SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 9
Issue: 9
Page N. 227-248
Year: 2025

Review Article

ww.wjahr.com

SPECTRUM OF DISORDERED PROLIFERATIVE ENDOMETRIUM AND ENDOMETRIAL HYPERPLASIA WITHOUT ATYPIA IN PERIMENOPAUSAL WOMEN; A THREE YEARS HISTOPATHOLOGICAL REVIEW STUDY

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Article Received date: 22 July 2025 **Article Revised date**: 11 Aug 2025 **Article Accepted date:** 31 Aug 2025

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ABSTRACT

Background: The dilemma of interpreting endometrial biopsies among pathologists is well known. Until, 2008, diagnosing endometrial hyperplasia through endometrial sampling presents significant challenges due to substantial diagnostic discrepancies that are influenced by both the adequacy of the sample and the interpretation of the existing histological characteristics. **Aim of the Study:** To assess the prevalence, underestimated and overestimated diagnosis of proliferative endometrium, disordered proliferative endometrium and endometrium hyperplasia without atypia among perimenopausal women with abnormal uterine bleeding according to last updatein diagnostic criteria. **Materials and methods:** In this observationalcross sectional study were 178 formalin fixed paraffin embedded (FFPE) tissue block and hematoxylin and eosin stained slides were retrospectively collected from Iraqi patients with Abnormal uterine bleeding having endometrium hyperplasia without atypia, disordered proliferative endometrium and proliferative endometrium. Results: Original endometrial diagnoses revealed that 40.4% of the cases (72 out of 178) were diagnosed as proliferative endometrium, 3.4% (6 out of 178) as disordered proliferative endometrium, and 56.2% (100 out of 178) as endometrial hyperplasia without atypia, The total number of cases analyzed was 178, representing 100% of the sample. The pathology panel diagnoses over 3 years showed that 39.9% of the cases (71 out of 178) were diagnosed as proliferative endometrium, 24.2% (43 out of 178) as disordered proliferative endometrium with a statistical significance (Sig.) of 0.01, and 36.0% (64 out of 178) as endometrial hyperplasia without atypia, which had statistical significance of 0.03. For Proliferative Endometrium, there is a consistent underestimation of 1.1% over the 3-year period and 2.8 % in 2023 (p=0.01), with no overestimation observed. In contrast, Endometrial Hyperplasia without atypia shows significant overestimation, with 20.2% over the 3-year period, 23.5 % in 2021, 28.5 % in 2022, and 11.2 % in 2023, all with statistical significance (p=0.01). Disordered Proliferative Endometrium shows minimal overestimation (0.6%) in the 3-year analysis and 1.4 % in 2023, with no underestimation observed. The data indicates consistent trends of underestimation in Proliferative Endometrium and overestimation in Endometrial Hyperplasia without atypia, with statistical significance in most cases. **Conclusion:** Proliferative endometrium is under-diagnosed to a negligible extent; but there is substantial overestimation of endometrial hyperplasia without atypia which may lead unnecessary close follow up and or medical and surgical therapeutic interventions.

1. INTRODUCTION

Abnormal uterine bleeding (AUB) is a common gynaecological complaint accounting for one third of patients visiting outpatient clinics. It is caused by a wide variety of disorders represented by an aberrant physiologic status at one hand to uterine malignancy at the other. Histopathological examination of endometrial biopsy, taken by dilatation and curettage, remains the standard diagnostic procedure for the diagnosis of endometrial pathology. It should be considered in all women if AUB does not resolve with medical management and particularly in those above the age of 40 years, and in women who are at increased risk of endometrial cancer.[1]

Anovulatory cycles result in exuberant disordered

proliferative endometrium, recognized by irregularity of glandular outlines, with more complexity of gland profiles than is encountered in normal proliferative phase. There is not sufficient glandular crowding to warrant a diagnosis of endometrial hyperplasia. The glandular epithelial cells lack atypia and show nuclear features similar to those of normal proliferative glands. There may be subnuclear vacuoles and apoptotic bodies within glands. Anovulatory cycles are common in PCOS but also very common at puberty and in the perimenopausal period.[2]

Endometrial hyperplasia (EH) is a pathological condition which occurs mainly in perimenopausal and postmenopausal women due to high level of estrogen. It is characterized by hyperplastic changes affecting both endometrial glands and stroma with increase in gland-to-stroma ratio (3:1).EH is one of the most frequent causes of abnormal uterine bleeding (AUB). Most cases occur in 5th or 6th decades of life.[3]

Endometrial hyperplasia without atypia occurs due to unopposed estrogenic effect on the endometrium. It is histologically similar to disordered proliferative endometrium as regards to the crowded and irregularly branched glands. However, when glands predominate over the stroma; the diagnosis of endometrial hyperplasia without atypia is appropriate. The risk of progression to endometrial carcinoma from this variant is low, not exceeding 1-3%.[3]

1.1. AIMS OF THE STUDY

1. To assess the prevalence of spectrum of disordered proliferative endometrium and endometrium hyperplasia without atypia among perimenopausal women with abnormal uterine bleeding.
2. Histopathological review study to assess the possible over or under estimationin diagnosis of endometrial hyperplasia without atypia and the disordered proliferative endometrium according to last updates in diagnostic criteria.

2. LITERATURE REVIEW

2.1 Anatomy and Physiology of the Female Reproductive System

The female reproductive system functions to produce gametes and reproductive hormones, just like the male reproductive system; however, it also has the additional task of supporting the developing fetus and delivering it to the outside world. Unlike its male counterpart, the female reproductive system is located primarily inside the pelvic cavity. Recall that the ovaries are the female gonads. The gamete they produce is called an oocyte.[4]

2.1.1 Uterus

Uterus is a hollow, pear-shaped organ responsible for various functions, such as menstruation, gestation and labor. On a coronal cut section, its cavity has an inverted triangle shape. Sometimes, the development in utero may be incomplete; this is called a Mullerian anomaly and can lead to many variants, ranging from a uterine septum to uterine didelphys (double uterus). Anatomically, the uterus is located in the female pelvis immediately posterior to the bladder and anterior to the rectum. The female uterus subdivides into four main anatomic segments (from superior to inferior): the fundus; a broad curved area in which Fallopian tubes connect to the uterus, the corpus (body); the main part of a uterus, and it starts directly below the level of fallopian tubes and continues downward, isthmus; a lower neck region of the uterus, and cervix; which extends downwards from the isthmus and opens in the vagina.[5]

Several ligaments support the uterus, including the utero-ovarian, round, broad, cardinal, and uterosacral ligaments. The pelvic diaphragm, urogenital diaphragm, and perineal body further support it (inferiorly). The uterus may naturally lie in different positions, such as anteverted/retroverted, anteflexed/retroflexed, or midline, and it may be rotated (especially during pregnancy). In 50% of women, the uterus most commonly lies in an anteflexed and anteverted position.[5] The average dimensions of the uterus in an adult female are 8 cm long, 5 cm across, and 4 cm thick. The uterine cavity has an average volume of 80 mL to 200 mL. The uterus is subdivided into three segments: the body, the cervix, and the fundus.[5]

The uterus has three tissue layers, which include the following:

- **Endometrium:** is the inner lining, consisting of the functional (superficial) and basal endometrium. The functional layer responds to reproductive hormones. When this layer sheds, it results in menstrual bleeding.[7]

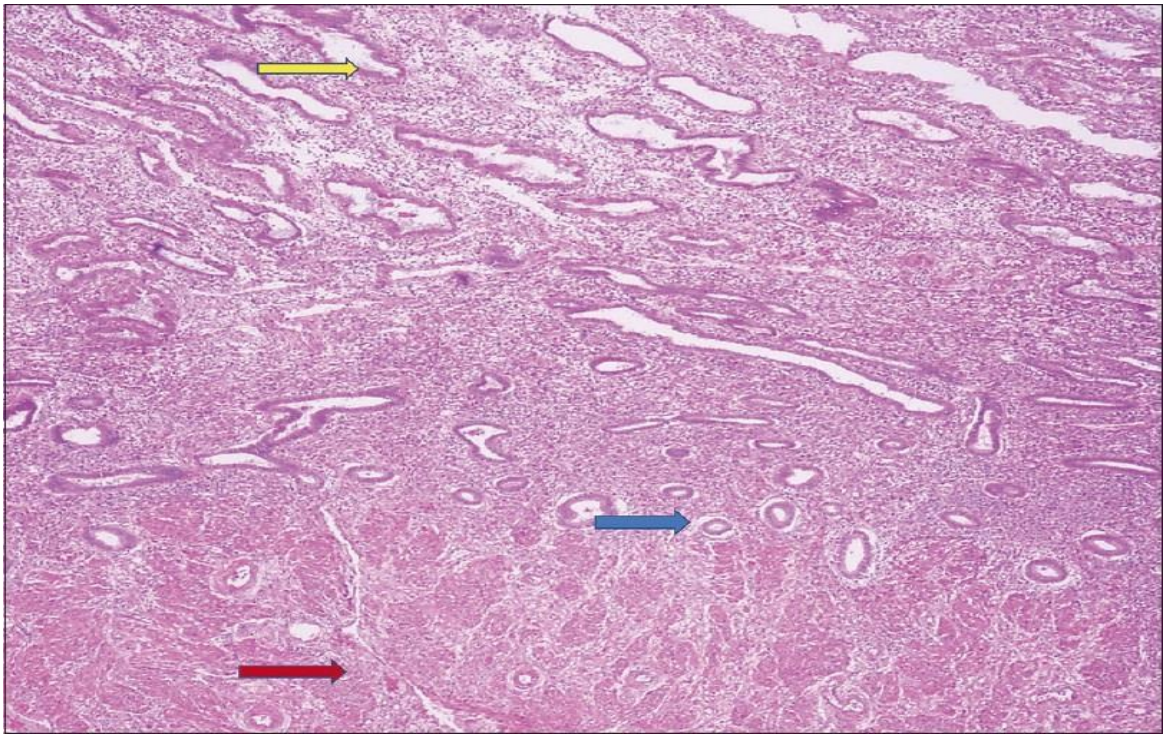

Figure 2.1: Layers of the endometrium. The stratum functionalis occupies the upper two-thirds and is showing secretory phase (yellow arrow). The lower one-third of the stratum basalis shows tubular glands with minimal morphologic alterations (blue arrow). The underlying myometrium (red arrow) shows fascicles of smooth muscle (HE stain, ×5)(6).

