Review

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Title: Histological structure and functional properties of the tunica albuginea of the ovary.
Short title: Tunica albuginea of the ovary.

Abstract

Just below the surface epithelium of the ovary is the tunica albuginea, which is a tight irregular connective tissue structure that gives the tissue its white color and contains fibroblast cells. Tunica albuginea, which is more resistant to environmental factors, contains fewer cells and is rich in collagen fibers, is observed as the niche of preantral follicles. It has been observed that fibroblasts forming collagen fibers provide the development of follicles with the paracrine factors and cytokines they secrete and function as a nourishing cell layer. After the graaf follicle forms the corpus luteum, fibroblasts in the adjacent tunica albuginea proliferate and the thickness of this structure increases. The tunica albuginea undergoes frequent renewal due to the corpus luteum structures formed in rats. When the corpus luteum is formed, new capillaries and venules are formed in the adjacent tunica albuginea. This structure may be a suitable model for investigating the migration of cells from the bone marrow to the ovary via vessels. It can be suggested that mesenchymal cells and very small embryonic-like stem cells (VSELs), which show pluripotent stem cell characteristics, may migrate from the bone marrow to the tunica albuginea through vascular structures and that the bone marrow may be the source of these cells, which have been previously shown to be present in the ovary. The aim of this review is to examine the effects of the tunica albuginea on the development of follicles and the dynamic structure of the ovary.

Key words: Ovary, tunica albuginea, collagen fibers, follicle, corpus luteum.

Makale başlığı: Ovaryum tunika albugineasının histolojik yapısı ve fonksiyonel özellikleri.
Kısa başlık: Ovaryum tunika albugineası.

Öz

Ovaryumda yüzey epitelinin hemen altında dokuya beyaz rengini veren, sıkı düzensiz bir bağ doku yapısında olan ve içinde fibroblast hücrelerini içeren tunika albuginea bulunur. Çevresel etkenlere daha dirençli olan, az sayıda hücre içeren ve kollajen liflerden zengin olan tunika albuginea preantral foliküllerin nişi olarak gözlenmektedir. Kollajen lifleri oluşturan fibroblastların salgıladıkları parakrin faktörlerle ve sitokinlerle foliküllerin gelişimlerini sağladıkları ve besleyici hücre tabakası gibi fonksiyon gördükleri izlenmiştir. Graaf folikülün korpus luteumu oluşturmasından sonra ise hemen bitişiğindeki tunika albugineadaki fibroblastların prolifere olduğu ve bu yapının kalınlığının arttığı izlenmiştir. Ratlarda oluşan korpus luteum yapıları nedeniyle tunika albuginea sık sık yenilenmeye uğramaktadır. Korpus luteum oluştuğu zaman bitişiğindeki tunika albugineada yeni kapillerler ve venüller meydana gelmektedir. Bu yapı; hücrelerin kemik iliğinden, damarlarla ovaryuma migrasyonlarının araştırılması için uygun bir model olabilir. Mezenkimal hücrelerin ve pluripotent kök hücre özelliği gösteren çok küçük embriyonik benzeri kök hücrelerin (VSELs) vasküler yapılar aracılığıyla kemik iliğinden tunika albugineaya gelebileceği ve ovaryumda bulundukları daha önce gösterilen bu hücrelerin kaynağının kemik iliği olabileceği ileri sürülebilir. Bu derlemedeki amacımız tunika albugineanın foliküllerin gelişimine ve ovaryumun dinamik yapısı üzerine olan etkilerini incelemektir.

Anahtar kelimeler: Ovaryum, tunika albuginea, kollajen lifler, folikül, korpus luteum.

Introduction

Ovarian histology

The ovary is a pinkish-white oval-shaped organ located on either side of the uterus. The ovary is defined as an exocrine gland because of gamete production and an endocrine gland because of hormone secretion [1]. The surface of the ovary is lined with single layer cubic epithelium and pseudo-multilayer epithelium in some areas and flat epithelium in some areas. The surface epithelium is rich in cytokeratin (CK) 7, 8, 18 and 19 and has intercellular desmosomes and tight junctions. Under the surface epithelium is a basal membrane consisting of two layers. One layer is the basal lamina made by epithelial cells. The second layer is the reticular lamina formed by fibroblasts [2-4]. Just below the basal lamina is the tunica albuginea, a tight connective tissue structure that gives the ovary a whitish colour (Figure 1, 2) [1, 4].

The surface epithelium of the ovary shows a highly dynamic structure. The surface of the ovary expands or narrows due to changes in the size of the follicles and corpus luteum. In addition, when the follicle wall ruptures during ovulation, repair occurs in the tunica albuginea and surface epithelium. This repair is thought to occur by the proliferation of surface epithelial cells with stem cell properties [4]. In the studies carried out at advanced ages, it is observed that the surface epithelium of the ovary turns into a multi-level flat epithelium and its structure becomes irregular. In some cases, after ovulation some of the ovarian surface epithelium becomes invaginated towards the cortex and continues along with some tunica albuginea and is called an inclusion cyst. In studies with neonatal rat ovary, it has been observed that the surface epithelium has an discontinuous basal membrane and consists of multiple cell layers. It is then observed that a continuous basal membrane forms under a pseudostratified surface epithelium. In the following process, it is observed that the surface epithelium is organized as a single-layer structure and a continuous basal membrane is formed. [5]. Ovarian follicles are surrounded by the basal lamina, a specialized form of extracellular matrix (ECM) that separates the granulosa cells from the stroma. This basal lamina is surrounded by a network of different macromolecules such as collagen IV, laminin, nidogen and perlecan produced by stromal cells and granulosa cells. Type IV collagen is the most abundant component in the basal lamina [6].

The ovary consists of two parts, the cortex and medulla layers, which have different histologic features. While these two layers can be easily distinguished in ovaries in the early reproductive period, these differences begin to diminish in later periods. The connective tissue in the tunica albuginea is an irregular tight connective tissue containing fibroblasts and fibrocyte cells, whereas the medulla is a loose connective tissue. In addition to fibroblast and fibrocyte cells, which are less abundant in the medulla, hilar cells, adipocytes, macrophages and vascular structures are present. Spiral arteries and arterioles are located parallel to the surface epithelium and tunica albuginea of the ovary. Branches of this artery extend into the cortex and medulla. It has been shown that perioverian adipose tissue is located immediately adjacent to the surface epithelium in the rats and there is a fibrous thin sheath between them (Figure 3-5).

The area where blood vessels and nerves enter the ovary is called hilus. Information on the hilar cells located in the ovarian hilus is limited. Hilar cells are often found in clusters associated with the nerve trunk. Hilar cells are found in the inner cortex and often in the medulla. They have been reported to synthesize and secrete androgens in response to luteinizing hormone (LH) stimulation, although their physiologic role is not well defined. Hyperplasia of these cells has been shown to play a role in virilization in postmenopausal women (Figure 6, 7) [1, 7].

The ovarian stroma contains ovarian-specific components including immune cells, blood vessels, nerves and lymphatic vessels, as well as the ovarian surface epithelium, tunica albuginea, intraovarian rete ovarii, hilar cells, stem cells and most of the incompletely characterized stromal cells, including fibroblast-like, spindle-shaped and interstitial cells. Studies have demonstrated that cortical stromal cells actively differentiate into teca cells in the presence of granulosa cells [8, 9].

The immune cells that support the physiological processes of the ovary are macrophages, B lymphocytes, T lymphocytes, natural killer cells (NK), dendritic cells, neutrophils, eosinophils, and mast cells [7].

Macrophages are the most abundant immune system cell community in the ovary. The ovary contains different types of macrophages, proinflammatory (M1) and anti-inflammatory (M2). IL4 and IL13, cytokines that induce M2 macrophage differentiation, are increased in the ovarian stroma in association with obesity and ageing. Increased proportions of M2 macrophages, monocyte-derived macrophages and multinucleated macrophages were found in mouse ovarian ageing. There is emerging evidence that macrophages play a role in ovarian dysfunction, particularly in polycystic ovary syndrome (PCOS), premature ovarian failure and endometriosis. Studies have shown infiltration of the ovary by both the yolk sac and fetal liver-derived macrophages during embryonic development. Bone marrow-derived monocytes have been shown to contribute to ovarian macrophages after birth. Consequently, both embryonic-derived and bone marrow-derived macrophages contribute to different ovarian macrophage subpopulations in adults [10, 11]. In the regressed corpus luteum, capillary endothelial cells, which do not express cytokeratin, recruit macrophages to this region (Figure 7, 5).

Embryology of the ovary

In mammals, primordial germ cells (PGC) were first identified in the posterior intestinal (hindgut) epithelium of the embryo and were assumed to originate from the yolk sac wall. The yolk sac originates from the extraembryonic endoderm differentiated from the hypoblast, whereas the hindgut develops from the embryonic endoderm differentiated from the epiblast. Therefore, PGCs were thought to originate from the hypoblast, but later studies showed that PGCs originate from the epiblast. In humans, PGCs are observed in the hindgut epithelium of the 3-week-old embryo. At 4 weeks, PGCs reach the dorsal mesentery and begin their migration. By 6 weeks of age, almost all PGCs have reached the gonads

Unlike mammals, avian PGCs do not cross the hindgut epithelium to reach the dorsal mesentery but instead are incorporated into the extraembryonic vascular network and pass into the peripheral circulation to reach the dorsal mesentery [12, 13].

