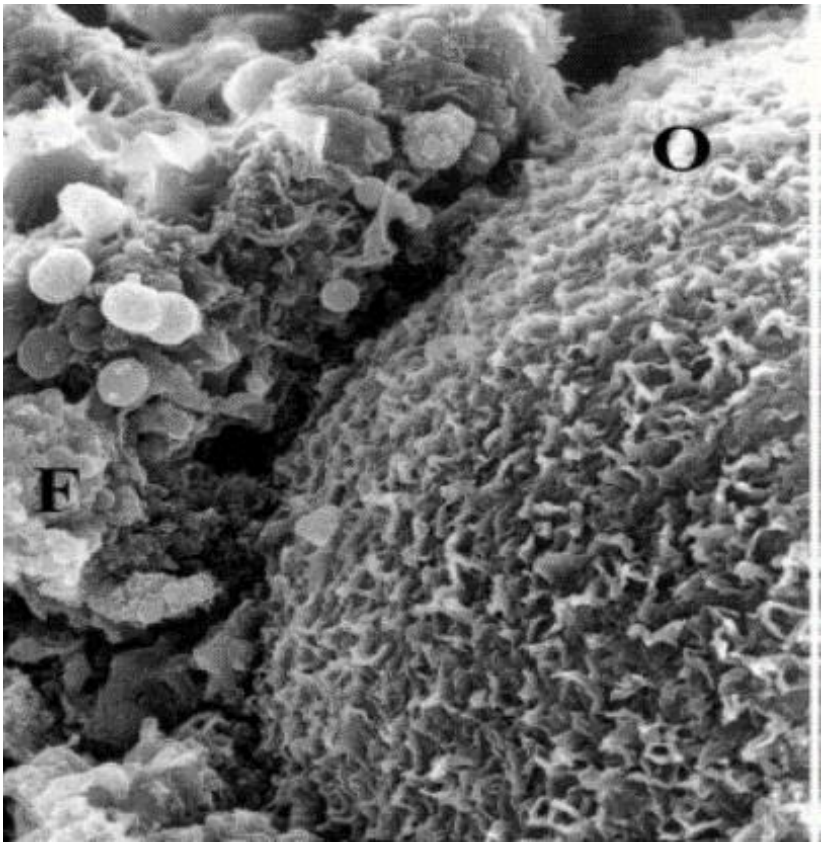

Figure 15. Human secondary oocyte. Follicle cells and ZP were mechanically removed from the oocyte (O). Oolemma covered with numerous and very short microvilli. F: follicle cell debris [22].

Mature Follicle

As the maturation process of the oocyte-follicle complex approaches, the vascularization of the theca interna and the permeability of the theca blood and lymphatic endothelial wall

increase strongly. In addition, the permeability of the follicular basal lamina also increases, allowing large amounts of blood and lymph filtrate to enter the follicular space. Thus, secondary antral follicles become more watery and more abundant and gradually fill the intercellular spaces, creating large spaces, and their fusion eventually leads to a single large space, the antrum follicles. At this stage of follicle maturation, smaller, fluid-filled spherical areas surrounded by granulosa cells characteristically arranged radially in a “rosette fashion” also appear. The formation of antrum folliculization brings together two different cellular populations, the cumulus oophorus and the parietal granulosa layer, the inner layer of which is in close contact with the oocyte in the granulosa compartment, called the corona radiata. The cumulus oophorus and the parietal granulosa layer are connected by a thin pedicle formed by several granulosa cells. When the follicle is fully mature, it emerges as a clear, fluid-filled sac that is clearly visible beneath the surface of the ovary. This is called "Graph follicle".

With TEM, it is seen that the mature oocyte is covered with a thick and dense ZP. The presence of the first polar body in the perivitelline space and the distribution of many dense cortical granules in the subplasmalemmal areas are observed. By TEM

and conventional SEM, cumulus cells appear polygonal in shape and are arranged in longitudinal groups positioned radially around the oocyte. By SEM, they show a smooth surface equipped with a few microvilli and isolated cilia on the cellular pole facing the antrum. Corona cells instead have a columnar, pear-shaped appearance and are equipped with long and irregular cytoplasmic extensions that pass through the ZP and reach the oocyte surface [22].