- **Myometrium:** the muscle layer and is composed of smooth muscle cells.

- **Serosa/Perimetrium:** the thin outer layer composed of epithelial cells.[7]

The uterus receives blood from the uterine and ovarian arteries, which arise from the anterior branch of the internal iliac artery. The uterine arteries are the main blood vessels that supply blood to the uterus. As the blood supply enters the myometrium, it branches into the arcuate arteries, which branch into the radial arteries. As they enter the endometrium level, they branch into the basal and spiral arteries.[5] Uterine arteries supply the different parts of the uterus and play an essential role in maintaining blood supply during menstrual cycle and pregnancy. The fundal area of the uterus chiefly drains into para-aortic lymph nodes along with the ovarian and fallopian tube lymphatic drainage. Some also drain into superficial inguinal lymph nodes along the round ligament. The lower portions of the uterus drain along uterine blood vessels into external and internal iliac lymph nodes.[8]

The internal pelvic organs receive nerve supply from the autonomic nervous system, sympathetic and parasympathetic nervous system. Autonomic T11 and T12 innervate the uterus, which derives its sympathetic nerve supply from the hypogastric plexus, and the parasympathetic supply is from S2 to S4. The uterus and cervix are sensitive to stretch (distension), and dilation of the cervix causes pain during normal vaginal delivery.[8]

2.1.2. Cervix

The uterine cervix is a tubular structure contiguous with the uterine cavity and the vagina, connect between the two. The inferior cervix opens into the upper vagina at the cervical os. The lining of the cervix that protrudes into the vagina is called the ectocervix and consists of stratified squamous epithelium. The lining of the inside of the cervical canal is the endocervix, comprised of columnar epithelium.[9]

The region where the ecto- and endocervix meet, characterized by the transformation from columnar to squamous epithelium, is the transformation zone. The transformation zone is the most frequent location for cervical dysplasia and malignant transformation.[9] The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.[10]

2.1.3. Fallopian tubes

Fallopian tubes, otherwise called oviducts or uterine tubes, are hollow seromuscular organs that originate at the uterine horns, extend laterally within the superior edge of the mesosalpinx of the broad ligament, and terminate near the ipsilateral ovary. They are 11 to 12 cm in length and have a lumen diameter of less than 1 mm.[11] In addition to providing a space for fertilization

to occur, the fallopian tubes function as a passageway for the ovum or gamete from the ovary to the uterus.[12]

2.1.4. Ovaries

The ovaries are the female gonads. Paired ovals, they are each about 2 to 3 cm in length, about the size of an almond. The ovaries are located within the pelvic cavity, and are supported by the mesovarium, an extension of the peritoneum that connects the ovaries to the broad ligament. Extending from the mesovarium itself is the suspensory ligament that contains the ovarian blood and lymph vessels. Finally, the ovary itself is attached to the uterus via the ovarian ligament.[4]

The ovary comprises an outer covering of cuboidal epithelium called the ovarian surface epithelium that is superficial to a dense connective tissue covering called the tunica albuginea. Beneath the tunica albuginea is the cortex, or outer portion, of the organ. The cortex is composed of a tissue framework called the ovarian stroma that forms the bulk of the adult ovary. Oocytes develop within the outer layer of this stroma, each surrounded by supporting cells. This grouping of an oocyte and its supporting cells is called a follicle. The growth and development of ovarian follicles will be described shortly. Beneath the cortex lies the inner ovarian medulla, the site of blood vessels, lymph vessels, and the nerves of the ovary.[4]

2.2. Physiology of Menstrual Cycle

The female reproductive system, unlike the male, undergoes regular cyclic changes known as the menstrual cycle, which serves as the body's periodic preparation for ovulation and potential pregnancy. The most noticeable aspect of the female reproductive system is menstruation, or cyclic vaginal bleeding, which occurs alongside a series of coordinated hormonal shifts. Menstruation, also known as menarche when it first begins, typically starts around puberty with a median age of 12.4.[13] Menstrual cycles cease at menopause, which has an average onset around age 51.[14]

When discussing timing within the menstrual cycle, the first day of heavy menstrual flow is considered day 1. According to the International Federation of Gynecology and Obstetrics (FIGO), normal menstrual cycles should have consistent frequency, regularity, duration, and volume of flow. Normal menstrual frequency is defined as cycles occurring every 24 to 38 days. Infrequent menstruation is defined as cycle lengths longer than 38 days, while frequent menstruation refers to cycle lengths shorter than 24 days. Amenorrhea describes the complete absence of menstrual bleeding. Normal menstrual duration is defined as bleeding lasting 8 days or less, while bleeding beyond 8 days is considered prolonged menses.[15]

The volume of menstrual flow is classified as light, normal, or heavy. No defined objective thresholds separate these classifications, as they are often impractical in clinical settings. For research purposes, heavy menstrual bleeding is defined as blood loss exceeding 80 mL per cycle, based on weighed menstrual products. Heavy menstrual bleeding is a subjective symptom rather than a formal diagnosis. The National Institute for Health and Care Excellence (NICE) defines it as excessive menstrual bleeding that interferes with a person's physical, social, emotional, and/or material quality of life. Notably, 2 patients with the same objective volume of blood loss may have significantly different perceptions of their flow volume.[15]

Light menstrual bleeding is rarely associated with underlying pathology, although it can occur in patients with intrauterine adhesions or cervical stenosis. For research purposes, light menstrual bleeding is typically defined as less than 5 mL of blood loss per cycle. Several factors can influence the volume of blood loss during menstruation, including medications, endometrial thickness, and bleeding or clotting disorders.[15]

Menstrual regularity is defined by the variation in cycle lengths from one cycle to the next. Although slight variations in cycle lengths are normal, cycles are considered regular if the difference between the shortest and longest cycle lengths is 7 days or less for individuals aged 26 to 41 and 9 days or less for those aged 18 to 25 or 42 to 45. FIGO notes that for practical purposes, normal variation in cycle length can also be expressed as an average cycle length of ±4 days.[15]

The menstrual cycle is considered irregular when cycle lengths vary by 8 days or more for individuals aged between 26 and 41 or by 10 days or more for those aged between 18 and 25 or between 42 and 45. For example, a patient aged 43 with cycle lengths of 25, 28, and 34 days has a 9-day difference between her shortest and longest cycles, indicating regular cycles for her age. In contrast, the same cycle history in a patient aged 26 would suggest an irregular cycle. Intermenstrual bleeding is defined as bleeding that occurs between cyclically regular menstrual periods. This type of bleeding can be random, meaning it is unpredictable or cyclic, indicating that it occurs consistently at the same point in each cycle.[15]

2.2.1. The Ovarian and Endometrial Cycles

The menstrual cycle comprises 2 distinct cycles—one within the ovary and another within the endometrium. The phases of the ovarian cycle include the follicular phase, ovulation, and the luteal phase. The endometrial cycle consists of the proliferative phase, the secretory phase, and the menstrual phase. Generally, the ovarian follicular phase corresponds to the menstrual and proliferative phases of the endometrium, while the luteal phase of the ovarian cycle corresponds to the secretory phase of the endometrial cycle. The complex nature of the menstrual cycle means that abnormal menstrual patterns often indicate underlying health issues. Clinicians must be familiar with what constitutes normal menstruation to effectively identify any abnormal

patterns. For example, for menstruation to occur, the hypothalamus-pituitary-ovarian (HPO) axis must function properly, the endometrium must be healthy, and the uterine outflow tract must be patent. Numerous conditions can impact the HPO axis, including endocrine, metabolic, inflammatory, infectious, autoimmune, infiltrative, genetic, and neoplastic processes.[16]

2.2.2. Hormonal Change during Menstrual Cycle

Hormones are secreted through both negative and positive feedback mechanisms to regulate the menstrual cycle Hormonal Secretion and Feedback Mechanism during the Menstrual Cycle. Hormonal regulation begins in the hypothalamus, where gonadotropin-releasing hormone (GnRH) is secreted in an increased, pulsatile fashion starting at puberty. GnRH is transported to the anterior pituitary, where it activates its G protein–coupled receptor, signaling the pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH then travel through the bloodstream to the ovaries, stimulating the production of sex steroid hormones from follicular cells.[17]

The ovarian follicle contains 2 cell types responsible for hormone production: theca cells and granulosa cells. LH stimulates theca cells to produce progesterone and androstenedione by activating the enzyme cholesterol desmolase. Androstenedione then diffuses into the adjacent granulosa cells, where FSH stimulates the enzyme aromatase within the granulosa cells to convert androstenedione to testosterone and then to 17-β estradiol. Both 17-β estradiol and progesterone are secreted into the bloodstream and affect various tissues, including the uterus and pituitary gland. In the uterus, these hormones promote the growth and maturation of the endometrium. At the anterior pituitary, these sex steroid hormones provide negative feedback, reducing the secretion of FSH and LH, which subsequently reduces the production of 17-β estradiol and progesterone by the ovaries.[18]

An exception to this negative feedback loop occurs around the time of ovulation. When a critical level of 17-β estradiol is reached, it provides positive feedback to the anterior pituitary, leading to a surge in FSH and LH production.