Although the reconstitution of adult ovarian blood vessels by angiogenesis is crucial for the regulation of female reproduction, studies on this process are limited. Long-term blockade of angiogenesis with drugs that specifically block the vascular endothelial growth factor (VEGF) signalling pathway has been shown to reduce ovarian follicle depletion and delay ovarian senescence, leading to prolonged reproductive life span in older females [14].

Human gonad development begins in the same way in males and females, with the embryonic urogenital ridge (gonadal ridge) containing the mesonephric duct and mesonephric tubules. The initially undifferentiated human embryonic gonad contains four elements: (a) the coelomic epithelium of the urogenital ridge; (b) the underlying mesenchyme; (c) the mesonephros; and (d) primordial germ cells (PGCs).

Sex differentiation of the undifferentiated human gonad into the ovary or testis is recognized morphologically by the appearance of testis- or ovary-specific features. In the male embryo, testicular cords appear at approximately 7 weeks of gestation. In the female embryo, ovary-specific features appear at 8 weeks of gestation: (a) a cortical region containing ovigerous cords and (b) a medullary region also containing cords. The ovigerous cords are separated from the stroma by a basal lamina [15-17].

In the human ovary at 10 weeks of gestation, PGCs mitotically proliferate to form germ cell nests. Moreover, these germ cell nests are evolutionarily conserved in males and females of insects, frogs, rodents and vertebrates. Mitotic proliferation results in the formation of interconnected clusters of oogonia. The oogonia then enter meiotic prophase I, during which they are called oocytes, and stop at this stage of meiosis. The germ cell nests then begin to fragment, during which the majority of oocytes are lost through apoptotic cell death, while the remaining oocytes are surrounded by pregranulosa cells, forming primordial follicles. Primordial follicles switch to primary follicles formed by oocytes surrounded by single-layer cuboidal granulosa cells. When multilayered granulosa cells surround an oocyte, secondary follicles emerge. More developed antral and preovulatory follicular stages occur postnatally (Figure 8, 9) [15, 18, 19].

During the development of the ovary, ovarian follicles are divided into two different groups. The first group, called medullary follicles, disappears before puberty. The second group, or cortical follicles, remain fixed until puberty. Along with puberty, 15-20 primary follicles are monitored in each menstrual cycle, but as a result, one oocyte matures in the dominant follicle. The primary oocyte completes meiosis I during this maturation, and the haploid is composed of a secondary oocyte and a nonfunctional polar body. The meiosis stops at the metaphase II stage and ends with fertilization by the sperm [20, 21].

Fetal ovarian histology and tunica albuginea

Unlike the adult ovary, the fetal ovary is long and flat in shape. The basic cellular components of the ovary are the surface epithelium, stroma and its derivatives, germ cells and granulosa cells that will surround the germ cells. The surface epithelium consists of a single layer of cuboidal to pseudostratified cells without a distinct basement membrane. In contrast to the adult ovary, the stroma of the fetal ovary is very scanty, because 90% of the cortex is composed of germ cells. At 21 weeks of gestation, the surface epithelium of the fetal ovary appears as a single layer of cuboidal cells without a distinct basement membrane. Throughout the fetal period, the tunica albuginea appears to develop significantly at 28 weeks [22].

The tunica albuginea is formed from the mesonephric stroma after the ovarian surface epithelium is formed. Given the proximity to the surface epithelium, it may be possible that factors from surface epithelial cells influence the transformation of adjacent stromal cells into fibrous tunica [23].

Structural characteristics of the tunica albuginea of the ovary

The tunica albuginea is a fiber-rich, hypocellular, tight, irregular, irregular avascular layer of connective tissue located beneath the surface of the ovary, consisting mainly of structural collagens and other extracellular proteins (collagen type I, collagen type 4, laminin, fibronectin, decorin, versican) [7, 23, 24]. It serves as a protective layer for the ovary. The tunica albuginea undergoes remodelling after ovulation [7].

Structural and physical properties of testicular tunica albuginea

The testicle is enclosed in a capsule consisting of 3 layers:

1) Tunica vasculosa (innermost)
2) Tunica albuginea (center)
3) Tunica vaginalis (outside)

Tunica vasculosa forms vascular plexus. Tunica albuginea forms an abundance of collagen fiber. Tunica vaginalis provides the connection between the peritoneal cavity and the scrotum [25].

Tunica albuginea is located in the central region of the testicular capsule and separates the capsule into the inner and outer region. This layer of fibroblasts, elastin fibers, collagen fibers (arranged in an organized wavy appearance), ectopic leydig cells, mast cells, blood vessels, nerve endings, etc, it is composed of myofibroblasts and an dense connective tissue composed of smooth muscle cells. The outer zone contains abundant myofibroblasts, while the inner zone is rich in smooth muscle cells. In the transition zone between the two, mast cells, ectopic leydig cells, myelin-free nerve fibers

and blood vessels are present. Previous findings that tunica albuginea exerts contractile properties raise the possibility that it may have physiological functions;

1) transport of sperm produced in the testicle to the epididymis
2) maintenance of interstitial pressure within the testis
3) control of blood flow through the testis

The human testicle finds a large amount of various contraction elements in the tunica albuginea. Complex and regionalized contraction regulated by cyclic guanosine monophosphate (cGMP)-mediated processes has important physiological roles, such as the continuous support of sperm transport within the rete testis [26, 27].

Structural differences of ovarium and testis tunica albuginea

The ovarian tunica albuginea is not as thick as the testicular tunica albuginea [23]. The ovary tunica albuginea shows a variable thickness ranging from almost undetectable to over 50 μm [28]. The thickness of testicular tunica albuginea varies with age, with younger males increasing from 400-450 μm to over 900 μm in older men [29].

There is a correlation between the density and thickness of the ovarian tunica albuginea and the age of the patient. It is observed that the area forming the ovarian tunica albuginea in elderly individuals is expanding and becoming more compact. As a result, with the formation of fibrosis areas under the tunica albuginea and the increase in the total volume of dense connective tissue under the surface of the ovary, the thickness of this area can be traced to increased [30].

The tunica albuginea of the ovaries contains more collagen, abnormal changes have been observed in tunica albuginea, such as polycystic ovary syndrome (PCOS), in which it exhibits a thicker property and also increases the thickness of cortical and subcortical stroma, which may adversely affect folliculogenesis and ovulation [23].

In polycystic ovary disease, bilateral ovaries expand due to a large number of follicle cysts. Since there is no ovulation, the surface of the ovary is smooth and white in color. Beneath the thickened tunica albuginea are numerous cysts and atrophic secondary follicles [31]. Although hormonal therapy is often administered, third-line therapy may be surgical in patients with resistance to pharmacological treatments [32]. Thus, ovulation is ensured without the physical barrier created by the pre-existing thickened tunica albuginea of the ovary [31].

Changes to tunica albugineada during ovulation

Tunica albuginea is rich in collagen fibers and undergoes post-ovulation reconstruction. As the ovary follicles examined by electron microscopy reach the preovulatory stage, a decrease in the presence of collagen fiber bundles in the apex of the follicles (the ruptured part in ovulation) has been observed. This deterioration is parallel to

the increase in apical fibroblasts with advanced cytoplasm and lysosome-like granules, which are estimated to contain collagenases for the breakdown of tunica albuginea [7].

A microscopic study with electrons suggests that in human follicles some of the collagen fibre bundles in the tunica albuginea and theca externa disappear before ovulation, and biochemical methods show that collagen fibre synthesis is present at the follicle apex. Tunica albuginea in the follicular apex region has been shown to contain less collagen than tunica albuginea in areas without follicles [33].

After ovulation in man, changes in the region-dependent collagen fiber content are observed in the tunica albuginea. The tunica albuginea in the apical region of the follicles contains less collagen fiber than in follicle-free areas, and the percentage of collagen fiber dissolved in acetic acid with pepsin is lower. These results show that collagen fibers are broken down in the apical tunica albuginea. Significantly low collagen fiber content within the tunica albuginea follicular wall resulting from local high collagenase activity has been claimed to be able to facilitate more stigma formation by reducing strain in the albuginea in the tunica [34].

Studies in rabbits have shown that the collagen layers in the tunica albuginea, which cover the teka layer inside, around and over, form the tensile strength of the follicle wall. A study in the Rat ovary pointed out that tunica albuginea contains a rich amount of interstitial collagen types I and III. Studies in rats and cows have shown that type IV collagen is present in both of the basal lamina that separates the cell layers from teka interna and granulosa, and the basal lamina between the surface epithelium of the ovary and tunica albuginea. These results show a difference in the composition between the surface epithelium basal lamina of the ovary and the teka/granulosa basal lamina [33].

