INTRODUCTION

Adenomyosis is a common gynecological disorder characterized by the growth and invasion of the endometrial tissue into the myometrium. It preferentially affects multiparous women in their reproductive or perimenopausal years, ranging from 14% to 66% in hysterectomy specimens ***(Vercellini, 2006).***

However the precise etiology and pathophysiology of adenomyosis is still unclear. Several studies have been taken to form explanations. It is considered that adenomyosis result of trauma, either mechanical or physiological peristaltic processes ***(Leyendecker, 2009).*** In addition, hormonal mediation, particularly estrogen secretion, has long been postulated as an early mediator ***(Huang, Chen, 2014).***

Locally, high level of estrogen may play an important role in endometrium invasion since high frequency of endometrial hyperplasia is found in women with adenomyosis**.** Estrogen is thus closely associated with the growth and development of adenomyosis. However, the molecular mechanism estrogen triggers adenomyosis is unclear and requires further research ***(Bulun, 2009)***.

Another one suggested and investigated the possible role of stem cells in the pathogenesis of adenomyosis. Adenomyotic tissues have been investigated for the characters of stem cells as self-renewal, colono-genicity and differentiation ***(Challen, 2006).***

Stem-like cells subpopulation; have been identified from adenomyotic tissue and it was proven that these cells display stem cell-like properties and may involve in the pathogenesis of adenomyosis ***(Huang et al., 2015, Challen, 2006).***Stem cells are undifferentiated cells that are defined by their ability to self –renew and differentiation into mature cells ***(Challen, 2006).***

This study intended to evaluate the differences between the adenomyotic tissue and eutopic endometrial tissue comparing between both of them pathologically and immuno-histochemically using estrogen and progesterone receptors as markers to study for the possible pathogenesis of adenomyosis and the probability of having a different cell origin (stem cell hypothesis).

AIM OF THE WORK

To study the differences between the adenomyotic tissue and endometrium proper of the same specimen histopathologically and immuno-histochemically using estrogen and progesterone receptors as markers. This might help in understanding the possible pathogenesis of adenomyosis.

Chapter (1)
Anatomy and histology of the uterus

Structure

The uterus is the organ which is responsible for receiving the embryo, sheltering the fetus during pregnancy and delivering the newborn at term ***(Krstic, 1997).***

The uterus is located inside the pelvis immediately dorsal to the urinary bladder and ventral to the rectum ***(Elsevier, 2011)***.

The human uterus is pear-shaped and about 3 inches. It is about 7.6 cm long, 4.5 cm broad and 3.0 cm thick. A non-pregnant adult uterus weighs about 60 grams ***(Elsevier, 2011 Kumar, 2008)***.

The uterus can be divided anatomically into four segments: The fundus, corpus, cervix and the internal os ***(Elsevier, 2011).***

Layers

The uterine corpus is composed of three layers; a modified mucosa known as the endometrium, a fibromuscular wall called the myometrium, and a serosal lining ***(McGraw, 2008).*** The three layers, from innermost to outermost**,** are as follows:

Endometrium

The lining of the uterine cavity is called the "endometrium' in which the implantation takes place. This layer experiences morphologic and functional changes that are closely associated with the cyclic release of sexual hormones. In absence of periodic hormonal influence, i.e., before puberty or following menopause, this tissue has a constant morphology and thickness ***(Krstic, 1997, Kaiserman, 1989).***

It consists of a single layer of columnar epithelium with or without cilia (depending on how far along the menstruation cycle is) and its basal membrane, uterine glands, and a specialized, cell-rich connective tissue (stroma) containing a rich supply of blood vessels (spiral arteries) and varies in thickness according to hormonal influences ***(McGraw, 2008, Lutz Slomianka*, *2009)***.