Granulosa cells within the feedback system also produce inhibin B and activin, which inhibit and stimulate FSH release from the anterior pituitary, respectively. This feedback mechanism is regulated by the upregulation or downregulation of GnRH receptors on the anterior pituitary.[16][17][18]

2.2.3. Follicular Phase

The menstrual cycle typically ranges from 21 to 35 days, with an average length of 28 days. Oligomenorrhea refers to infrequent periods with menstrual cycles longer than 35 days, while polymenorrhea describes frequent periods with cycles shorter than 21 days. Notably, the duration of the follicular phase can vary depending on the overall length of the cycle, whereas the luteal phase is usually stable and lasts 14 days. In a 28-day cycle, the follicular phase extends from the first day of menstruation (day 0) to the start of ovulation (day 14).[19]

When the previous menstrual cycle completes and the corpus luteum breaks down, the levels of estrogen, progesterone, and inhibin A decrease. This chain of events triggers positive feedback to the hypothalamus and anterior pituitary, leading to a pulsatile release of gonadotropin-releasing hormone (GnRH) and follicle-stimulating hormone (FSH) into circulation. The increase in FSH stimulates the granulosa cells of the ovaries, prompting the recruitment of several follicles from each ovary. These follicles mature, but only one Graafian follicle will undergo ovulation during that cycle. The rise in FSH also stimulates the secretion of inhibin B by the granulosa cells. Inhibin B subsequently suppresses FSH secretion toward the end of the follicular phase. Inhibin B levels peak during the luteinizing hormone (LH) surge before ovulation and then decline rapidly.[19]

The level of FSH can vary based on the age of a female. As women age, ovarian function declines, leading to reduced inhibin production in the preceding luteal phase. Lower inhibin levels result in a higher release of FSH compared to younger females. Elevated FSH levels enhance the recruitment of ovarian follicles, potentially increasing the occurrence of more than 1 ovulation per cycle. As follicles are recruited at an increased rate, the overall duration of the follicular phase shortens, and the follicle released for ovulation may be less mature. Due to these age-related changes in the early follicular phase, physicians can evaluate suspected infertility by measuring serum FSH and estradiol levels around day 3 of the cycle. Additionally, ovarian reserve can be assessed by monitoring serum levels of anti-Müllerian hormone (AMH), which is produced by granulosa cells and plays a crucial role in folliculogenesis. AMH levels can be measured at any point during the menstrual cycle.[20],[21],[22]

The mid-follicular phase begins with a rise in estradiol and inhibin B levels produced by the ovarian follicles in response to increased FSH. This rise results in negative feedback, leading to decreased FSH levels. During this phase, the selection of the follicle destined for ovulation occurs, and this follicle is termed the dominant follicle. Various theories explain how the dominant follicle is determined. One theory suggests that the follicle with the highest number of FSH receptors promotes its own growth and ovulates, while other follicles are suppressed and undergo atresia. Another theory posits that the AMH plays a role in selecting the dominant follicle.[23],[24],[25]

In response to elevated FSH levels during the early follicular phase, granulosa cells proliferate, leading to an increase in FSH receptors in these cells. The higher FSH

levels enable granulosa cells to produce estradiol, which in turn stimulates the production of LH receptors in the granulosa cells. With LH receptors currently present, granulosa cells also produce small amounts of progesterone and 17-hydroxyprogesterone. The progesterone released by granulosa cells regulates their proliferation and ultimately slows follicular growth as the follicular phase comes to an end, estradiol levels rise rapidly, causing the negative feedback loop to switch to positive feedback. While the exact reason for this switch is unclear, it is believed that kisspeptin neurons may have a role. The positive feedback from estradiol stimulates the hypothalamus and anterior pituitary, triggering a surge in LH, which signals the end of the follicular phase and the onset of ovulation.[26]

2.2.4. Ovulation

Ovulation is a physiologic process defined by the rupture of the dominant follicle of the ovary. This releases an egg into the abdominal cavity. It then is taken up by the fimbriae of the fallopian tube where it has the potential to become fertilized. The ovulation process is regulated by fluxing gonadotropic hormone (FSH/LH) levels. Ovulation is the third phase within the larger uterine cycle (ie, menstrual cycle). The follicular release follows the Follicular phase (ie, dominant follicle development) and precedes the luteal phase (ie, maintenance of corpus luteum) that progresses to either endometrial shedding or implantation. Follicular release occurs around 14 days prior to menstruation in a cyclic pattern if the hypothalamic-pituitary-ovarian axis function is well regulated. Ovulation occurs around day 14 of a typical 28-day cycle. Estrogen levels rise as a result of increased estrogen production by hormonally active granulosa cells within the follicle. One of the estrogen levels reaches a critical point and remains at that level for 2 days, and estrogen transitions from a negative feedback modulator of GnRH to a positive feedback modulator on the hypothalamus. This transition point leads to an increased frequency of GnRH secretion onto the anterior pituitary, leading to an LH surge. The LH surge increases intrafollicular proteolytic enzymes, weakening the wall of the ovary and allowing for the mature follicle to pass through.[27]

The surge also causes the luteinization of thecal and granulosa cells, forming the corpus luteum, which is responsible for progesterone synthesis levels. Once the follicle is released, it is caught by the fimbriae of the fallopian tubes. The oocyte remains in metaphase II of meiosis II unless fertilization occurs.[27]

2.2.5. Luteal phase

The luteal phase begins after ovulation. It lasts about 14 days (unless fertilization occurs) and ends just before the next menstrual period. During the luteal phase, luteinizing hormone and follicle-stimulating hormone levels decrease. The ruptured follicle (left on the ovary after ovulation) forms a structure called the corpus luteum. The corpus luteum produces progesterone and a small amount of oestrogen. This combination of hormones causes further thickening of the lining of the uterus, to prepare for possible implantation.[28]

From the time of ovulation, the life span of an egg is around 24 hours. For pregnancy to occur the egg must be fertilised by a sperm in this time. If it is not fertilised within 24 hours, pregnancy is not possible. Fertilisation is more likely when sperm are present in the reproductive tract before the egg is released. Most pregnancies occur when sex has occurred in the couple of days before ovulation.If a fertilised egg (embryo) implants in the lining of the uterus, it begins to produce a hormone called human chorionic gonadotropin (hCG). This hormone maintains the corpus luteum, which continues to produce progesterone, until the growing foetus can produce its own hormones. If pregnancy does not occur, the corpus luteum degenerates and levels of progesterone and oestrogen decrease and a new menstrual cycle begins.[28]

2.2.6. Menstruation

Menstruation (also called the menstrual period or menses) is the first phase of the uterine cycle. It occurs if fertilization has not taken place during the preceding menstrual cycle. During menstruation, the endometrium of the uterus, which has built up during the preceding cycle, degenerates and is shed from the uterus. The average loss of blood during menstruation is about 35 mL. The flow of blood is often accompanied by uterine cramps, which may be severe in some people.[29]

2.2.7. Proliferative phase

During the proliferative or follicular phase (day 1 to 14), estrogen signaling dominates.[30] Under the influence of follicle-stimulating hormone (FSH) secreted by the pituitary gland, ovarian follicles develop and secrete estrogens. E2 plasma concentration fluctuates between 31–90 pg/mL and could reach 500 pg/mL just before the ovulatory phase, typically around the 14th day of the menstrual cycle.[31] The rise in estrogen levels promotes the proliferation of epithelial and stromal cells in the endometrium, contributing to its reconstruction.[32] Notably, the proliferation of the epithelium results from a paracrine signaling initiated by the stromal cells. Moreover, cilium differentiation is engaged, glands become straight and narrow, and the stroma thickens and vascularizes. This hormonal surge also stimulates the production of cervical mucus, facilitating the transit of spermatozoa.[33] During the early phase (which occurs immediately after menses), the endometrium begins to regenerate and forms a thin endometrial tissue layer. The endometrium begins to heal and strengthen itself after the effects of menstruation. Granulation tissue is involved in this process, just as it's involved in wound healing in other parts of the body. The uterine glands during this early phase are straight, short, and narrow. The endometrial stroma contains cells that are closely bunched and spindle-shaped. During the mid-phase, occurring during the follicular phase (which spans from

approximately day 8 to day 10 of the menstrual cycle), columnar epithelial cells within the uterine glands become more curved and elongated. In the late phase, also occurring during the follicular phase (around day 11 to around day 14), the endometrial glands become more closely packed and coiled. They also begin to undergo nuclear pseudostratification and active mitosis (cell division). Throughout the various phases, cervical fluid changes. It becomes more thin, watery, and slippery. The changes also make the vagina less acidic, so it's a more hospitable environment for sperm.[34]