Matrix metalloproteinase-1 (MMP-1) and Matrix metalloproteinase-3 (MMP-3) are proteolytic enzymes that play a role in reshaping the extracellular matrix of the ovary during the menstrual cycle. Compared to tunica albuginea from follicle-free areas, less MMP-1 is detected in the apical wall of atretic follicles. These data are associated with low MMP-1 concentrations of atresia in the apical wall of the follicle, indicating that both MMPs play an important role in the final stage of atresia [35].

In ovulatory follicular rupture studies, it is observed that connective tissue degeneration starts at the ovarian surface and progresses towards the follicular wall. The proteolytic enzymes released from the ovary epithelium degenerate the tunica albuginea and the underlying teka layer, weakening the apical follicular wall.

Plasmin (fibrinolysin) is derived from zymogen plasminogen by enzymatic activation. There are two types of plasminogen activators (PA), urokinase (u) and tissue (t) types, in vertebrates. The increase in the biosynthesis of plasmin in the apical and adjacent tunica

albuginea of preovulatory follicles in sheep has been attributed to the secretion of upA by the surface epithelial cells of the ovary. It has been found that teka and granulosa cells secrete uPA and tPA in rodents.

With the secretion of plasminogen activator (PA), a localized increase is observed in the level of plasmin. As a result, collagenases are activated and the tumour necrosis factor (TNF-) in teka cells is released. TNF causes collagen degradation by inducing the gene expression of MMP-1 and MMP-2 [36].

The contractions of the tunica albuginea in the ovary facilitate oocyte and fluid movements, ovulation in the ovary [37, 38]. The study in cattle showed increased gene expression of G-protein-coupled receptor (GPCR) and cyclic adenosine monophosphate (cAMP) in tunica albuginea compared to stroma. The bovine ovary suggests that the tunica albuginea may be contractile, as in the fish-aquarium tunica and the mammalian testicle tunica albuginea. In addition, granulosa cells of preovulatory follicles express endothelin 2, causing ovarian contraction [38].

The relationship of the ovarium surface epithelium with tunika albuginea

The surface epithelium of the ovary is connected to the basal membrane, which continues with the underlying tunica albuginea with collagen fibrils [38]. The mesenchymal cells in the human ovary tunica albuginea express cytokeratin (CK) and can differentiate into surface epithelial cells through the mesenchymal-epithelial transition [39, 40]. Bipotent mesenchymal cells in the tunica albugineada layer can form granulosa cells and germ cells in the ovary cortex. The mesenchymal cells in the adult ovary tunica albuginea can differentiate into the surface epithelium of the ovary by mesenchymal-epithelial passage. These cells may have the ability to become granulose or germ cells depending on the effects of the stromal cells (microenvironment). The result is that tunica albuginea fibroblasts, which exhibit a transient CK immune expression, have been shown to differentiate into surface epithelial cells through the mesenchymal-epithelial transition process. This process can result in the formation of surface epithelial channels and cords in the ovary cortex, or by differentiation into the surface epithelial cells of the ovary, depending on the factors not yet explained [28].

The fibroblasts in tunica albuginea support the development of follicles with the paracrine factors they secrete and function like a nutritious cell layer. The thickening or degeneration of tunica albuginea in diseases such as chemotherapy or polycystic ovary syndrome can affect the development of follicles. Chemotherapy agents may also cause premature ovarian failure, in which loss of primordial follicles is seen [41, 42].

In ovulatory follicular rupture studies, it is observed that connective tissue degeneration starts at the ovarian surface and progresses towards the follicular wall.

(Figure 10). A week after the transplantation of mesenchymal stem cells marked green fluorescence protein (GFP) into the femoral bones of rats as intramedullary, the study of these cells by fluorescence microscopy of ovarian tissue in the tunica albuginea, they have been shown to disperse into the follicles and more often the corpus luteum (Figure 11). In one study, cells isolated from the ovarian and testicular tissues by explant culture technique showed fibroblast-like morphology (Figure 12).

Another study showed that tunica albuginea, adjacent to the corpus luteum, which occurs from the Graaf follicle after ovulation, has been reconstructed. Concentric collagen fibers, which form the tunica albuginea adjacent to the ever-expanding corpus luteum, were previously reported to have a 1-2-row sequence, followed by a regression of 5-6 rows and thickened. It has also been suggested that corpus luteum structures that reach quite large volumes may cause them to alter localizations of the preantral follicles in particular and may direct them to atresia by affecting their development [43].

As a result, the tunica albuginea may be a suitable model for the study of the migration of pluripotent and multipotent stem cells from the bone marrow to the ovary via vascular structures. After the formation of the corpus luteum, numerous capillaries and venules form in the adjacent tunica albuginea. During the reproductive period, proliferating fibroblasts differentiate from mesenchymal cells in the stroma. In addition, mesenchymal cells can come from the bone marrow through vascular structures and differentiate into fibroblasts in these regions. Fibroblasts in the tunica albuginea also undergo continuous renewal due to estrous cycles. Studies have shown that a large number of Very small embryonic/epiblast like stem cells (VSELs) are present in ovarian tissue. The potential of these cells to migrate from the bone marrow through vascular structures to form follicles in the tunica albuginea could be investigated. Fibroblasts in various layers of the corpus luteum, antral follicles and atretic follicles create a niche for the development of primordial follicles in different locations of the ovary. Thus, in addition to the fibroblasts in the tunica albuginea, new septa-like regions are formed in which preantral follicles can develop. Further studies are needed to investigate the contribution of the tunica albuginea to the development of follicles and the dynamic structure of the ovary, the structure and functions of which have not been sufficiently investigated so far.

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Authors' contributions to the article

M.S.U. have constructed the main idea and hypothesis of the study. M.S.U., H.Y., C.K. and A.C.T. developed the theory and edited/evaluation the introduction and results section. Written by H.Y., M.S.U., C.K. and A.C.T. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

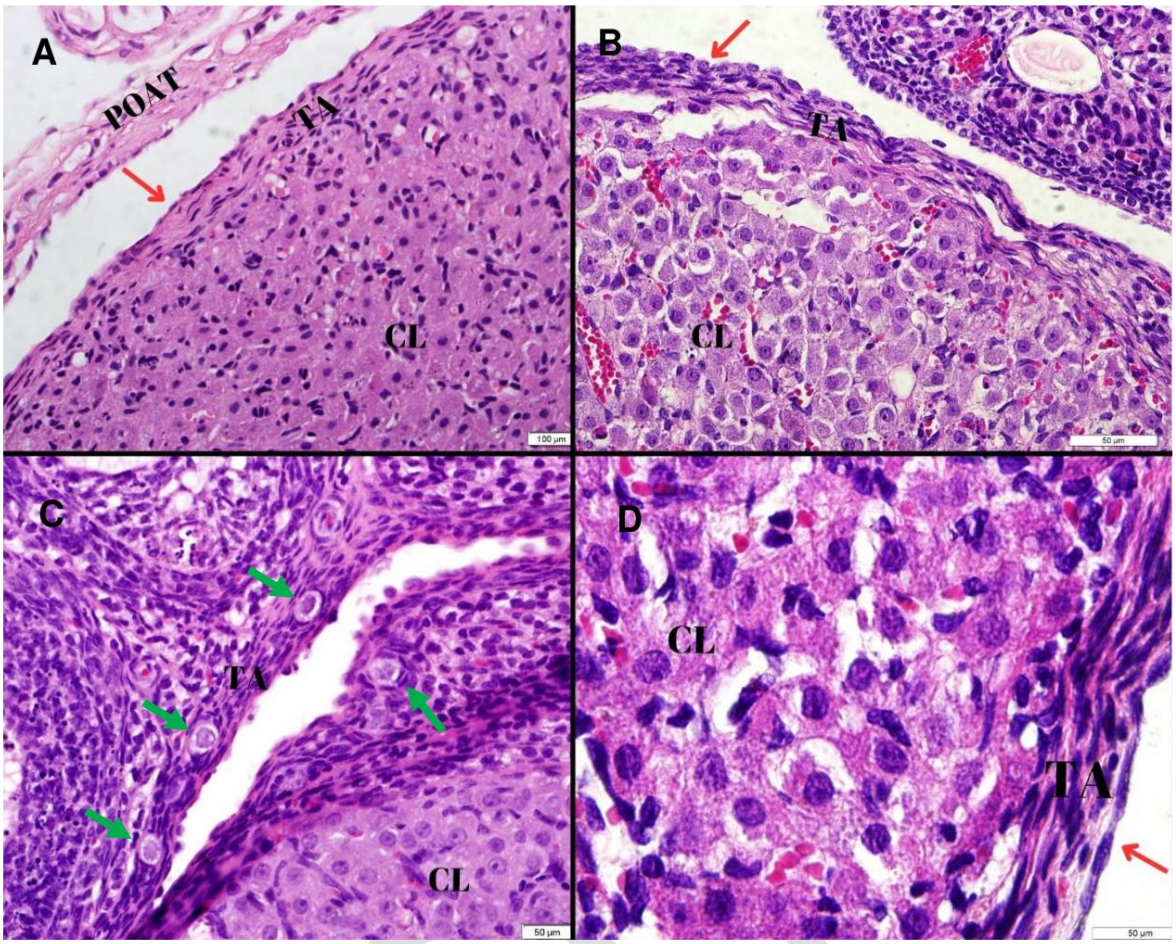

Figure 1. A-B: Tunica albuginea and surface epithelium adjacent to the corpus luteum, C: Primordial follicles within the tunica albuginea, D: Tunica albuginea and surface epithelium adjacent to the corpus luteum, green arrow indicates primordial follicle, red arrow indicates ovarian surface epithelium