In a woman of reproductive age, three layers of endometrium can be distinguished: stratum compactum, stratum spongiosum (which make up the functional layer during the first half of the menstrual cycle) and basalis layer***(Lutz Slomianka*, *2009).***The functional layer is highly responsive to hormonal ovarian influence in contrast to the basalis***(karger, 2012).***

Throughout the fertile years of a female and for some time beyond the reproductive function of the uterus is subject to hormone production, cell regeneration and other biological activities. The functional layer builds up periodically after the end of the menstruation during the first part of the previous menstrual cycle this proliferation is induced by estrogen(follicular phase of menstrual cycle), and later changes in this layer are engendered by progesterone from the corpus luteum (luteal phase). It is adapted to provide an optimum environment for the implantation and growth of the embryo ***(Takasaki, 2010).***

In absence of progesterone, the arteries supplying blood to the functional layer constrict, so that cells in that layer become ischaemic and die and completely shed leading to menstruation ***(Taketani, 2010).***

The basal layer, adjacent to the myometrium and below the functional layer, is not shed at any time during the menstrual cycle, and from it the functional layer develops ***(Shimamura, 2010).***

The endometrial glands

The endometrial glands are simple tubular glands lined by columnar epithelium or tall, narrow and closely packed cells with elongated and parallel nuclei with dense chromatin. Nucleoli are usually not visible. Cell borders are ill-defined. Endometrial epithelial cells occur in sheets or cohesive groups, seldom with a honeycomb pattern. The morphology of the endometrial glands changes during the different phases of the menstrual cycle ***(Guyton et al, 2006).***

Endometrial Epithelial Cells

The cells of endometrial glands and surface epithelium both are columnar or cylindrical. Their morphology changes from the proliferative to the secretory phase. Ciliated glandular cells can be identified in a few cases, often in estrogen-stimulated endometrium ***(kumar, 2008, karger, 2012)***.

Endometrial epithelial cells occur in sheets or cohesive groups, seldom with a honeycomb pattern. Isolated cells are common. They show little variation in size and shape with scanty cytoplasm and round, ovoid or elongated nuclei with dense chromatin. Nucleoli are usually not visible. Cell

borders are ill-defined. Mitotic figures are common in the proliferative phase ***(Shimamura, 2010)***.

The morphology seen in the secretory phase may appear more hyperchromatic and more pleomorphic with somewhat more prominent nucleoli than in conventional smears ***(kumar, 2008).***

The endometrial stroma

The endometrial stroma consists of pluripotent mesenchymal cells, which at the beginning of the menstrual cycle are spindle-shaped, poorly differentiated and joined to one another by cytoplasmic processes. The cells lie firmly anchored within a network of reticulum fibers. The stroma of the basalis is more cellular than that of the functional layer of the endometrium and nucleocytoplasmic ratios are high. Thick-walled arteries, lymphocytes and lymphoid aggregates are present ***(kumar, 2008, Guyton et al, 2006).***

Stromal Cells of the Endometrium

The endometrial stromal cells are mesodermal cells, mainly of fibroblastic, seldom of histiocytic type. In the endometrial brush smears the morphology of the endometrial stromal cells varies with the clinical status of the patient and with the phase of the menstrual cycle. In the early

proliferative phase the stromal cells occur singly or in loose groupings, they have scant cytoplasm and ovoid or fusiform nuclei. In the late proliferative and early secretory phases the stromal cells appear as more cohesive groups of spindle cells. Variable degrees of predecidualization, form small isolated stromal cells to large predecidual cells with abundant cytoplasm and ovoid or vesicular nuclei and seldom with obvious nucleoli, can be seen during the later secretory phase ***(kumar, 2008, karger, 2012***).

Different histological pattern of the endometrium

The endometrial changes throughout the menstrual cycle:

Proliferative Phase

Proliferative phase is facilitated by follicular stimulating hormone (FSH) that generates an estrogenic state which is responsible for the proliferation of the endometrium (intensive mitosis in the glandular epithelium and in the stroma).

In this stage the uterus epithelium clothes the surface again and a certain number of epithelial cells equipped with cilia can be recognized. The endometrium thickens; connective tissue is renewed, along with glandular structures and spiral arteries ***(Shimamura, 2010).***

In the early proliferative phase:

The glands are straight and narrow and the glandular epithelium is cubo-columnar. Nuclear chromatin appears dispersed and mitotic figures are present ***(Kumar, 2008)***

The stromal cells also show mitotic activity and have ill-defined borders ***(Shimamura, 2010)***.