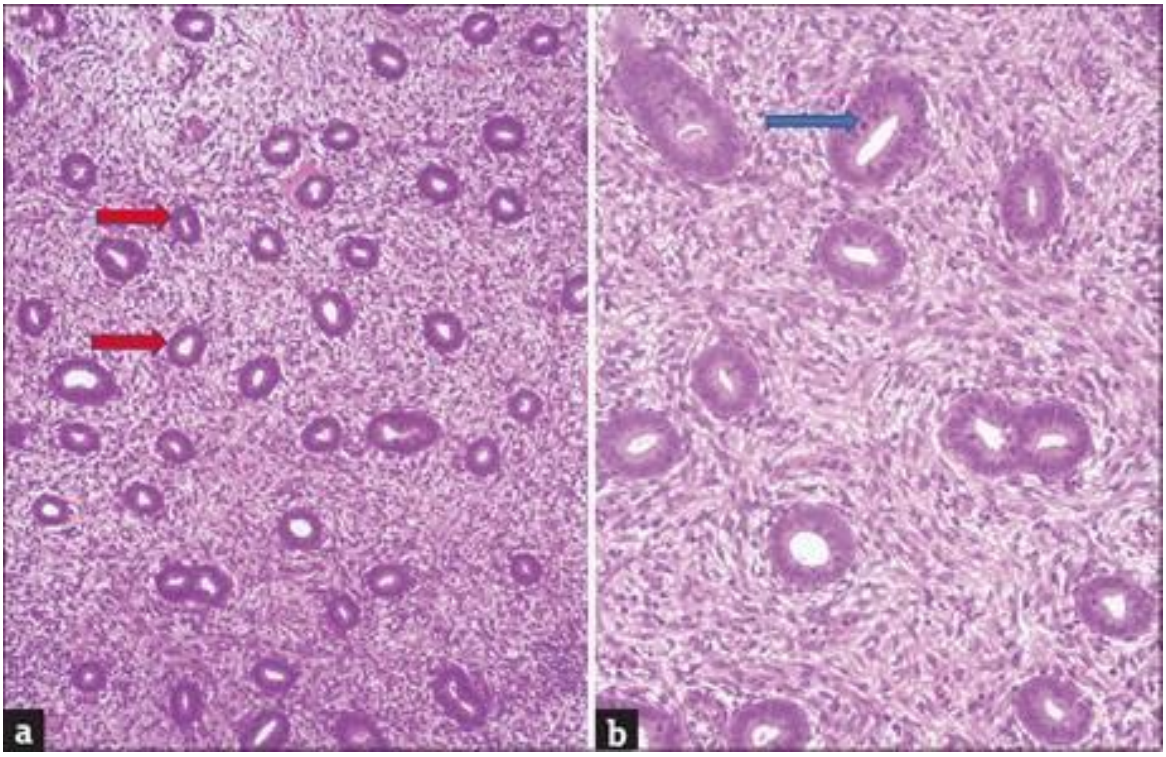

Figure 2.2: (a) Proliferative phase endometrium composed of evenly spaced tubular glands (red arrow), with compact, cellular surrounding stroma (HE stain, ×5). (b) Glands showing mitoses (blue arrow) help differentiate from inactive atrophic glands (HE stain, ×20).[6]

2.2.8. Secretory phase

The secretory phase is the final phase of the uterine cycle and it corresponds to the luteal phase of the ovarian cycle. During the secretory phase, the corpus luteum produces progesterone, which plays a vital role in making the endometrium receptive to the implantation of a blastocyst (a fertilized egg, which has begun to grow).[35] Progesterone secreted by the corpus luteum stimulates the further build- up of the cells in the endometrium of the uterus. Progesterone also stimulates the glands in the uterus to secrete substances that maintain the endometrium and keep it from breaking down. For this reason, this phase of the menstrual cycle is called the secretory phase.[36] Glycogen, lipids, and proteins are secreted into the uterus[37] and the cervical mucus thickens.[38] In early pregnancy, progesterone also increases blood flow and reduces the contractility of the smooth muscle in the uterus and raises basal body temperature.[39]

2.3. Abnormal uterine bleeding

Abnormal uterine bleeding (AUB) is any bleeding that deviates from normal menstruations. It may differ in terms of frequency of bleeding, durations, and the pattern of bleeding during menstrual cycle or menopause.[40] In this review, we define the "perimenopausal AUB" as any abnormal menstrual bleeding during menopausal transition or within the first year after menopause.[41] AUB is a medical term proposed in recent years. Bleeding from the uterine and cervical uterine cavity both belong to the AUB category.[15]

Judgment and description of normal menstruation are from the following four respects commonly. (I) Regularity refers to the small difference in the length of two periods, that is, the difference between two periods is less than seven days, which is called menstrual regularity. (II) The normal length of menstrual cycle is 24 to 38 days, and too short or too long are abnormal. (III) Menstrual volume: the average amount of blood loss in each menstrual period is about 80 mL. It is difficult to describe the amount of blood loss with specific milliliters in daily life. General clinicians will ask how many pieces of sanitary napkin a day and if each sanitary napkin can be soaked and so on to estimate the amount of blood loss. (IV) Length of menstrual period: normally, it should be about seven days from the beginning of menstruation to complete cleanliness, and prolonged menstrual period also belongs to AUB.[15][42] It is a common gynecological problem for medical visits

among women of reproductive age group that have a long list of causes in different age groups.[43] AUB accounts for up to one third of office visits prior to perimenopause. while in perimenopausal and postmenopausal age, this condition accounts for up to 70% of new gynecological consultations.[44]

Perimenopause, or menopause transition, is defined as the period prior to menopause when a woman may experience irregular or variable menstrual cycles and fluctuations in reproductive hormones, and may last up to 2 to 8 years.[45] The median age of perimenopause is 47.5 years, and 87% of women are perimenopausal or postmenopausal by the age of 51. Perimenopause can be associated with a wide spectrum of disorders, and AUB is one of the most common health problems encountered in women of the perimenopausal age group. As a result of hormonal changes in the hypothalamic-pituitary-ovarian axis, ovulations are irregular during perimenopause.[46]

In early perimenopause, inhibin B levels decrease, which results in a rise in the follicle-stimulating hormone (FSH). The rise of FSH is periodic, and it may rise during some cycles and return to premenopausal levels in subsequent cycles. Similarly, concentrations of estradiol may also rise or even decline in perimenopausal women, which is predominantly a consequence of the decline in ovarian follicle numbers.[46,47]

It has been proposed that an increase in menstrual blood loss in perimenopausal women is likely to be a result of ovulatory cycles, which are followed by prolonged periods of anovulation with elevated concentrations of estradiol. This contributes to abnormal proliferative changes in the endometrium and variable ovulatory cycle length. However, the etiology and pathogenesis of AUB in perimenopausal women are not yet completely known and understood.[48] Rarely, the cause of AUB in perimenopausal women could be the clinical presentation of benign or malignant lesions of the female reproductive organs.[49] However, most of the cases of AUB in perimenopausal age are of benign nature without requiring any invasive surgeries. Endometrial biopsy obtained by dilatation and curettage is the preferred modality of investigation to determine the causative pathology of AUB.[50]

It occurs during a women's problem with medically, mentally, and socially ill. In addition to this, it is one of common causes of anemia in women, especially in developing world. Abnormal menstruation is impact on the health of women in the negative way: It can limit daily activities of women and prevent the women not to go away from the house. In general, it affects maternal quality of life, socially and physically.[44]

The International Federation of Gynecology and Obstetrics (FIGO) systems for nomenclature of symptoms of normal and abnormal uterine bleeding (AUB) in the reproductive years (FIGO AUB System 1) and for classification of causes of AUB (FIGO AUB System 2; PALM-COEIN) were first published together in 2011 and revised in 2018. The PALM-COEIN classification outlines both the structural (polyp, adenomyosis, leiomyoma, malignancy/hyperplasia) and nonstructural (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, not otherwise classified) factors leading to AUB during the reproductive years.[51]

FIGO defines AUB as a bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration and occurs in the absence of pregnancy; the main symptoms placed under the umbrella term "AUB" are HMB, irregular menstrual bleeding and intermenstrual bleeding.[52]

2.4. Dilation and curettage

It is one of the most common invasive procedures in the United States. The procedure can be performed on a pregnant or nonpregnant patient and be either diagnostic or therapeutic. Sometimes the circumstances lead to a diagnostic procedure becoming therapeutic.[53] A D&C may be performed in the evaluation of abnormal uterine bleeding. However, with the advent of aspiration devices for endometrial biopsy and advances in ultrasound technology, the D&C is rarely the first step in the evaluation. D&C may also be used to manage abnormal uterine bleeding refractory to medical therapy.[54]

D&C removes tissue from the endometrial cavity. In a nonpregnant patient, the endometrial lining is sampled and sent for pathological evaluation. Current recommendations for endometrial sampling include hysteroscopy with directed endometrial sampling, However, if necessary resources are unavailable, a simple D&C may be performed to acquire tissue for histologic evaluation. In the absence of pregnancy, the endometrium has 2 distinct histophysiologic layers; the stratum basalis and the stratum functionalis. The goal of a D&C in a nonpregnant patient is the removal of the stratum functionalis. Removal of this endometrial layer does not affect the hypothalamic-pituitary-ovarian axis and does not affect ovulation or future menses.[55] If there is damage to basal endometrium, these can result in the formation of adhesion and fibrosis (ASHERMAN SYNDROME).[7]

Therapeutically a D&C may be used in a nonpregnant patient with excessive uterine bleeding who has failed medical management or become hemodynamically unstable. In this circumstance, the D&C alone is inadequate as a complete evaluation of the uterine disorder but usually provides a temporary reduction in bleeding.[56]

2.5. Endometrium hyperplasia

The endometrium, the innermost glandular layer of the uterus, is a dynamic tissue that goes through a series of alterations (proliferation, secretion and

menstruation/shedding) during the menstrual cycle in a woman's reproductive years. This cyclic phase involves a complex interaction between the two female sex hormones, estradiol, and progesterone.[57]

Estrogen promotes epithelial cell proliferation , while progesterone encourages epithelial cell differentiation and the secretory phase of the endometrial cycle ,The fine equilibrium between endometrial proliferation and apoptosis is maintained by an intricate process involving a number of factors including hormonal balance, molecular mechanisms, environment, age, and so forth; accordingly, it is prone to various disturbances leading to several endometrial abnormalities.[57] Endometrial hyperplasia (EH) is a pre-cancerous, non- physiological, non-invasive proliferation of the endometrium that results in increased volume of endometrial tissue with alterations of glandular architecture (shape and size) and endometrial gland to stroma ratio of greater than 1:1. Currently, the incidence of EH is indistinctly reported to be around 200,000 new EH cases per year in Western countries.[58]