TA: Tunica Albuginea CL: Corpus Luteum, POAT: Periovarian Adipose Tissue, Magnification (A, B, C: 400X, D: 1000X)

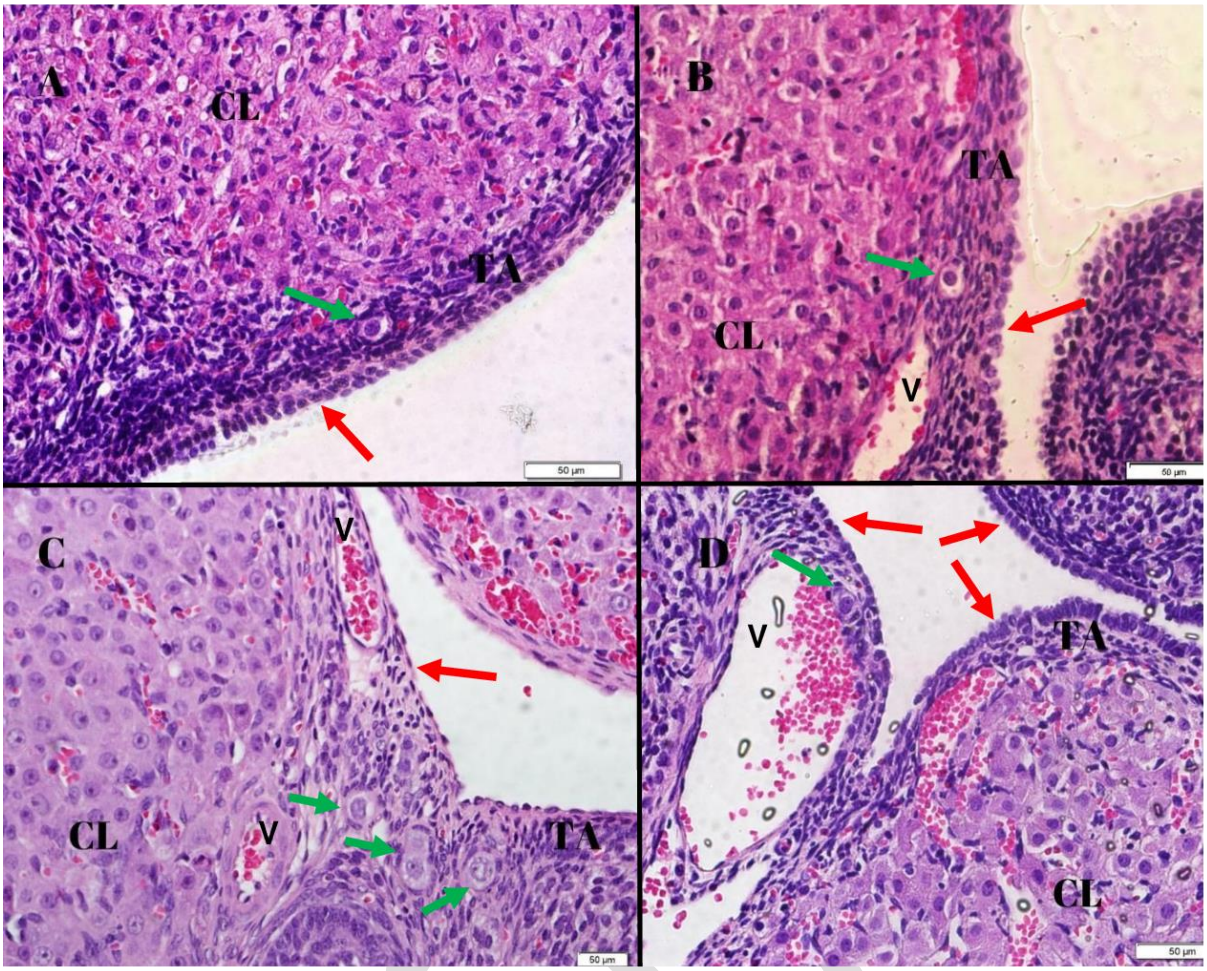

Figure 2. A-B-C-D: The tunica albuginea adjacent to the corpus luteum and primordial follicles within it. Green arrow indicates primordial follicle, red arrow indicates ovarian surface epithelium

TA: Tunica Albuginea CL: Corpus Luteum V: Vascular Structures, Magnification (A, B, C, D: 400X)

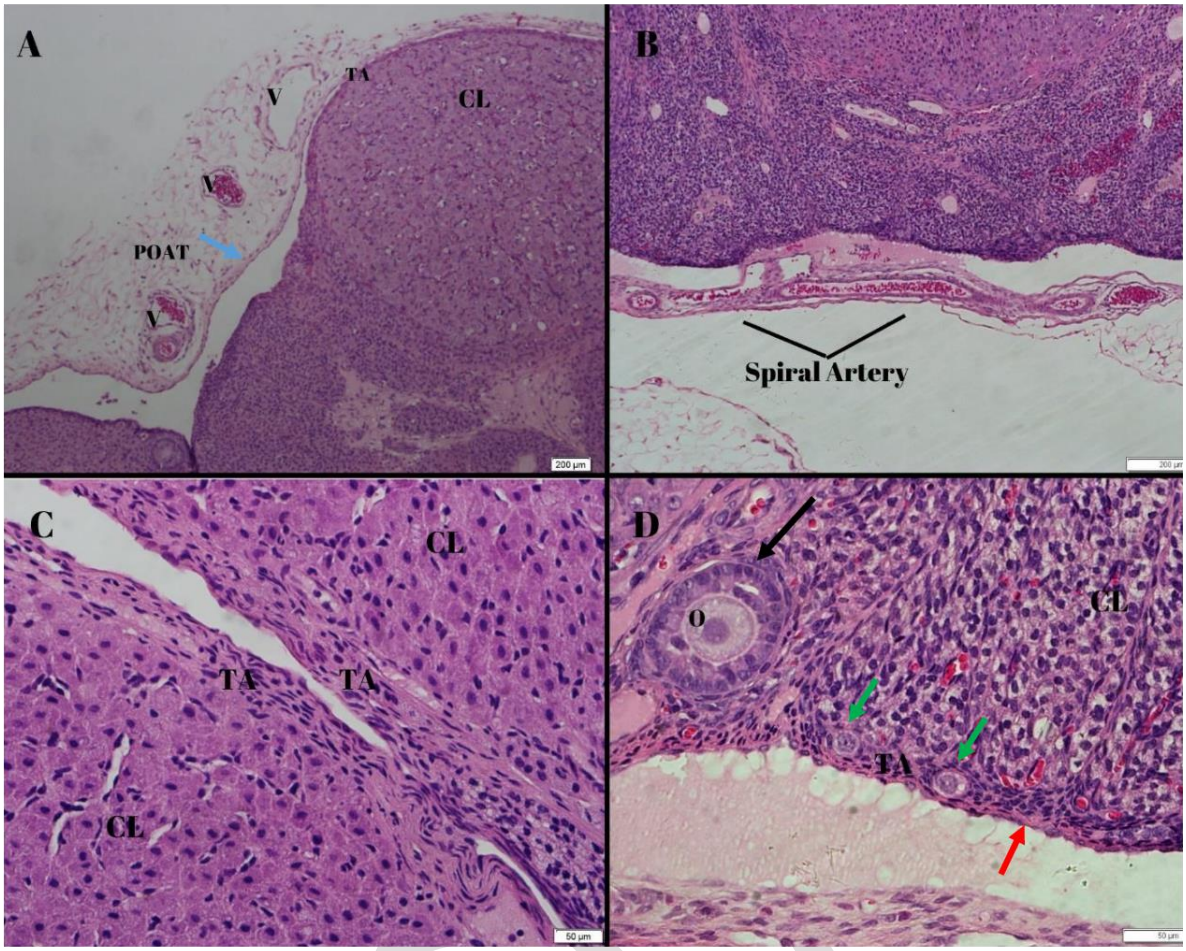

Figure 3. A: Tunica albuginea and surface epithelium adjacent to the corpus luteum, B: Spiral artery extending parallel to the cortical layer of the ovary, C: Tunica albuginea and surface epithelium adjacent to the corpus luteum, D: Tunica albuginea adjacent to the regressed corpus luteum and primordial and primary follicles within it. Blue arrow indicates fibrous sheath, green arrow indicates primordial follicle, black arrow indicates primary follicle, red arrow indicates ovarian surface epithelium