In the late proliferative phase:

The glands increase in size and appear tortuous with pseudostratification of the epithelium showing nuclei at different levels, (figure 1), ***(karger, 2012).***

The stromal cells are small and spindle-shaped similar to predecidual cells **(*Arias-Stella, 2002)***.

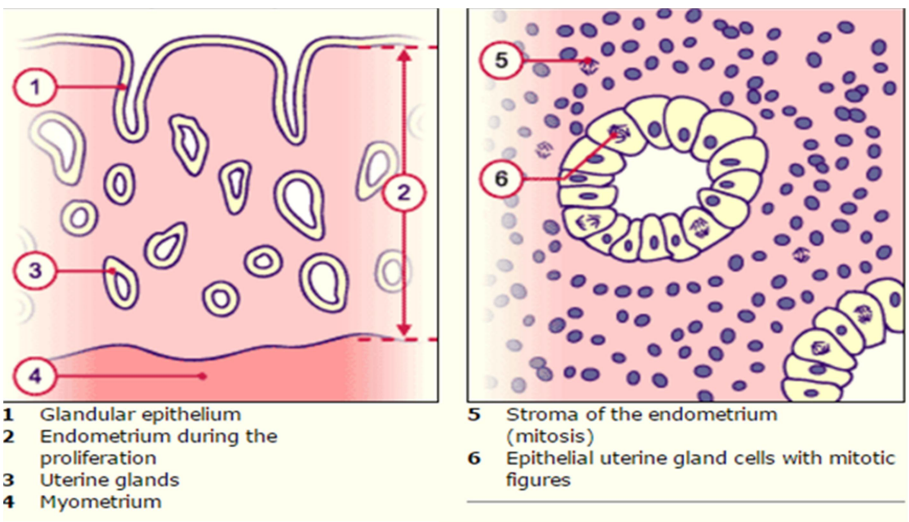

Figure (1): proliferative phase: thickened endometrium with an increased number of glands and mitosis, visible in the glandular epithelium and stroma, ***(Kaiserman, 1989, karger, 2012)***

Secretory Phase

In the early secretory phase:

The endometrium differentiates itself due to the influence of progesterone (from the corpus luteum) and attains its full maturity. The endometrial glands undergo progressive distension, appear plumper and more tortuous become cork-screw shaped and are lined by low columnar cells. Subnuclear cytoplasmic glycogen vacuoles may discharge into the gland lumina**,** (figure 2), ***(Kumar, 2008).***

In the late secretory phase:

Stromal cells increase in size and volume and they acquire an epitheloid appearance called predecidual cells. The finding of spiral arteries surrounded by a cuff of predecidual stromal cells is useful in diagnosis ***(karger, 2012).***

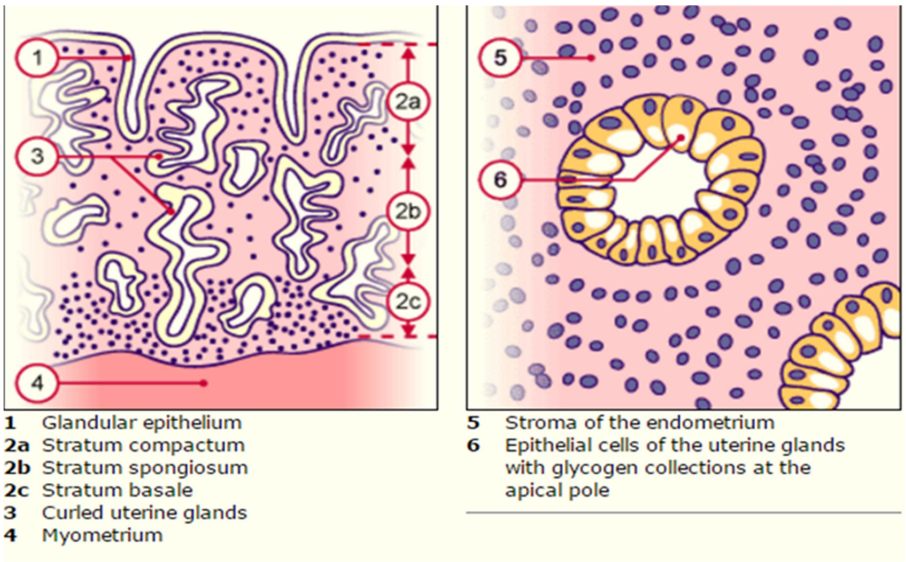

Figure (2): secretory phase: The endometrium is now mature; the glycogen migrates from the basal to the apical pole, whereby the nuclei of the epithelial cells are shifted to the basal pole. The secretion containing glycogen is released into the glandular lumen. ***(karger, 2012)***