The majority of cases of EH arise in the presence of chronic exposure to estrogen unopposed by progesterone such as in earlier forms of hormone replacement therapy. Overproduction of estrogen by fat cells also contributes to the higher risk of EH and endometrial cancer (EC) in obese women.[58] In addition to inducing proliferation of the uterus , estrogen induces morphometric alterations in the uterus that include changes in the type of luminal and glandular epithelia, the number and shape of glands, the gland to stroma ratio, and the morphology of epithelial cells.EH also occurs after menopause, when ovulation stops and progesterone is no longer produced, as well as during perimenopause when women experience irregular ovulation.Perimenopause generally refers to the transition period from premenopause to menopause in women.[59] The average duration of this period varies between 4 and 11 years, starting from the last menstrual cycle. While most women show menopausal symptoms in their 40s, some exhibit symptoms in their 50s, and only 10% show symptoms in their 30s.[60][61]

The most common symptom of EH is abnormal uterine bleeding including, menorrhagia, intermenstrual bleeding, postmenopausal bleeding, and irregular bleeding when on hormone replacement therapy or tamoxifen. Currently, the treatment approaches for EH are limited, such as hysterectomy or hormone therapy. EH without atypia is generally treated with progestins, while hysterectomy is the best treatment option for EH with atypia.[62] Since EH with atypia may progress to or coexist with EC, it is of clinical importance and should not be ignored. Moreover, conservative treatment with progestins is designed to regress hyperplasia to normal endometrium to prevent subsequent development of adenocarcinoma.[57]

2.5.1. Classification of endometrial hyperplasia

Up to now, the correct clinical evaluation of endometrial hyperplasias was made more difficult by the different classification systems still in use: in Germany hyperplasias are sometimes still differentiated according to the classification "glandular-cystic hyperplasia" and "adenomatous hyperplasia grade I to III". In 1994, the WHO classified endometrial hyperplasias into 4 categories[63]:

- Simple hyperplasia without atypia
- Complex hyperplasia without atypia
- Simple atypical hyperplasia
- Complex atypical hyperplasia.

While categories 1, 2 and 4 were generally accepted, pathologists continued to debate the existence of group 3-type hyperplasias. Hyperplasias without atypia (categories 1 and 2) are considered benign pathologies which will regress with conservative treatment (oral gestagens, gestagen IUD, elimination of the cause of anovulation/corpus luteum insufficiency).[63]

A large percentage (up to 60 %) of atypical endometrial hyperplasias (categories 3 and 4) are found to be coexistent with invasive endometrial carcinoma or develop into invasive endometrial carcinoma within the space of just a few years. Hysterectomy is therefore the treatment of choice for atypical endometrial hyperplasia or – in selected patients, i.e. younger patients wanting to have children – high-dose gestagen therapy with appropriate close histological monitoring.[63]

The WHO classification of 1994 and even more so the parallel use of the older classification system led to confusion among clinicians. The consequence of this was inadequate diagnosis, with hysterectomies performed for hyperplasias without atypia or gestagens administered in HRT dosages for atypical hyperplasia. Pathologists also experienced difficulties with categorization. This was made even more difficult by the development and parallel use of a further classification system[63]:

- Benign hyperplasia
- Endometrial intraepithelial neoplasia (EIN).

In its latest classification published in 2014, the WHO has clarified the matter: it now only differentiates between 2 categories of endometrial hyperplasia[63]:

1. Hyperplasia without atypia
2. Atypical hyperplasia/endometrioid intraepithelial neoplasia.

This reduction to 2 categories was not only due to the need to do away with the confusing multitude of terms currently in use. Rather, it reflects a new understanding of molecular genetic changes.[63]

2.6. Endometrial hyperplasia without atypia

Endometrial hyperplasia without atypia is defined as the proliferation of endometrial glands of irregular size and

shape without significant cytological atypia. The ratio of glands to stroma increases compared to the normal proliferative phase endometrium, exceeding the ratio of 3:1 in hyperplasia. The cytological diagnostic criteria is characterized by the appearance of clusters of dilated glands without cellular atypia (The nuclear atypia is characterized by enlargement, rounding, pleomorphism, and presence of nucleoli. Quite apart from these descriptive terms, the presence of cytologic atypia is most reliably recognized by comparison of the cytologic features in the hyperplastic focus to those of proliferative endometrial glandular epithelial cells outside the area of hyperplasia).

[2]However, owing to the varying degrees of appearance of dilated and branched clusters, some non-hyperplastic lesions are difficult to distinguish from endometrial hyperplasia without atypia. These lesions include "disordered proliferative-phase (DPP) endometrium as a benign reactive change." DPP is a lesion caused by the repeated, sequentially occurring anovulatory cycle and appears as one of the functional bleeding disorders.[64] This variant occurs due to unopposed estrogenic effect on the endometrium. It is histologically similarto disordered proliferative endometrium as regards to the crowded and irregularly branched glands. However, when glands predominate over the stroma; the diagnosis of endometrial hyperplasia without atypia is appropriate. The risk of progression to endometrial carcinoma from this variant is low, not exceeding 1-3%.[3] progression to invasive disease may occur if the endocrine disorder persists over the long term.[65]

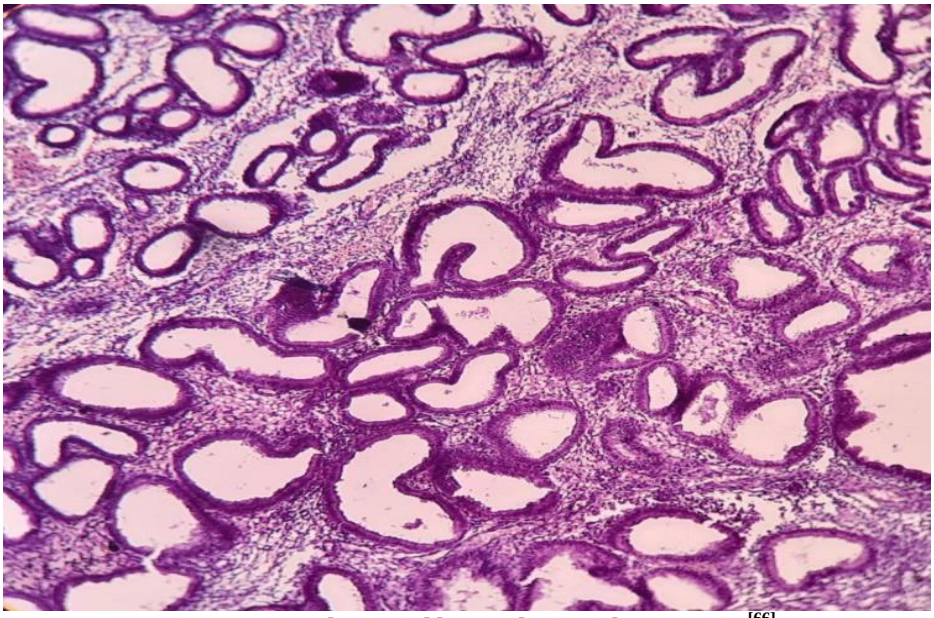

Figure 2.3: Endometrial hyperplasia without atypia.[66]

2.6.1. Regulation of Endometrial Function by Gonadal Hormones and Implications for EH without atypia

Gonadal hormones are secreted in a regulated manner throughout the menstrual cycle, regulating the functions of the endometrium. Endometrial thickness is minimal at the end of menstruation, increases during the follicular phase due to estradiol secretion from the dominant follicle, and reaches maximum thickness in the mid-luteal phase due to increased glandular secretion influenced by progesterone.[67] Estrogens play a role in regulating events such as endometrial cell proliferation, angiogenesis, and inflammation.[68]

In addition to promoting endometrial cell proliferation, estrogen hormones induce morphometric changes, including alterations in glandular epithelial type, gland numbers and shapes, gland-to-stroma ratio, and epithelial cell morphology(69),(70). EH results from changes in the shape and size of glandular tissue and an increase in the endometrial gland-to-stroma ratio(71). Non-atypical hyperplasia are benign changes that regress when hormonal changes or endocrine disorders return to normal(72). It is noted that the risk of untreated EH progressing to cancer can range from 3% in cases of non-atypical EH to 29% in cases of atypical EH.[73]

2.6.2. Etiology

The most important risk factor for endometrial hyperplasia and, in turn, endometroid adenocarcinoma is the aforementioned chronic imbalance of or "unopposed" estrogen.[74] The source of exposure to excessive estrogen without the protective effects of progestin can be endogenous, exogenous, or genetic.[75]

2.6.2.1. Endogenous Sources

- **Obesity:** An increase in adrenal secretory activity is often observed in obese patients, leading to increased androgen precursors, which are converted to estradiol in peripheral tissues. The conversion rate of androstenedione to estrone and estradiol by aromatase rises in obese patients. Higher estradiol

concentrations can be found in obese patients as plasma levels of estradiol- binding sex hormone-binding globulin (SHBG) are typically diminished in this patient population.[75]

- **Chronic anovulation:** When anovulation occurs, sex hormone production is not happening cyclically, and estrogen levels dominate without the opposing effect of progesterone produced by the corpus luteum after ovulation. This imbalance leads to a continued proliferation of the endometrium. Conditions associated with anovulation include polycystic ovary syndrome (PCOS), hyperprolactinemia, and perimenopausal hormonal status. Early menarche, typically defined in individuals younger than 12. Late menopause, usually described in those aged 55 and older.[76]
- **Presence of estrogen-secreting tumors:** Granulosa cell tumors represent potentially estrogen-secreting tumors of the ovary. Accordingly, endometrial hyperplasia is diagnosed in 25% to 50% of women with granulosa cell tumors of the ovary.[76] If endometrial hyperplasia is diagnosed in a patient without known risk factors, estrogen-secreting tumors should be excluded.