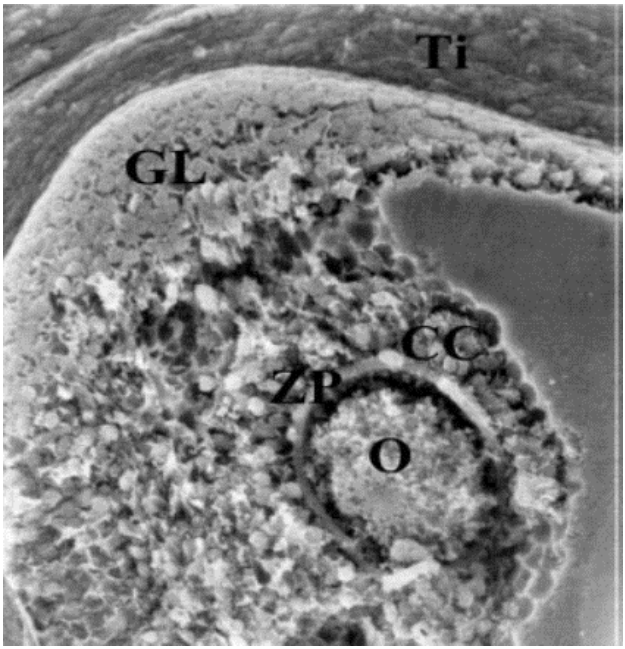

Figure 16. Adult human ovary: Antral follicle. oocyte (O), zona pellucida (ZP), cumulus - corona cells (CC) and parietal granulosa layer (GL), Ti: Theca interna [22].

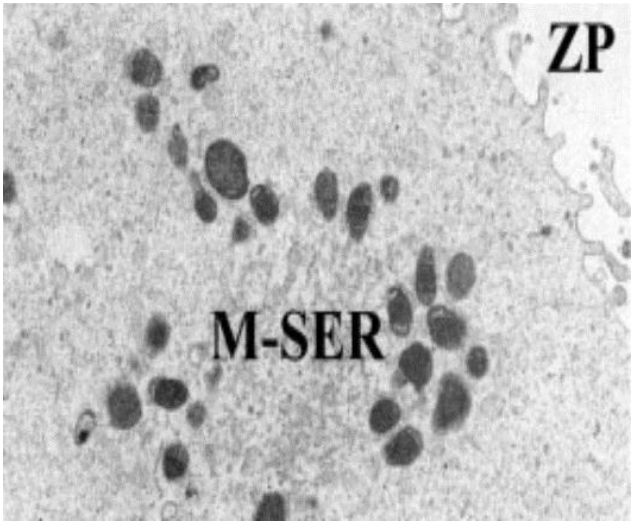

Figure 17. Preovulatory oocyte showing numerous cortical granules (C) and numerous mitochondria beneath the plasma membrane. ZP:zona pellucida [22].

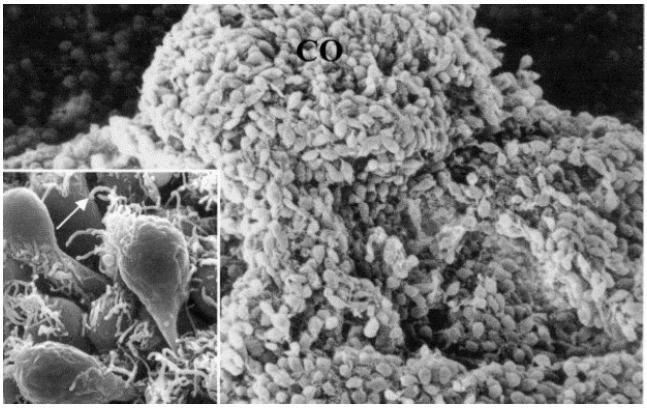

Figure 18. Adult human ovary. A mature follicle with an intact cumulus oophorus (CO). The oocyte (not seen in the figure) is completely covered by cumulus cells. A group of cumulus cells is shown in detail in the inset. They appear to have an elongated, smooth surface and have a few microvilli and isolated cilia (arrow) at the pole facing the oocyte [22].

OVARIUM DISEASES

It can be seen in two forms: non-neoplastic cysts and neoplasias. Non-neoplastic cysts; follicular cysts, lutein cysts, polycystic ovaries, theca-lutein cysts, chocolate cyst (endometrioma).