Menses

Decreased levels of luteinizing hormone (LH) and progesterone result in the menstrual phase, or menses. During menses; shedding of the uterine lining, which occurs if the egg is not fertilized, the spiral arterioles in the functional layer contract, resulting in ischaemia, and degeneration of the functional layer. The arteries rupture, and the rapid blood flow dislodges the necrotic functional layer, which is lost, (figure3)***, (karger, 2012, Kumar, 2008).***

The basal layer is unaffected, because it is supplied by straight arteries ***(Kumar, 2008).***

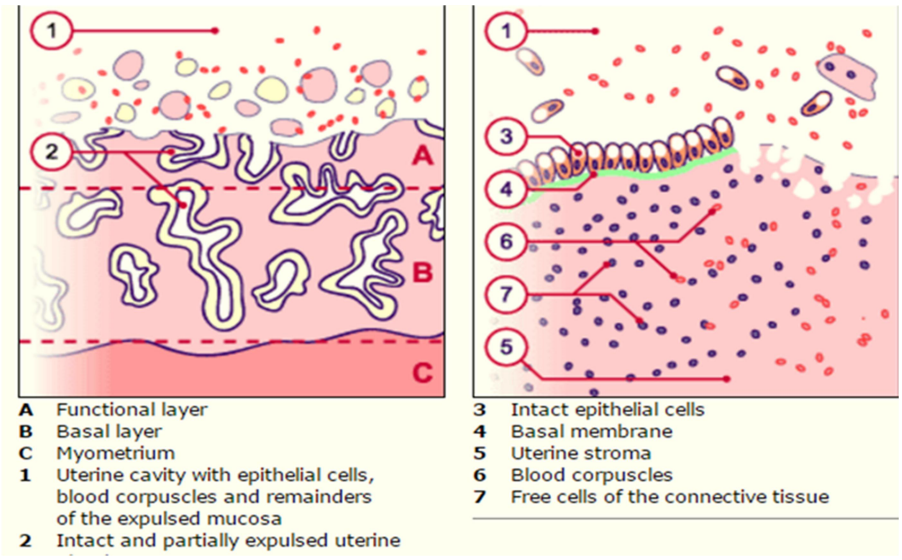

Figure (3): end.changes during menstrual phase, expulsion of the functional layer of the endometrium (spongiosa and compacta) mixed with blood, endometrial debris and lymphocytes,***(Kumar, 2008)***.