2.6.2.2. Exogenous source

Tamoxifen, a selective estrogen receptor modulator (SERM), one of the most common medications used for endocrine treatment of hormone receptor- positive breast cancer, has been associated with an increased risk for developing endometrial hyperplasia in postmenopausal women.[77]

2.6.3. Risk factors

- Age greater than 35 years.
- Nulliparous woman.
- Personal history of certain conditions such as
- Diabetic Mellitus, Polycystic Ovarian Syndrome,
- Gall bladder disease or Thyroid disease.
- Obesity.
- Family history of ovarian, colon or uterine cancer.
- Smoking.
- Caucasian origin.[78]

High-Risk Populations for the Development of EH without atypia: Two particularly high-risk patient populations have been identified.[79]

The first comprises peri- or postmenopausal women who are obese due to excessive adiposity in the abdominal region. This leads to a significant conversion of androgens in adipose tissue to estrogen by the action of the aromatase enzyme.[79] It is known that insulin-like growth factor 1 (IGF-1) and its binding protein (IGF binding protein-1) support endometrial cell growth. Elevated levels of IGF have been reported in obese women, which may contribute to EH development by predisposing them to endometrial cancer.[80] Additionally, in obese women with diabetes mellitus (DM), high insulin resistance has been observed, leading to a decrease in sex hormone-binding globulin (SHBG) concentration due to increased insulin levels, resulting in elevated estrogen levels.[81]

The second high-risk group for EH development consists of premenopausal women with polycystic ovary syndrome (PCOS) characterized by hyperandrogenic activity. While endometrial stimulation by estrogens is considered a primary risk factor for EH development, other factors, such as immunosuppression, may also play a role.[82] The chronic exposure of the endometrium to high levels of estrogen without the counterbalancing effect of progesterone leads to increased cell proliferation and a heightened risk of malignant transformation.[83]

2.6.4. Clinical presentation

- Abnormal uterine bleeding
- Menorrhagia
- Intermenstrual bleeding
- Post-menopausal uterine bleeding
- Bleeding in between periods.[78]
- Irregular bleeding
- In some rare causes they occur asymptomatic.[84]

2.7. Disordered proliferative endometrium

Disordered proliferative endometrium is an exaggeration of the normal proliferative phase without significant increase in the overall ratio of glands to stroma and is due to persistent oestrogen stimulation.[85] This pattern is particularly seen in perimenopausal women. The disordered proliferative endometrium resembles normal proliferative tissue in consisting of glands lined by cytologically bland, pseudostratified, proliferative, mitotically active epithelium and in having a normal ratio of glands to stroma. It differs from the normal proliferative endometrium in the absence of uniform glandular development. Disordered proliferative pattern lies at one end of the spectrum of proliferative lesions of the endometrium that includes carcinoma at the other end with intervening stages of hyperplasias.[86]

Disordered proliferative endometrium is abnormal proliferative endometrium with architectural changes due to persistent unopposed estrogen stimulation, considered benign, not precancerous It is common in patients with polycystic ovarian syndrome, obesity, and perimenopausal women associated with anovulation and can be treated with progesterone Unopposed estrogen on disordered proliferative endometrium in the early phase can later develop into hyperplasia.[87]

Disordered proliferative endometrium is an exaggerated proliferative phase representing chronic anovulation in the perimenopausal years. As a result of the anovulation, the corpus luteum does not develop, culminating in relative increase in estrogen levels and a relative decrease in progesterone levels. This chronic prolonged unopposed estrogen stimulates disorderly proliferation of the endometrium with mild glandular architectural distortion, making the endometrium fragile, unstable and

susceptible to subsequent shedding.[88]

The term "disordered proliferative endometrium" has been used in a number of ways and is somewhat difficult to define. It denotes an endometrial appearance that is hyperplastic but without an increase in endometrial volume. It also refers to a proliferative phase endometrium that does not seem appropriate for any one time in the menstrual cycle, but is not abnormal enough to be considered hyperplastic. Disordered proliferative pattern resembles a simple hyperplasia, but the process is focal rather than diffuse.[86] DPE is characterized by irregularly shaped, cystically dilated glands producing a disordered arrangement (branched, convoluted, scalloped outer contours; > 10% of overall glands).True gland cribriforming is not seen and the epithelium remains as a single layer without stratification. Metaplastic changes are common, including tubalor eosinophilic syncytial metaplasia. Other changes associated with endometrial stromal breakdown are common. Most importantly, the endometrium retains a relatively normal gland to stroma ratio. When the gland: stroma area exceeds 50% (1:1), the term "hyperplasia without atypia used.[89]

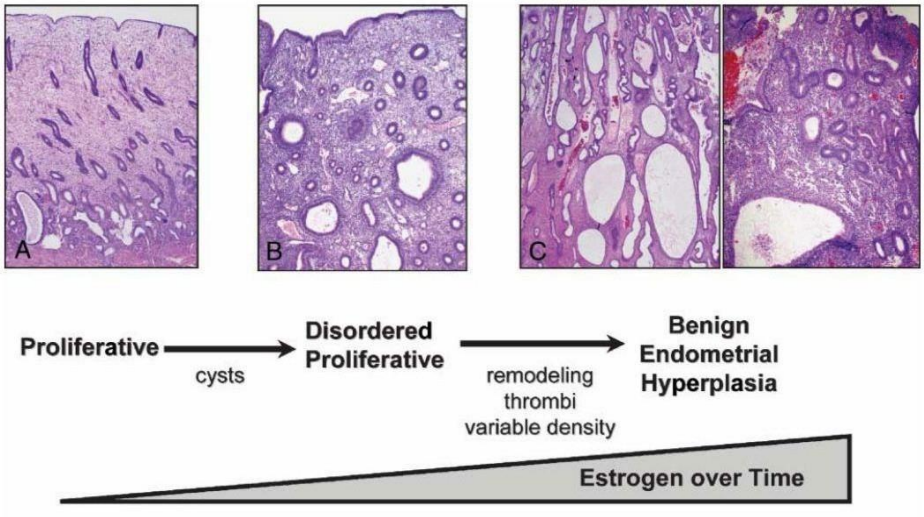

Figure 2.4: Progressive effects of unopposed estrogens.[90]

3. MATERIALS AND METHODS

3.1 Study design and setting

An observational cross sectional study design that has been conducted at Al- Kufa training center- Iraqi Council of Medical Specialization, at Al-sadder Teaching Medical City Laboratory in Al-Najaf. The research was performed in the period from 1st June 2024 to 1st December 2024. All cases incorporated in the current study were collected from a private laboratory in Al-Najaf governorate. In this study were 178 formalin fixed paraffin embedded (FFPE)tissue block and hematoxylin and eosin stained slides were retrospectively collected from Iraqi patients with Abnormal uterine bleeding having endometrium hyperplasia without atypia,disordered proliferative endometrium and proliferative endometrium.

3.2. Selection of samples

A. Sample collection: 178 cases of abnormal uterine bleeding with endometrium hyperplasia without atypia, disordered proliferative endometrium and proliferative endometrium were incorporated in this study. The specimens of D & C were formalin fixed paraffin embedded (FFPE) tissue block.

B. Inclusion and exclusion criteria:

1. Inclusion criteria

- Women in perimenopausal aged 41-50years with abnormal uterine bleeding.
- Tissue samples diagnosed with proliferative endometrium.
- Tissue samples diagnosed with disordered proliferative endometrium.
- Tissue samples diagnosed with endometrial hyperplasia without atypia.

2. Exclusion criteria

- Women aged <41 and >50.
- Precancerous causes of abnormal uterine bleeding including atypical endometrial hyperplasia.
- Organic causes of abnormal uterine bleeding like polyp, adenomyosis, and endometrial carcinoma.
- Women with coagulation disorders

3.3. Approval and official permission

An official letter of approval has been obtained from the scientific committee of the scientific council of Histopathology Iraqi Board for Medical Specialization.

3.4. Microscopic examination and evaluation

The approach was achieved to assess microscopic examination of slides by light microscopy and adding the results in Microsoft Excel 2019. The collected[124] hematoxylin and eosin stained slides were re-examined by expert histopathologist using light microscope. The remaining[54] FFPE tissue block were sectioned by

microtome, deparaffinized for 60 minute at 50 ℃ using Memmort oven.

3.5. Hematoxylin and eosin staining procedure

- Xylene for 5 minute twice.
- Ethanol alcohol in different concentration ranging from 100%, 90%, 80%, 70% each for 2 minute.
- Distal water for 1 minute.
- The slides stained by hematoxylin for 40 seconds then rinse in tap water for 10 minute.
- The slides dips in eosin then ethanol alcohol in different concentration (70%, 80%, 90%, 100%) each for 2 minute.
- The slide was air dried followed by xylene for 5 minute.
- Mounting by DPX.
- The slides examined under light microscope.

From (178) re-examined cases there was (39) cases over or underestimated results was re-examined by second expert histopathologist to confirm the diagnosis with 100 % concordance rate between first and second pathologist.

3.6. Statistical analysis

IBM SPSS statistical package was used to analyze the data version (29.0.1.0). Qualitative variables were presented as number and percentage. Chi-square test was used compare differences in proportions. Level of significance was considered at $p \leq 0.05$.