TA: Tunica Albuginea CL: Corpus Luteum O: Oocyte, Magnification (A, B: 200X C, D: 400X)

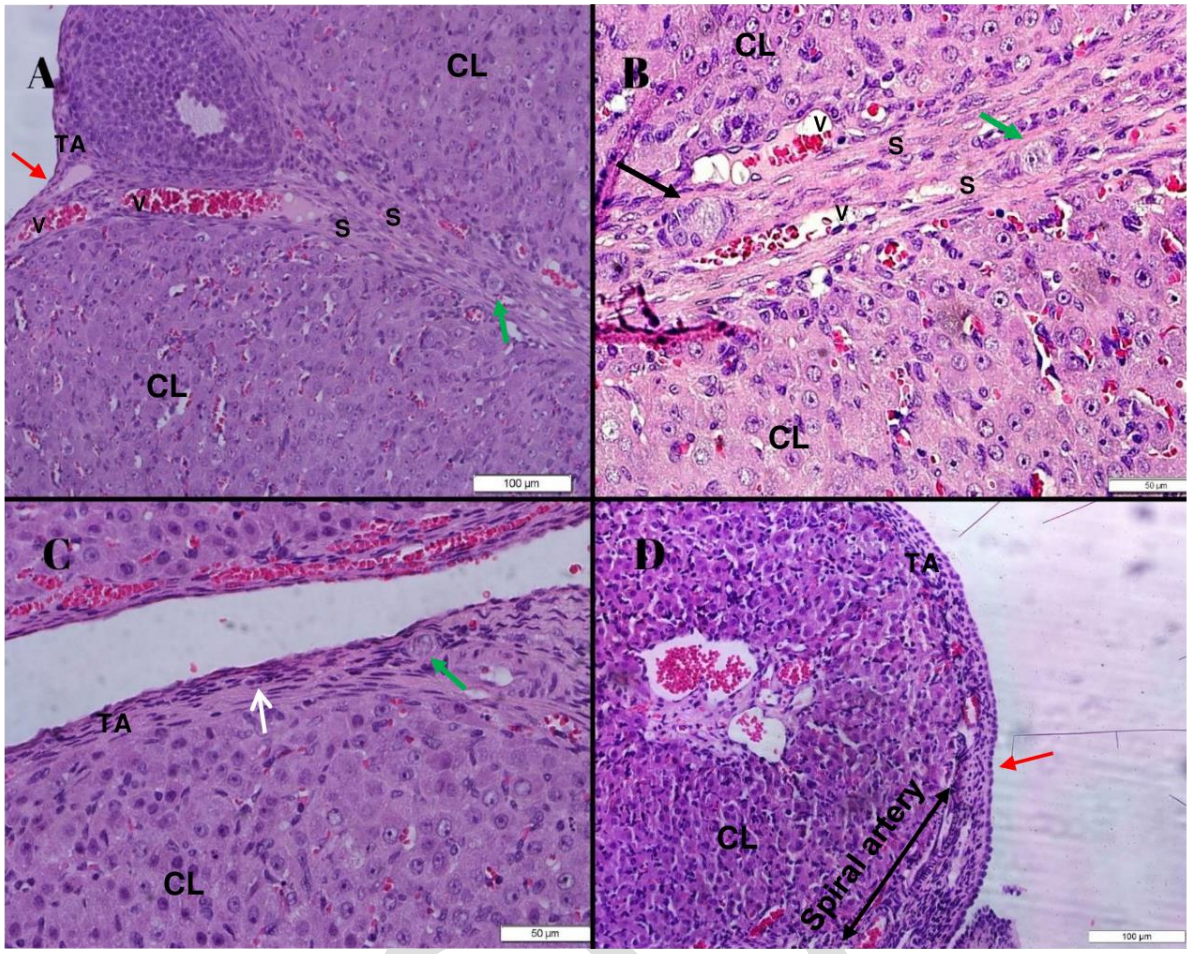

Figure 4. A-B-C-D: The tunica albuginea adjacent to the corpus luteum and the primordial and primary follicles within it. Green arrow indicates primordial follicle, black arrow indicates primary follicle, red arrow indicates ovarian surface epithelium, white arrow indicates germ cells

TA: Tunica Albuginea CL: Corpus Luteum V: Vascular structures S: Septa, the outer part of the corpus luteum containing fibroblast cells and collagen fibers, Magnification (A, D: 200X B, C: 400X)

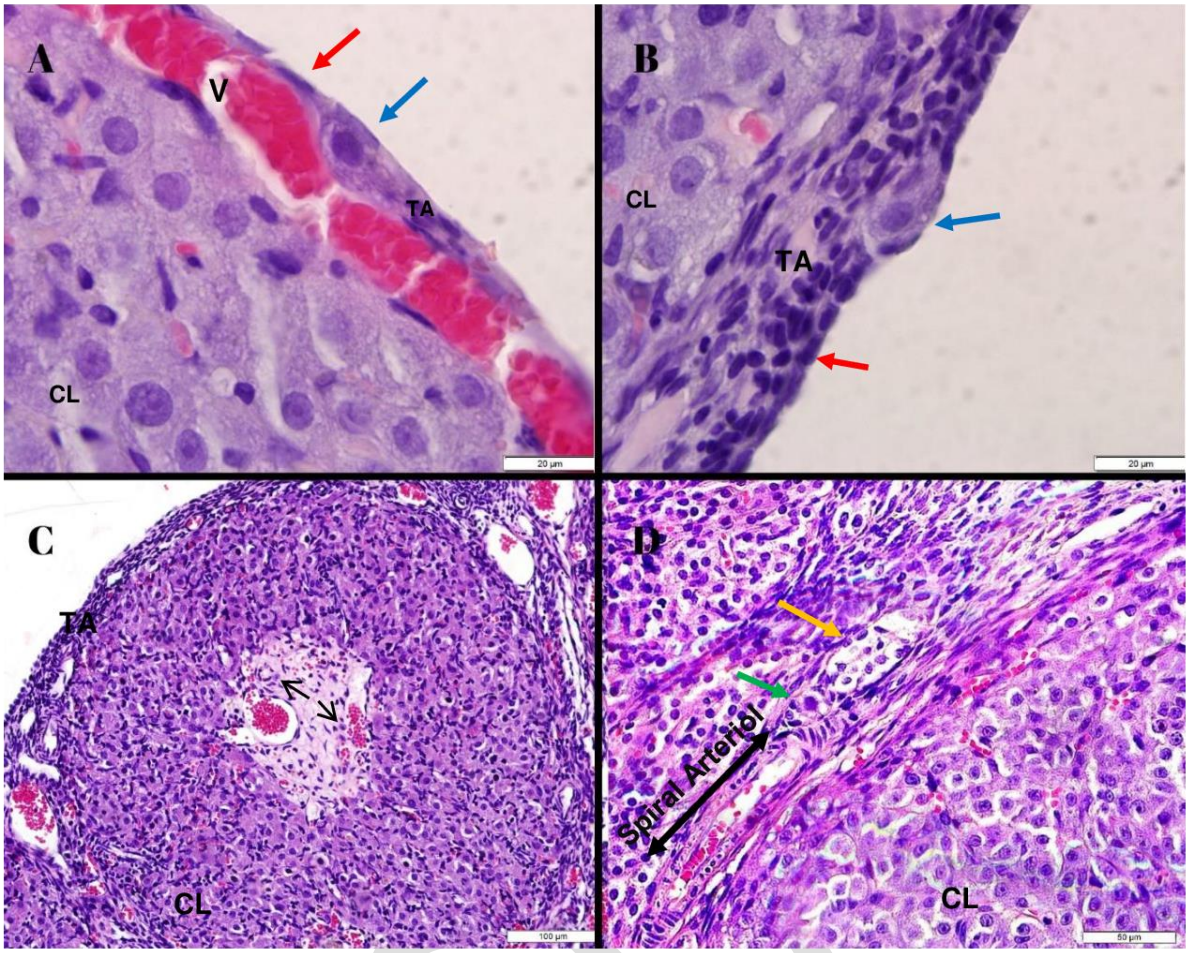

Figure 5. A-B: Granulosa lutein cells eccentrically located in the tunica albuginea adjacent to the corpus luteum, C: Macrophages seen in the regressed corpus luteum, D: Spiral arteriole, primordial follicle and rete ovarii adjacent to the tunica albuginea of the corpus luteum. Blue arrow indicates granulosa lutein cell, black arrow indicates macrophage, red arrow indicates ovarian surface epithelium and yellow arrow indicates rete ovarii

TA: Tunica Albuginea CL: Corpus Luteum V: Vascular structures, Magnification (A, B: 1000X C: 200X D: 400X)