Follicular cysts: Graafian follicles that cannot rupture, follicles that rupture and become blocked immediately, are mostly multiple clear, filled with serous fluid and can reach a diameter of 2 cm (5 cm!). Rarely, follicular cysts larger than 2 cm can be recognized during examination or ultrasonography. It may cause pelvic pain. Microscopy; The cyst lined with granulosa cells can be distinguished when the intraluminal pressure is not high. Luteinization may develop in the theca cells surrounding the follicle cells (Hyperthecosis). It can be noticed due to the pale cytoplasm that develops due to luteinization. In cases where hyperthecosis is evident, estrogen production may increase and endometrial abnormalities may occur.

Lutein cysts: Lined with bright yellow tissue containing luteinized granulosa cells. It rarely causes a peritoneal reaction. It occurs due to rupture. It may be difficult to differentiate from endometriotic cysts. It occurs due to the presence of old areas of bleeding and fibrosis.

Polycystic ovary syndrome: It is a complex endocrine disease. It is characterized by hyperandrogenism. Menstrual abnormalities are observed. It is often accompanied by oligomenorrhea. There is chronic anovulation. There is reduced fertility. It affects 6-10% of women of reproductive age. It is characterized by numerous follicular cysts. Since polycystic ovaries can be detected in 20-30% of patients, this finding is not specific to the disease. In patients; Permanent anovulation, obesity (40%), Type 2 diabetes, hirsutism (50%), rarely virilism are observed. In macroscopy; The ovaries are usually twice as large as normal. The outer surface is smooth, gray-white in color. There are swellings due to subcortical cysts with a diameter of 0.5-1.5 cm. Microscopy; Thickened, fibrotic superficial cortex, numerous follicular cysts underneath, hyperplasia of theca interna, follicular hyperthecosis, and corpus luteum are often absent. The events that initiate PCOS are not clear. The main feature of the disease is the increase in androgens due to dysregulation of the enzymes involved in androgen synthesis. FSH is low; Excess androgens secreted from the ovaries are converted to estrone in the peripheral fat tissue. FSH release from the pituitary gland via the hypothalamus is prevented. LH increased; It can stimulate the theca-lutein cells of the follicles.

Theca lutein cysts: These are multiple, bilateral, luteinized follicular cysts. It is common when serum hCG level increases [23,24].

Endometrioma (Chocolate cyst): It is the appearance of endometrium tissue in the ovaries outside the uterus and has an effect on the ovarian reserve. Chocolate cyst is the cystic structure formed by endometriosis in the ovaries. Endometriosis is seen in women after the age of 35; Ovarian cysts go clinically, resulting in pain and infertility. There are ovaries that contain chocolate-looking fluid, which is why it gets this name. Their risk of developing into ovarian cancer is less than 1%. The definitive diagnosis of endometriomas can only be made surgically histopathologically [25].

Cortical stromal hyperplasia (Stromal hyperthecosis): It is a disorder of the ovarian stroma. It is mostly seen in postmenopausal women. It can also be seen in younger women along with PCOS. It is characterized by uniform growth of the ovary. It can reach up to 7 cm. It is usually bilateral. The cut surface may vary from white to skin color [23,24].

Ovarian Tumors

Ovarian Cancers are examined under 3 basic headings according to their origin; These are Germ Cell Ovarian Cancers, Sex-Cord Stromal Cancers and Epithelial Ovarian Cancers. Tumors are divided into classes according to their origin in the ovary. Tumors that develop from the epithelium are called superficial epithelial ovary tumors. Cancers arising from the sex cells in the ovary are called germ cell, while tumors originating from the connective tissue are called sex-cord stromal. In addition, it metastasizes to malignant tumors that develop in other parts of the body, mostly from the stomach, intestine and breast, to the ovary [24].

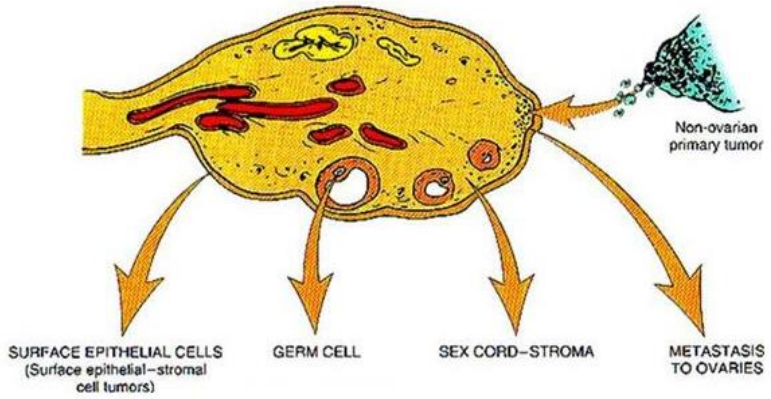

Figure 19. Structures from which ovarian tumor originates [25].