4. RESULTS

Original endometrial diagnosis revealed that 40.4% of the cases (72 out of 178) were diagnosed as proliferative endometrium, 3.4% (6 out of 178) as disordered proliferative endometrium, and 56.2% (100 out of 178) as endometrial hyperplasia without atypia, The total number of cases analyzed was 178, representing 100% of the sample. The pathology panel diagnosis over 3 years showed that 39.9% of the cases (71 out of 178) were diagnosed as proliferative endometrium, 24.2% (43 out of 178) as disordered proliferative endometrium with a statistical significance (Sig.) of 0.01, and 36.0% (64 out of 178) as endometrial hyperplasia without atypia, which had statistical significance of 0.03. The total number of cases analyzed was 178, representing 100% of the sample, table 4.1 and figure 4.1.

Table 4.1: Prevalence of Original Endometrial Diagnosis and Pathology Panel Diagnosis Over 3 Years.

Characteristic	Endometrium diagnostic	Prevalence %	N	Sig.
Original diagnosis	proliferative endometrium	40.4%	72	Reference
	disordered proliferative endometrium	3.4%	6	
	endometrial hyperplasia without atypia	56.2%	100	
	Total	100.0%	178	
3 years pathology panel diagnosis	proliferative endometrium	39.9%	71	No.sig
	disordered proliferative endometrium	24.2%	43	0.01
	endometrial hyperplasia without atypia	36.0%	64	0.03
	Total	100.0%	178	

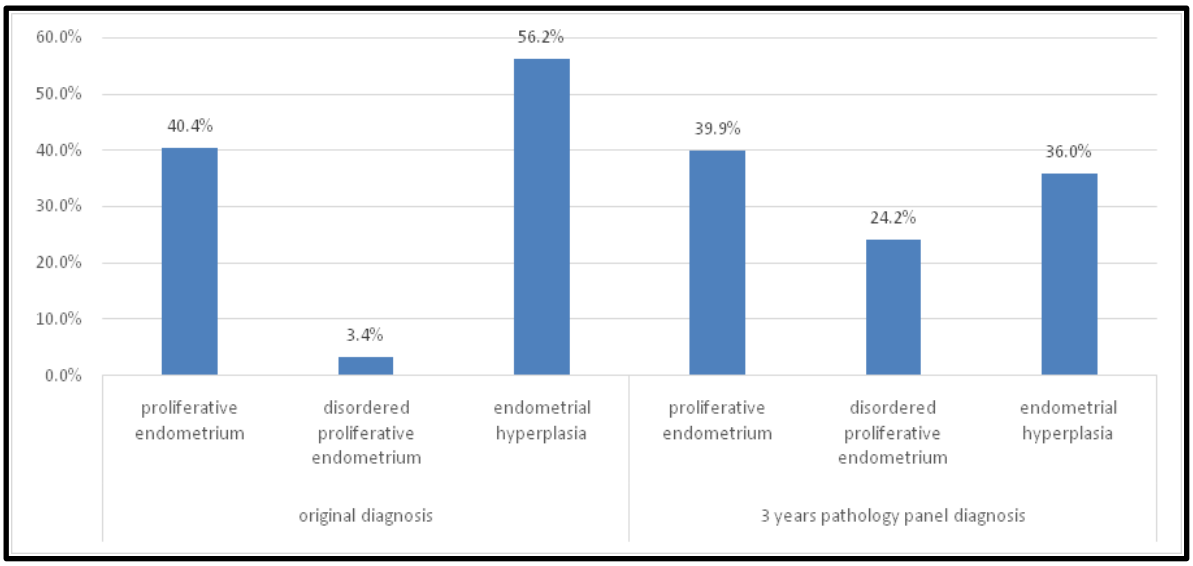

Figure 4.1: Prevalence of endometrial Pathology over 3 years.

Table 4.2 compares the prevalence of three endometrial diagnostic categories (Proliferative Endometrium, Disordered Proliferative Endometrium, and Endometrial Hyperplasia without atypia) between original diagnosis and pathology panel diagnosis for 2021, 2022, and 2023. In original diagnosis, Proliferative Endometrium shows

varying prevalence (49% in 2021, 30.4% in 2022, 42.3% in 2023), while Disordered Proliferative Endometrium is absent in 2021 and 2022 but appears in 2023 (8.5%), and Endometrial Hyperplasia without atypia is highly prevalent (51% in 2021, 69.6% in 2022, 49.3% in 2023).

In pathology panel diagnosis, Proliferative Endometrium remains consistent (49% in 2021, 30.4% in 2022, 40.8% in 2023), with no significant differences in 2021, 2022, and 2023 (p=No.sig). Disordered Proliferative Endometrium is significantly higher in panel diagnosis (23.5% in 2021, p=0.00; 28.6% in 2022, p=0.00; 21.1% in 2023, p=0.03), and Endometrial Hyperplasia without atypia shows reduced prevalence (27.5% in 2021, p=0.01; 41% in 2022, p=0.02; 38.1% in 2023, p=0.04). These results indicate that the pathology panel tends to increase the detection of Disordered Proliferative Endometrium and reduce the prevalence of Endometrial Hyperplasia without atypia compared to original diagnosis, with statistically significant differences in most cases.

Table 4.2: Prevalence of Endometrial Diagnosis (Original and Pathology Panel Diagnosis for 2021, 2022, and 2023).

Characteristic	Endometrium diagnostic	Prevalence %	N	Sig.
original diagnosis 2021	proliferative endometrium	49%	25	Reference
	disordered proliferative endometrium	0%	0	
	endometrial hyperplasia without atypia	51%	26	
	Total	100.0%	51	
original diagnosis 2022	proliferative endometrium	30.4%	17	Reference
	disordered proliferative endometrium	0%	0	
	endometrial hyperplasia without atypia	69.6%	39	
	Total	100.0%	56	
original diagnosis 2023	proliferative endometrium	42.3%	30	Reference
	disordered proliferative endometrium	8.5%	6	
	endometrial hyperplasia without atypia	49.3%	35	
	Total	100.0%	71	
Pathology panel diagnosis 2021	proliferative endometrium	49%	25	No.sig
	disordered proliferative endometrium	23.5%	12	0.00
	endometrial hyperplasia without atypia	27.5%	14	0.01
	Total	100.0%	51	
Pathology panel diagnosis 2022	proliferative endometrium	30.4%	17	No.sig
	disordered proliferative endometrium	28.6%	16	0.00
	endometrial hyperplasia without atypia	41%	23	0.02
	Total	100.0%	56	
Pathology panel diagnosis 2023	proliferative endometrium	40.8%	29	No.sig
	disordered proliferative endometrium	21.1%	15	0.03
	endometrial hyperplasia without atypia	38.1%	27	0.04
	Total	100.0%	71	

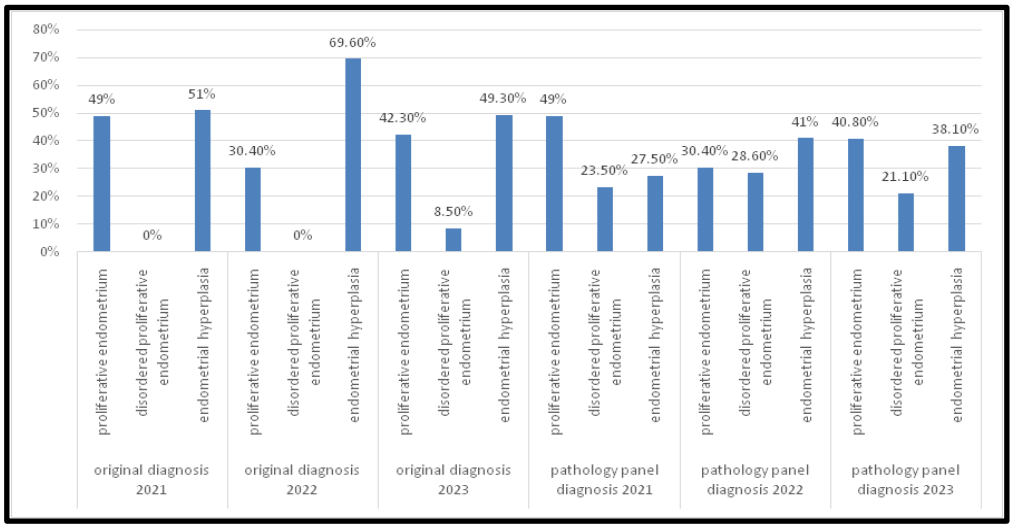

Figure 4.2: Prevalence of endometrial Pathology over 2021, 2022, and 2023.

Table 4.3 analyzes underestimation and overestimation percentages for three endometrial diagnostic categories (Proliferative Endometrium, Disordered Proliferative Endometrium, and Endometrial Hyperplasia without atypia) across 2021, 2022, 2023, and a combined 3-year period based on pathology panel diagnosis. Proliferative Endometrium shows consistent underestimation, with rates of 0.0% in 2021 and 2022, and 2.8% in 2023 (p=0.01).

Disordered Proliferative Endometrium exhibits minimal overestimation, with rates of 0.6% over the 3-year period, 0.0% in 2021 and 2022, and 1.4% in 2023, with no underestimation (0.0%) detected in any year. Endometrial Hyperplasia without atypia is significantly overestimated across all years, with rates of 20.2% over the 3-year period, 23.5% in 2021, 28.5% in 2022, and 11.2% in 2023, all with statistical significance (p=0.01). These findings indicate that the pathology panel tends to underestimate Proliferative Endometrium, overestimate Endometrial Hyperplasia without atypia consistently, and show slight overestimation for Disordered Proliferative Endometrium, with significant differences in most cases.