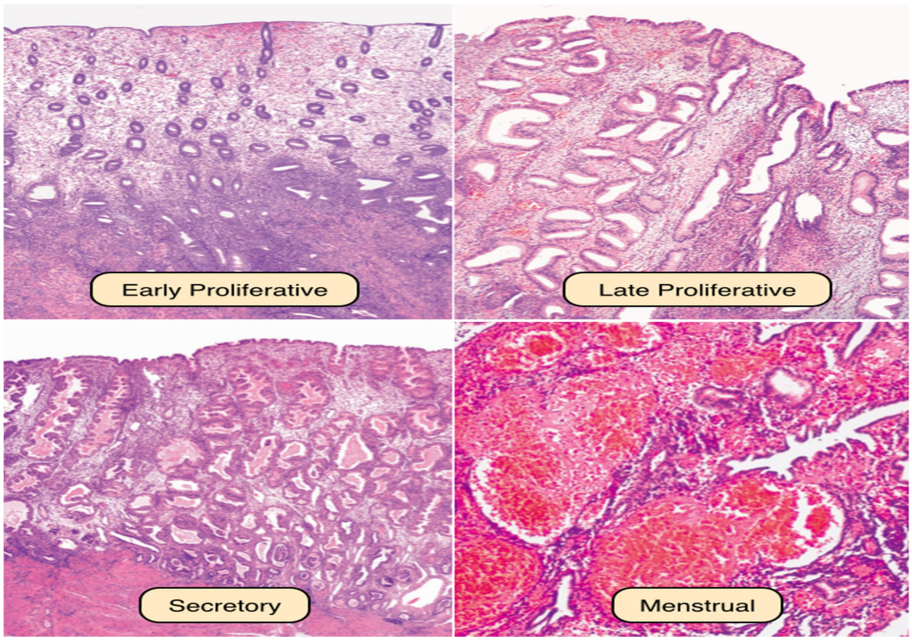

Figure (4): endometrial changes during menstrual cycle,***(karger, 2012, Kumar, 2008).***

Endometrial changes during pregnancy:

Chorionic tissue can result in marked endometrial changes, known as an Arias-Stella reaction, that have an appearance similar to cancer. Historically, this change was diagnosed as endometrial cancer and it is important only in so far as it should not be misdiagnosed as cancer ***((Kumar, 2008, Arias-Stella, 2002)***

Endometrial changes during menopause:

Following the physiological decline of ovarian function with a fall in the secretion of both progesterone and estrogen, the postmenopausal non-functional endometrium usually changes progressively over a few years into an atrophic endometrium. But in 20–30% of women this transformation may take several years. More commonly than atrophy; is proliferative endometrial activity which sometimes may persist for many years. A third common pattern of menopausal endometrium is senile cystic atrophy ***(Dreisler et al, 2013).***

Atrophic Endometrium; narrow glands lined by Low cuboidal or columnar epithelium with small inactive nuclei with no mitotic figures, supported by a dense fibrous stroma of spindle cells. The functional layer is difficult or

impossible to separate from the basalis (figure 5) ***(Dreisler et al, 2013)***.

Senile cystic atrophy is seen when the last cycles were anovulatory or had irregular proliferative phases, the glands vary in size, some of them are narrow and tubular, but many are dilated and cystic, the glandular epithelium is cuboidal and inactive but has a tendency to become polygonal and the stroma becomes fibrous. This histological pattern may be mistaken for glandular-cystic hyperplasia ***(Kumar, 2008)***

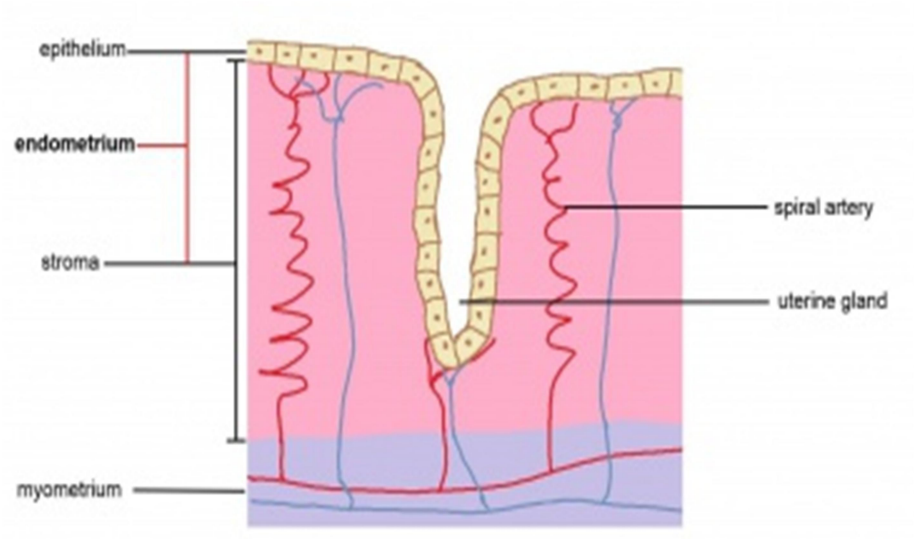

Figure (5): Atrophic endometrium, narrow gland lined with cuboidal epith ***(karger et al, 2012)***