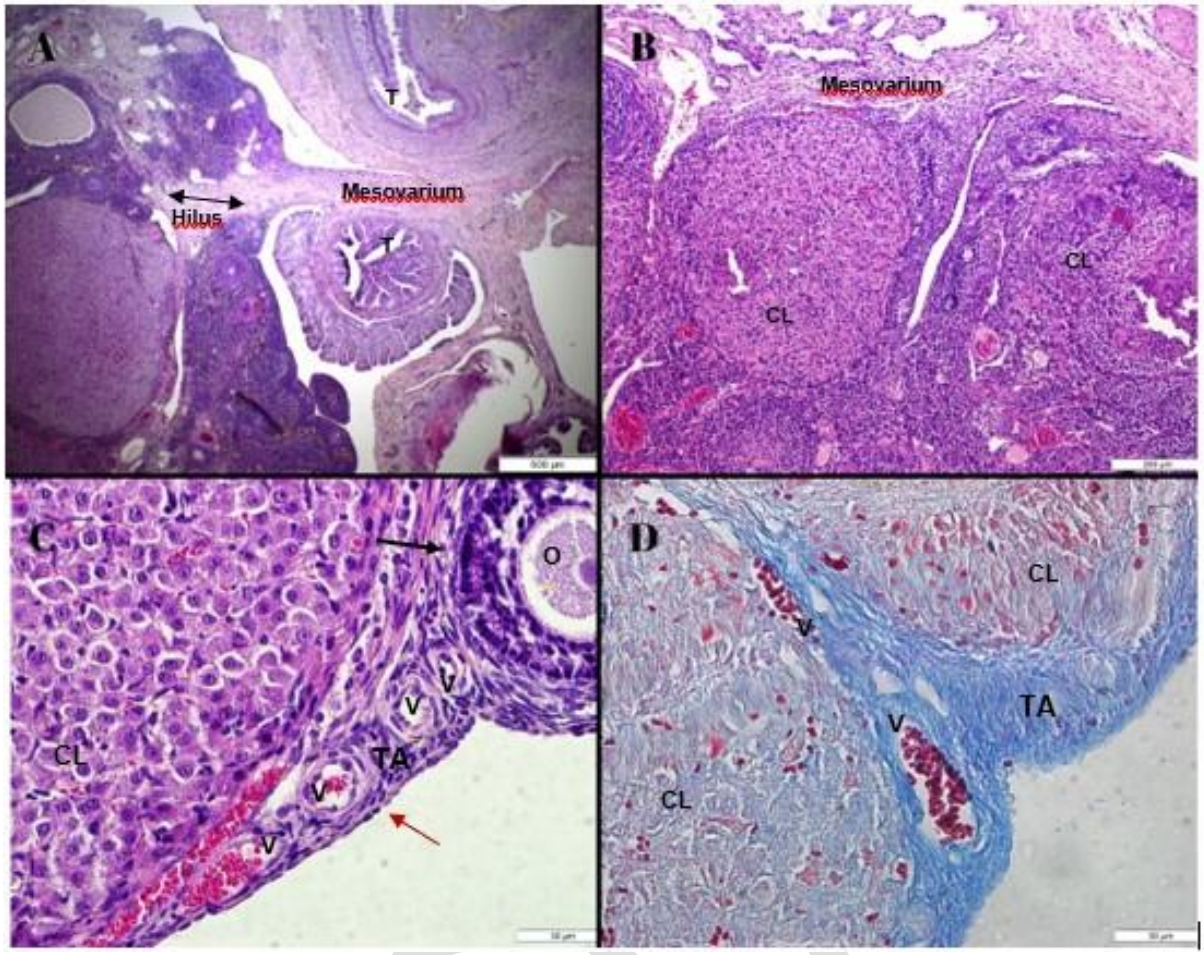

Figure 6. A-B: Adjacency of the tunica albuginea, cortex and mesovarium of the ovary, C: Venule and arteriole structures seen in the tunica albuginea adjacent to the corpus luteum, D: Tunica albuginea adjacent to the corpus luteum (Masson Trichrome staining). Black arrow indicates secondary follicle, red arrow indicates ovarian surface epithelium

TA: Tunica Albuginea CL: Corpus Luteum O: Oocyte T: Tuba Uterina V: Vascular structures, Magnification (A: 40X B: 200X C, D: 400X)

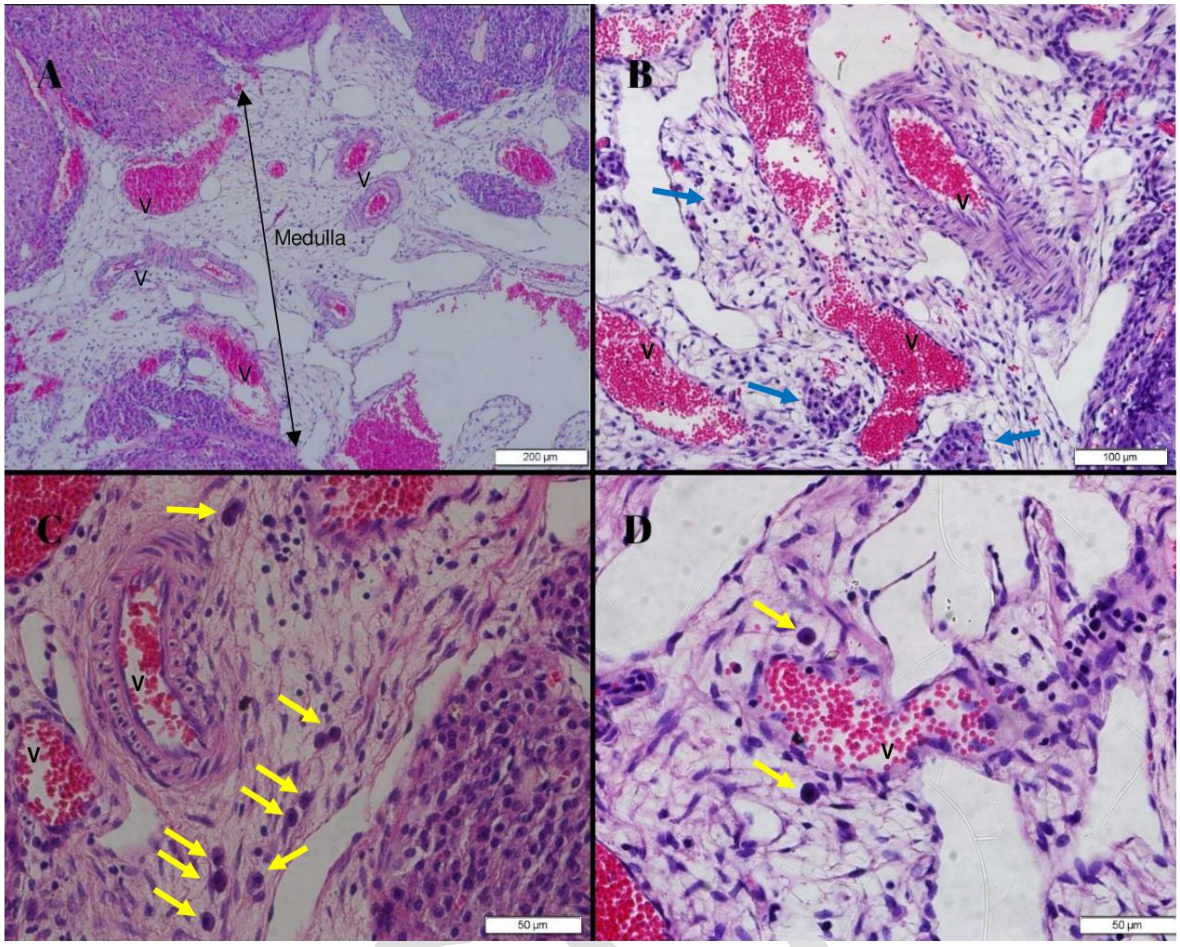

Figure 7. A-B-C-D: The medulla of the ovary is a loose connective tissue layer containing vascular structures, adipocytes, fibroblasts, macrophages and hilar cells. Blue arrow indicates hilar cells and yellow arrow indicates macrophages

V: Vascular structures, Magnification (A: 40X B: 200X C, D: 400X)