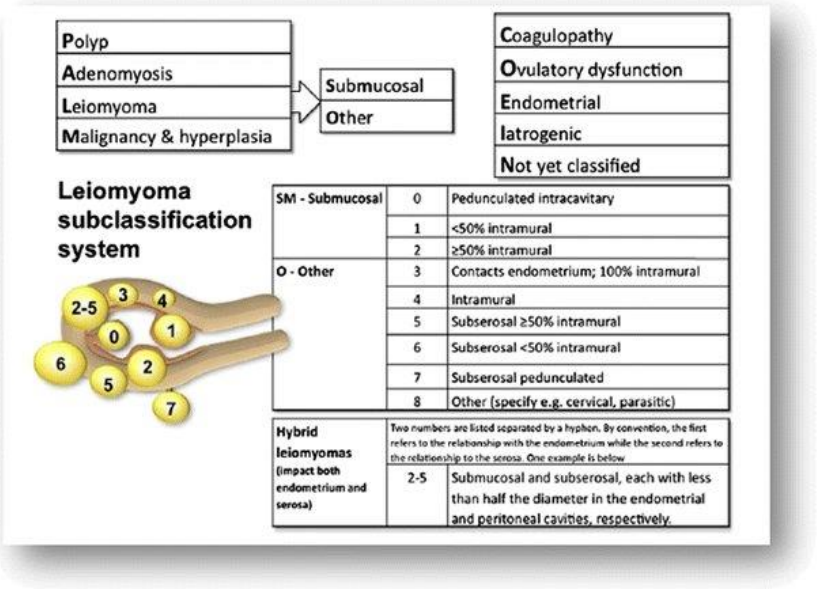

Figure 20. FIGO classification [26].

Epithelial tumors: Mucinous, serous, endometrioid, clear cell, mixed tumors and transitional cell tumors

Germ cell tumors: Embryonal carcinoma, teratomas, endodermal sinus (yolk sac) tumor, and Dysgerminoma

Sex-cord stromal tumors: Granulosa cell tumor, Leydig and Sertoli cell tumors, andrenoblastomas [24, 27].

Factors That Increase the Risk for Ovarian Cancer

- Advanced age (mostly seen after 40 years of age, 50% of them are in people older than 65 years of age)
- Never giving birth (Nulliparity)
- Family history
- Late menopause
- Environmental factors and nutrition
- Early menstruation
- Tobacco and Smoking
- Hormone replacement therapy [27].

Epithelial Ovarian Cancer

It is the gynecological cancer that causes most deaths. It constitutes 27% of gynecological cancers and 4% of total female cancers. 70% of the cases are at an advanced stage at diagnosis. 5-year survey varies between 25-45%.

Incidence and epidemiology: It is generally seen over the age of 50. The age at which it occurs is 59, and the age group in which it is most frequently encountered is 60-64. The average risk of developing ovarian cancer is 1.4%.

Etiology: The real underlying cause is not clear. These factors are mainly divided into endocrine, environmental, genetic and other factors. Most of these factors increase the risk of developing ovarian cancer [28].

Epithelial Ovarian Ca subtypes

1. Mucinous
2. Undifferentiated
3. Clear cell
4. Endometrioid
5. Serous [28]

GERM CELL OVARIAN CANCERS

It constitutes 20-25% of ovarian cancers. It is generally seen at a young age. They constitute approximately 10% of ovarian tumors. They are examined in 7 main groups.

Classification of germ cell ovarian tumors.

1. Germinoma
2. Dysgerminoma (ovarian)
3. Seminoma (testicular)
4. Immature teratoma
5. Embryonal carcinoma
6. Endodermal sinus tumor
7. Choriocarcinoma
8. Polyembryoma
9. Mixed forms

Clinical: They become clinical quite quickly. They may cause pelvic pain due to hemorrhage, capsular distension, torsion, necrosis or rupture. Pelvic mass is the most important examination finding. In pelvic masses, tumor markers such as

Human chorionic gonadotropin (hCG) (for Choriocarcinoma and embryonal carcinoma), Alpha fetoprotein (AFP), Placental alkaline phosphatase (PLAP) (for dysgerminoma), Lactic dehydrogenase (LDH) help in the differential diagnosis. The diagnosis is made by evaluating the clinic, symptoms, tumor markers and risk factors (such as age) all together. Pelvic masses larger than 2 cm in pre-adolescent individuals or larger than 8 cm in the reproductive period should be subjected to surgical exploration. Karyotyping is necessary in pre-adolescent girls considering the possibility of dysgenetic gonads [24].