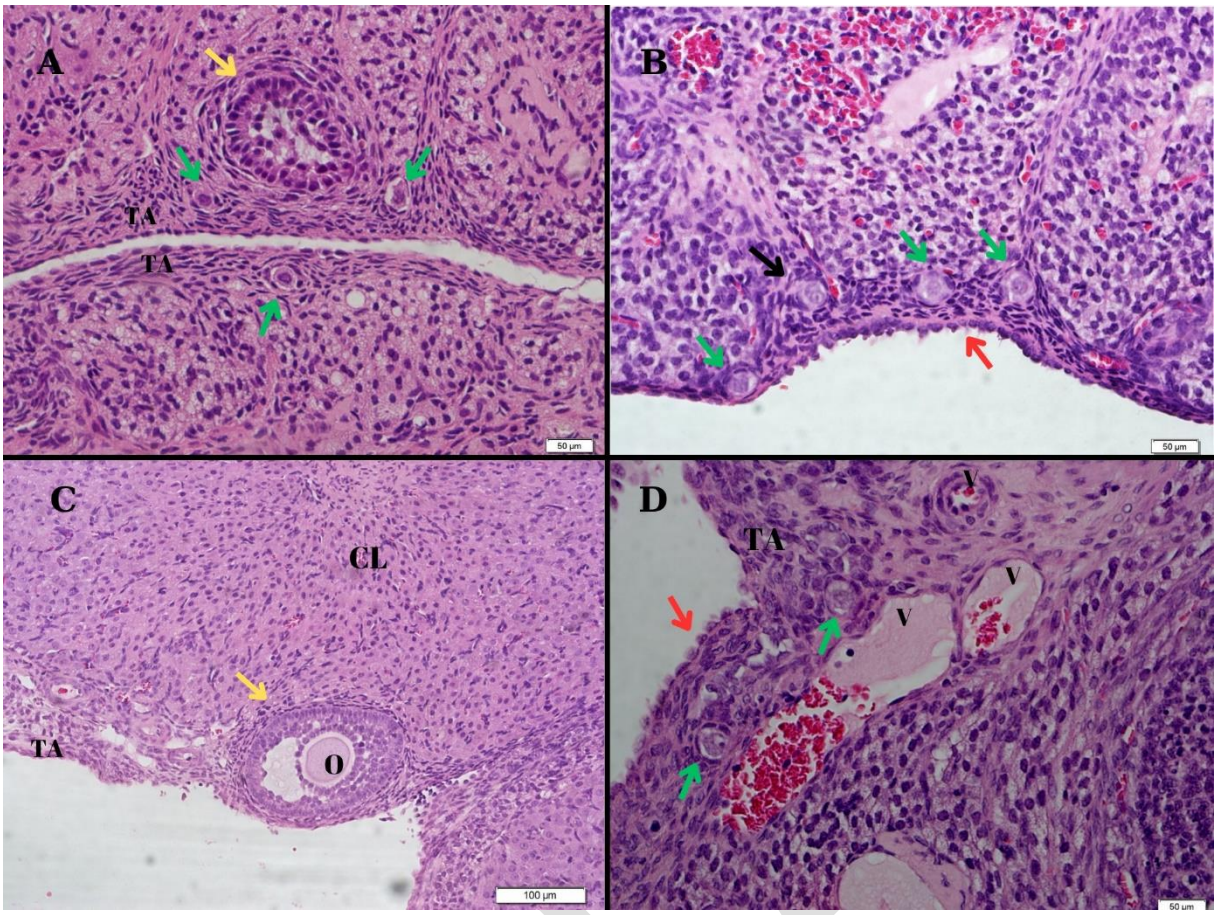

Figure 8. A: Tunica albuginea and primordial follicles within it, B: Primordial and primary follicles within the tunica albuginea, C: Secondary follicle within the corpus luteum,
D: Primordial follicles within the tunica albuginea. Green arrow indicates primordial follicle, orange arrow indicates secondary follicle and red arrow indicates ovarian surface epithelium

TA: Tunica Albuginea CL: Corpus Luteum O: Oocyte V: Vascular structures Magnification (A,B,D: 400X C: 200X)

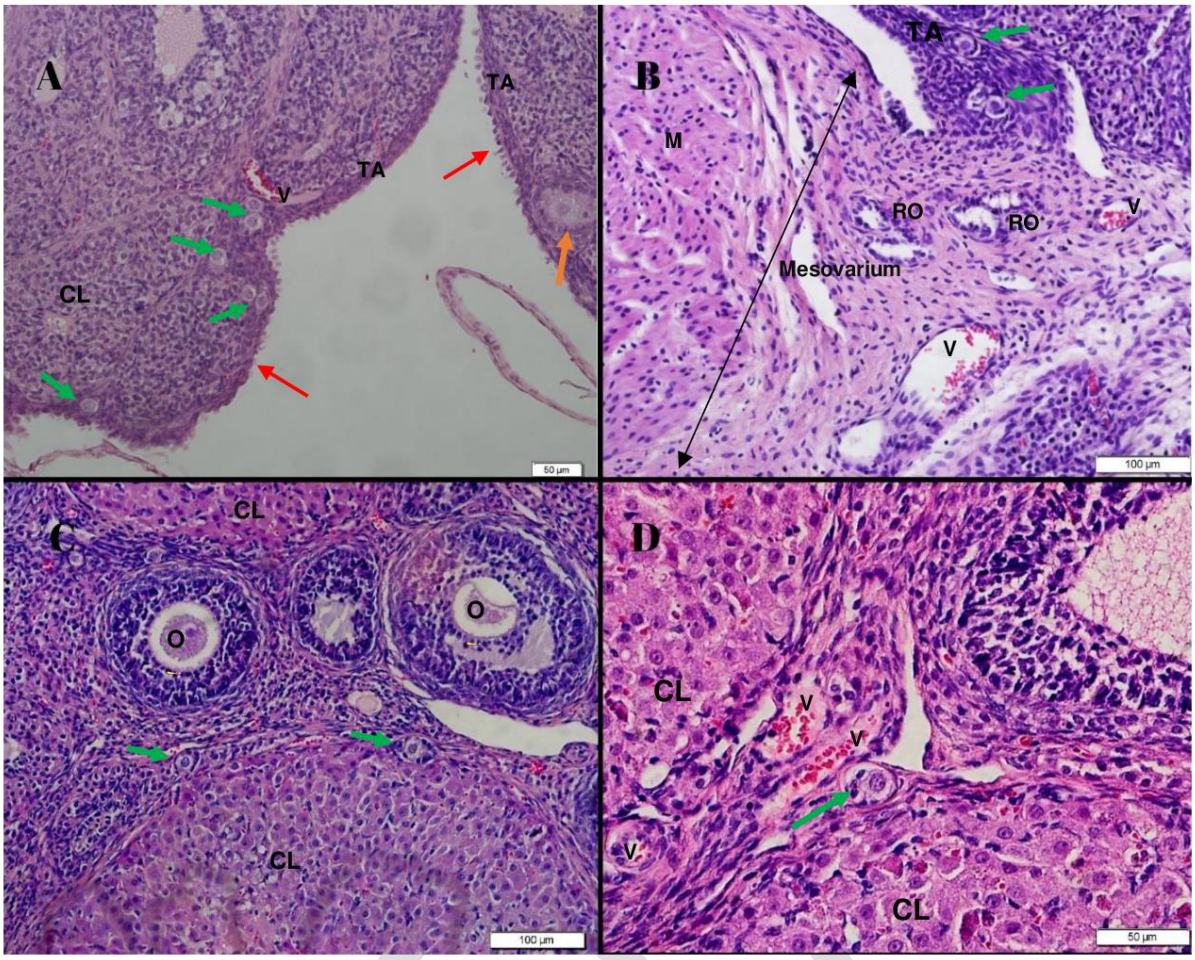

Figure 9. A: Tunica albuginea and primordial follicles within it, B: Mesovarium adjacent to tunica albuginea and primordial follicles within it, C-D: Tunica albuginea adjacent to corpus luteum and primordial follicles within it. Green arrow indicates primordial follicle, orange arrow indicates secondary follicle and red arrow indicates ovarian surface epithelium

TA: Tunica Albuginea CL: Corpus Luteum O: Oocyte V: Vascular structures, Magnification (A: 40X B, C: 200X D: 400X)