Dysgerminoma: Malignant ovarian tumors of childhood are extremely rare. Dysgerminoma is the most common malignant ovarian tumor in children and accounts for 26.8% of all pediatric malignant ovarian tumors [29]. It is a pathology that occurs with severe distension due to an intra-abdominal mass. Life-threatening liver pathologies may occur as a result of dysgerminoma metastasizing [30]. Nowadays, the use of USG in the check-ups of girls has increased the number of diagnosed cases. Frequent use of USG after the detection of this pathology helps in planning and monitoring the treatment of girls. The defined treatment for this disease is surgical excision. Surgery alone is appropriate in stage IA of the disease. Today, effective

multiple chemotherapy (platinum, etoposide and bleomycin) has replaced radiotherapy after surgery [31]. Clinical spectrum of dysgerminoma; It varies from abdominal pain to symptoms related to digestive and urinary system obstructions that occur due to the severity of the pressure exerted by the pelvic mass. In the differential diagnosis of the mass detected on USG; Other diseases such as mesenteric cyst, omental cyst and ovarian cyst should also be considered [31]. The prognosis for patients diagnosed with an intra-abdominal mass in girls can be quite variable. If dysgerminoma is encountered in girls, a treatment such as total excision can be applied under general anesthesia.

Immature teratomas: Teratomas are the most common germ cell tumors. They can be mature or immature. The most common location of germ cell tumors seen in children and pubertal girls is the ovary. Ovarian teratomas are benign or malignant neoplasms originating from the primordial germ cells of the ovary. 18% of ovarian masses are mature teratomas and have a benign character and a distinct cystic structure [32]. The presence of immature neuroepithelial (neuroectoderm) tissue in immature (malignant) teratomas indicates that the tumor is malignant and will follow an aggressive course. Mature cystic teratomas, also known as dermoid cysts, are cystic structures containing at least two germ

layers (ectoderm, mesoderm or endoderm). In mature (benign) teratoma, ectodermal components (hair, teeth, skin, hair…) are at the forefront. Although mature cystic teratomas are usually asymptomatic, they may sometimes present with findings such as abdominal pain and swelling, abdominal mass, constipation, nausea, vomiting, infection, abnormal vaginal bleeding, torsion or rupture [33]. Mature teratoma typically contains various adult tissues such as muscle, bone, cartilage, neural, thyroid tissue, squamous epithelium, bronchial epithelium, or intestinal wall within a fibrous or myxoid stroma. Immature teratomas contain tissues with histological characteristics seen in embryonic and fetal development [24].

Endodermal sinus tumor (EST): These tumors, also called yolk sac tumors, behave quite malignantly in areas outside the gonad. It is the most common malignant germ cell tumor in children. In newborns and infants, they most commonly arise from the sacrococcygeal region. They are more common in the ovaries in older children and adolescents. These tumors, which are also seen in the testicles, are the most common malignant testicular tumors. The majority of endodermal sinus tumors originating from the testicle are localized and survival rates are around 70%, depending on age. A different approach is taken in treatment for

patients under 2 years of age and patients over 2 years of age. Under the age of two, the testicle is surgically removed and the spermatic cord is tied high. There is no need to perform lymph node sampling in patients who do not show involvement in the lymph nodes behind the peritoneum and persistent AFP or beta hCG elevations on ultrasonography and CT. In stage I patients without metastasis and without elevated enzyme levels, no treatment other than surgery is required, but patients should be closely monitored with radiology and enzyme measurements. The chance of survival in these patients is 85-90%. In tumors limited to the testicle with high AFP over the age of two, removal of the testicle and the lymph nodes behind the peritoneum should be chosen. If a tumor is detected in the lymph nodes on the side of the tumor, the lymph nodes on the opposite side should also be examined. In stage II or III patients, surgery and lymph node removal should be performed after initial chemotherapy. Combination chemotherapy is the same as given for other germ cell tumors. Overall survival for the entire group is around 75%.
Endodermal sinus tumors originating from the ovary are seen in post-pubertal adolescents. These fast-growing tumors show widespread metastasis. This tumor is the most aggressive malignant ovarian tumor. It metastasizes to the liver, lung, lymph nodes and rarely to bone. In stage I patients, one-sided ovary and

tuba are surgically removed. In more advanced stage patients, the lymph nodes behind the omentum and peritoneum are also removed. Chemotherapy should be administered after surgery in all cases. In patients who cannot undergo surgery initially, chemotherapy should be given, and surgery should be performed after the tumor shrinks. The tumor is resistant to radiotherapy. The prognosis depends on the stage of the disease. With appropriate chemotherapy, survival can be up to 80% [24, 34].

Embryonal carcinoma: It can be seen in pure form or within malignant teratoma. Those seen in the testicles usually appear in late adolescence or early adulthood. It manifests itself as a growing mass in the scrotum, a metastatic intra-abdominal mass or a mediastinal mass. Serum AFP or beta hCG may increase. Treatment varies depending on AFP level and tumor stage. In stage I and II patients, radical testicular removal and removal of the lymph nodes behind the peritoneum are performed. With good monitoring of patients treated only with surgery and appropriate treatment for those who will receive chemotherapy, the chance of complete recovery from this tumor is very high. Embryonal carcinoma originating from the ovary differs from endodermal sinus tumor in every respect. It is seen in adolescent girls at the

average age of 15. It is treated like an endodermal sinus tumor of the ovary [35].

Choriocarcinoma of the ovary: Pure nongestational choriocarcinoma of the ovary is a very rare tumor. Histologically, it has the same appearance as gestational choriocarcinomas that have metastasized to the ovaries. Most patients are under 20 years of age. The presence of hCG is important in monitoring patients' response to treatment. In the presence of high hCG levels, isosexual precociousness can be seen in 50% of those whose lesions are discovered before menarche [36, 37].

Polyembryoma: Malignant mixed germ cell tumors of the ovary are rare tumors seen in young women. The presence of distinct embryoid bodies in these tumors is extremely rare. [24, 26]

STROMAL SEX CORD OVARIAN CANCERS

Ovarian sex cord stromal cancers cover 4-9% of all ovarian malignant cancers. These tumors develop from the ovarian mesenchyme and sex cord.

Granulosa cell tumors: Seen in reproductive age. They frequently secrete estrogen. However, there are also types that

secrete androgens or do not secrete hormones. It often causes menstrual disorders. It causes endometrial cancer in about 6% of cases and endometrial hyperplasia in 15-30% of cases. Symptoms and findings are nonspecific and similar to other ovarian cancers. They are examined as low-grade malignancy [28].

Sertoli-Leydig cell tumor: These are very rare tumors. They are seen in the 30s and 40s. They have low-grade biology. They cause 70-85% clinical virilization because they secrete androgens [26].

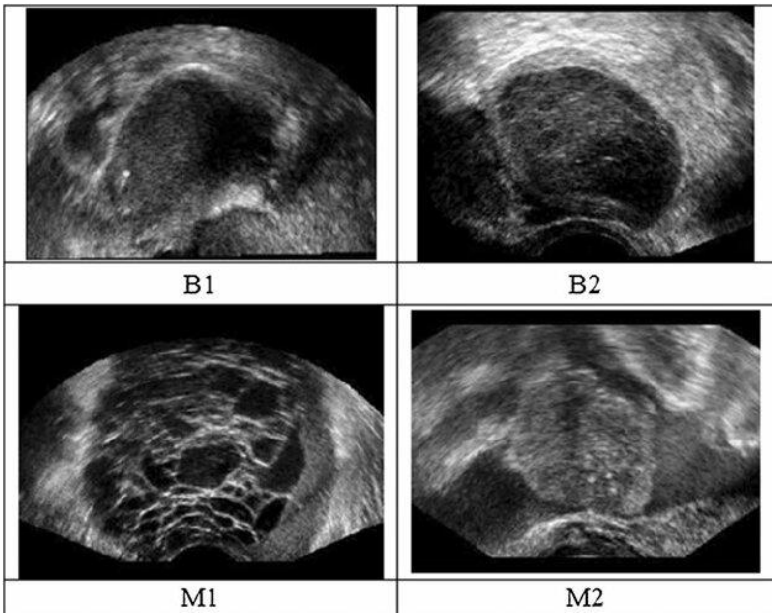

Fıgure 21. Ovarium Diseases USG Image [28].

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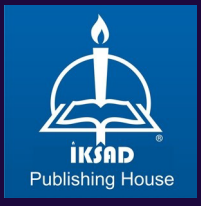

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