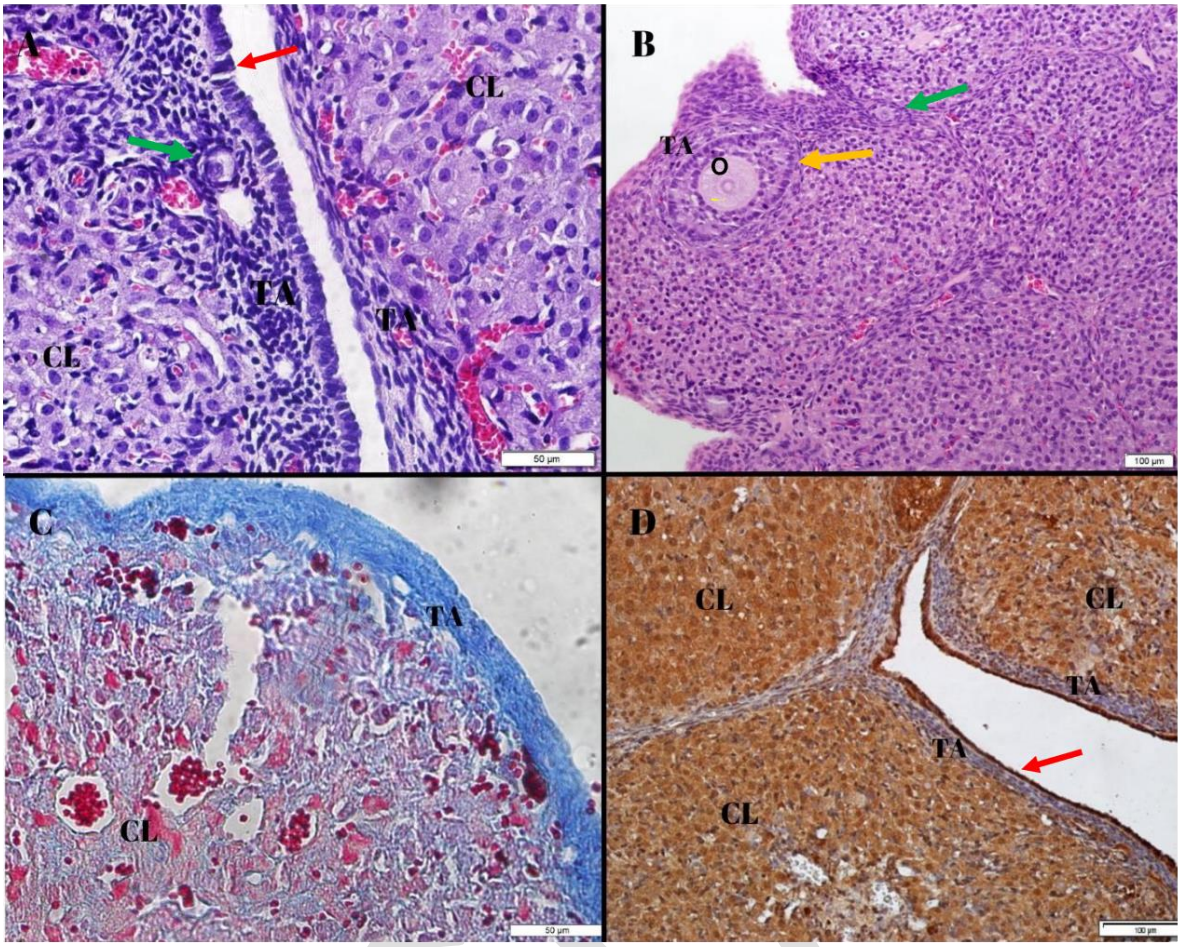

Figure 10. A: Tunica albuginea adjacent to the corpus luteum and primordial follicles within it, B: Secondary follicle within the corpus luteum and primordial follicle within the tunica albuginea, C: Tunica albuginea adjacent to the corpus luteum (Masson Trichrome staining), In rats treated with, D: Cyclophosphamide chemotherapy, the tunica albuginea of the corpus luteum reacted less with caspas-3 reactivity, an apoptotic marker, than granulosa lutein and teka lutein cells. Green arrow indicates primordial follicle, orange arrow indicates secondary follicle, red arrow indicates ovarian surface epithelium

TA: Tunica Albuginea CL: Corpus Luteum O: Oocyte, Magnification (A, C: 400X B, D: 200X)

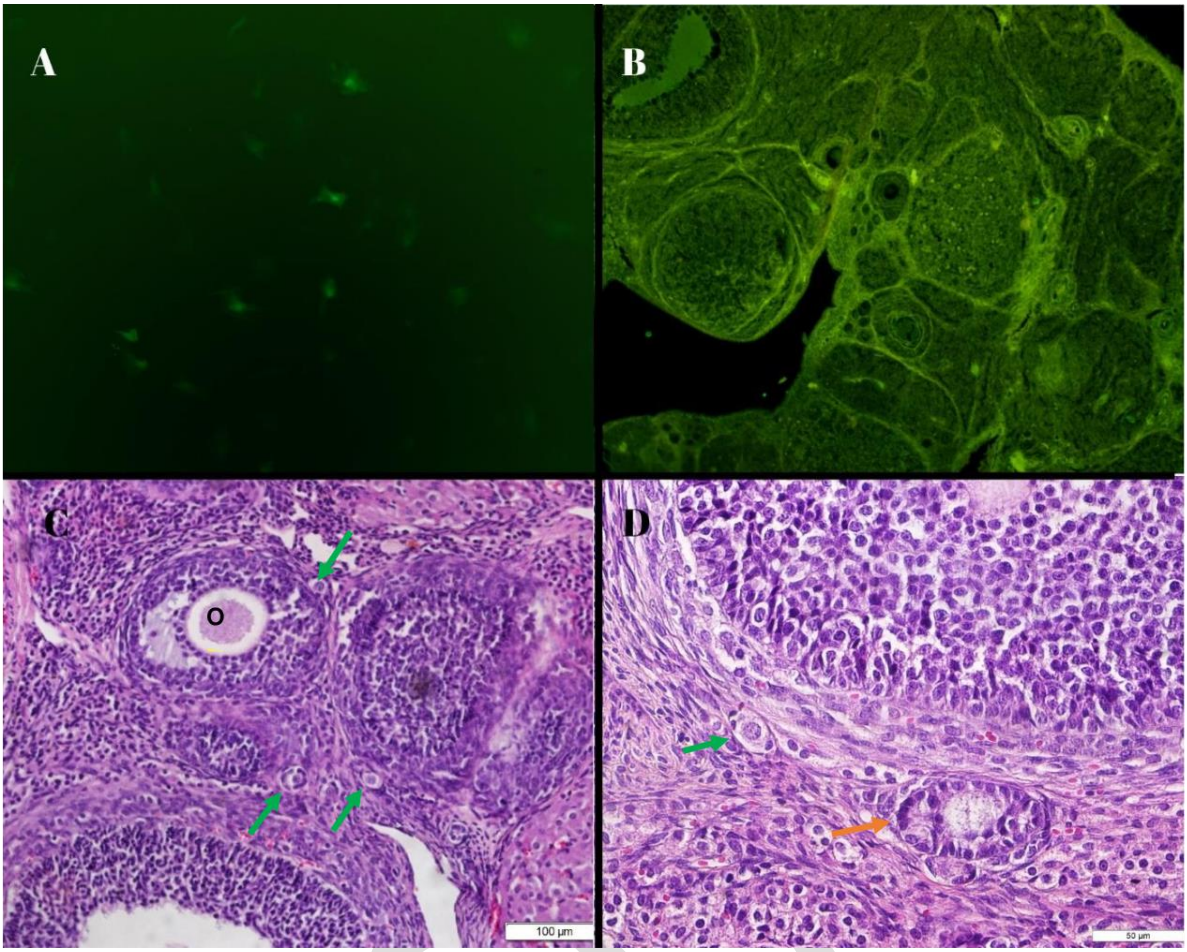

Figure 11. A-B: Fluorescence microscope view of the distribution of GFP-linked mesenchymal stem cells intramedullaryly injected into the femur bone into the tunica albuginea, cortex and medulla of the ovary, C-D: Primordial follicles seen between fibroblasts in the tica interna tica externa layer of the secondary and graaf follicle. Green arrow indicates primordial follicle and orange arrow indicates secondary follicle

O: Oocyte, Magnification (C: 200X D: 400X)

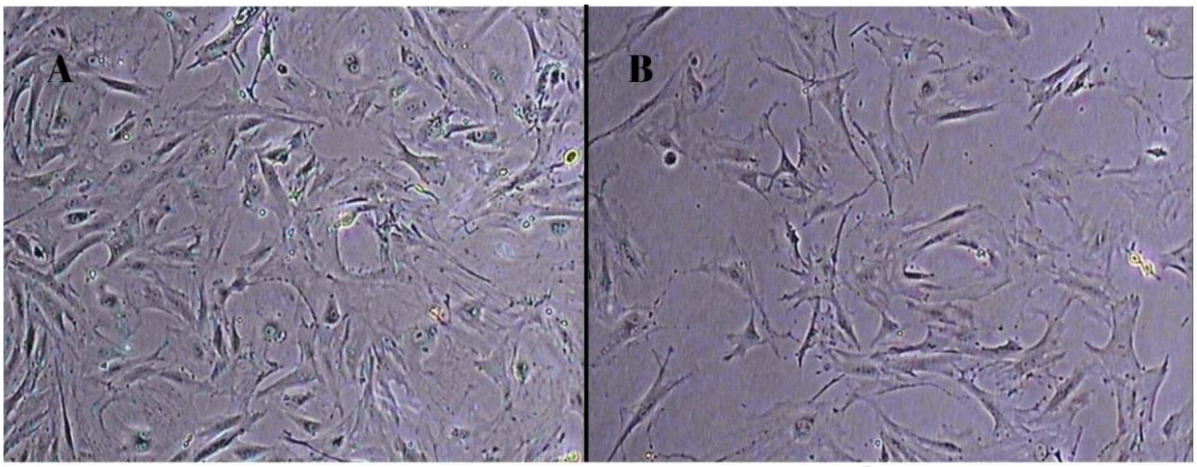

Figure 12. A-B: Fibroblast-like cells isolated from explant culture of ovarian and testicular tissues (Magnification: 100X)

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