Table 4.3: Overestimation and Underestimation of Endometrial Diagnosis (Pathology Panel Diagnosis Over 3 Years and for 2021, 2022, and 2023).

Characteristic	Endometrium diagnostic	N	Underestimation %	Sig.	N	Overestimation %	Sig.
3 years pathology panel diagnosis	proliferative endometrium	2	1.1	0.01	0	0	0.01
	disordered proliferative endometrium	0	0		1	0.6	
	endometrial hyperplasiawithout atypia	0	0		36	20.2	
pathology panel diagnosis 2021	proliferative endometrium	0	0	no.sig	0	0	0.01
	disordered proliferative endometrium	0	0		0	0	
	endometrial hyperplasia without atypia	0	0		12	23.5	
Pathology panel diagnosis 2022	proliferative endometrium	0	0	no.sig	0	0	0.01
	disordered proliferative endometrium	0	0		0	0	
	endometrial hyperplasia without atypia	0	0		16	28.5	
pathology panel diagnosis 2023	proliferative endometrium	2	2.8	0.01	0	0	0.01
	disordered proliferative endometrium	0	0		1	1.4	
	endometrial hyperplasia without atypia	0	0		8	11.2	

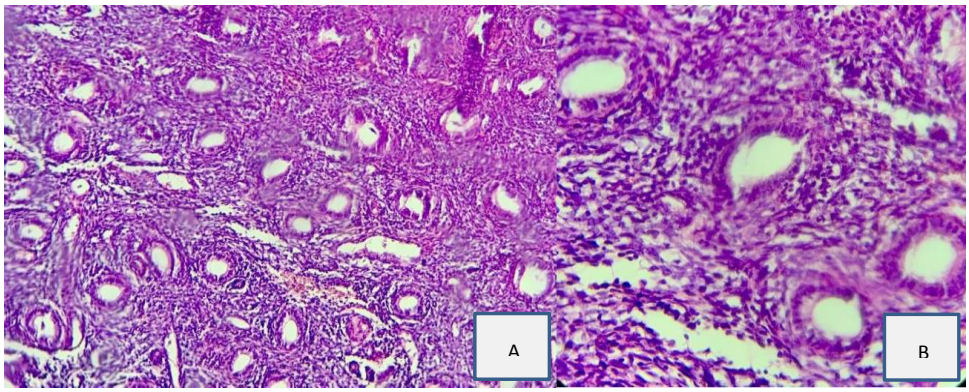

Figure 4.3: Proliferative endometrium. H&E. A. X100. B. X400.Pictures show Cellular blue appearance Round to tubular glands Even, regular spacing between glands.

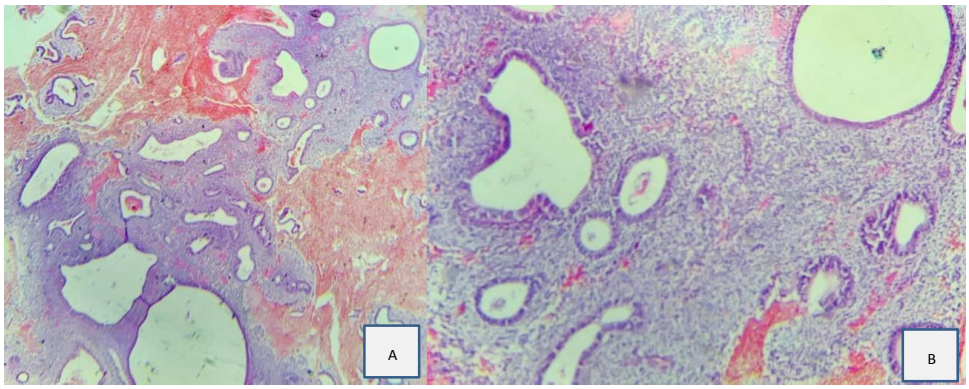

Figure 4.4: Disordered proliferative endometrium. H&E. A. X100. B. X400. Pictures show Cystically dilated glands randomly interspersed among proliferative endometrial glands.

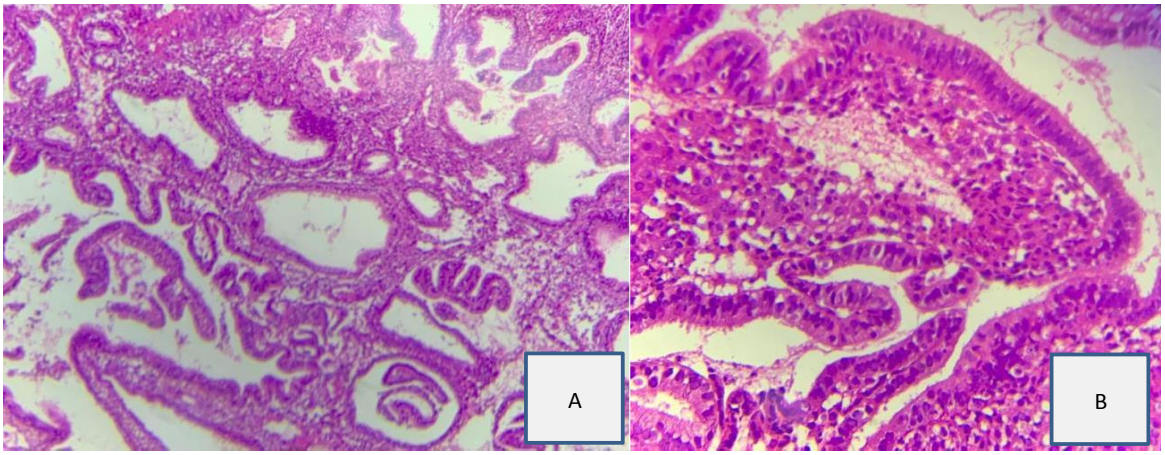

Figure 4.5: Endometrial hyperplasia without atypia. H&E. A. X100. B. X400.Pictures show Closely packed glands such that gland to stroma ratio is > 3:1 but stroma is still present between glandular basement membranes.

5. DISCUSSION

The dilemma of interpreting endometrial biopsies among pathologists is well known.[91] Indeed, one of the earliest reports about the difficulties facing pathologists in categorizing endometrial biopsies was published by Daud et al.[92] Daud et al. conducted a retrospective type of study comparing the pathological reports of 280 women before and after hysterectomy, i.e. comparing the surgical pathology reports describing endometrial biopsies to those describing hysterectomy specimen and they found that the false positive diagnosis of endometrial hyperplasia was made in 1.8 % cases and that false negative diagnosis of endometrial hyperplasia was seen in 13.2 % of cases; they claimed that sample inadequacy and/or miss-orientation of obtained tissues in endometrial biopsy samples are the main reason behind such discrepancy between the results.[92] Numerous scholarly investigations have indicated that inadequate resources represent the primary factor contributing to diagnostic inaccuracies.[91]

In the present study, the objective was to apply the recently updated microscopical criteria used to categorize endometrial samples (those obtained during D and C procedure) and to compare the outcome results with those issued in the retrieved pathological reports. The cohort of women selected in this study was picked up to be within 41 up to 50 years of age, with presentation of abnormal uterine bleeding. The targeted pathologies were confined to three well defined categories: proliferative endometrium, disordered proliferative endometrium and endometrial hyperplasia without atypia. Endometrial hyperplasia devoid of atypia constitutes a benign pathology characterized by the absence of substantial somatic genetic alterations, and the hyperplastic modifications frequently undergo regression upon the restoration of physiological progesterone levels or the administration of therapeutic progestins. Moreover, endometrial hyperplasia without atypia exhibits a low propensity for progression to endometrial carcinoma.[93]

The main findings of the present study were the existence of underestimation of proliferative endometrium; however, with a more or less negligible percentage of (1.1%), but, the significant and substantial overestimation of endometrial hyperplasia (20.2%). In line with current study observation, it has been stated that endometrial hyperplasia is one of most commonly misdiagnosed lesions (overdiagnosed).[94]

Until, 2008, diagnosing endometrial hyperplasia through endometrial sampling presents significant challenges due to substantial diagnostic discrepancies that are influenced by both the adequacy of the sample and the interpretation of the existing histological characteristics. Although procuring supplementary tissue may enhance the consistency of diagnostic outcomes, variations in the interpretation of critical histological attributes continue to be predominant factors that exacerbate diagnostic discordance.[91]

The accurate clinical assessment of endometrial hyperplasia is rendered more complex due to the various classification systems that persist in application. The preeminent classification framework for endometrial hyperplasia is the 2014 World Health Organization (WHO) Classification System, which delineates between endometrial hyperplasia devoid of atypia (benign endometrial hyperplasia) and atypical endometrial hyperplasia/endometrial intraepithelial neoplasia.[95]

In the year 2016, the collaborative guidelines established by two prominent committees were disseminated: the Royal College of Obstetricians and Gynaecologists (RCOG) and the British Society for Gynaecological Endoscopy (BSGE), pertaining to the treatment and classification of hyperplasia. These guidelines endorsed the WHO2014 classification system, which categorizes endometrial hyperplasia into two distinct classifications: hyperplasia devoid of atypia and atypical hyperplasia.[96]

In the year 2008, Sherman et al. executed a two-member panel examination involving 209 endometrial

biopsy/curettage specimens that were initially classified as incident endometrial hyperplasia within the context of a progression study; the preliminary diagnoses encompassed the following categories: disordered proliferative endometrium, simple hyperplasia, complex hyperplasia, and atypical hyperplasia; the diagnoses rendered by the panel also incorporated negative findings and carcinoma; the authors evaluated the percentage of concordance between the panel's conclusions and the original diagnostic reports.[97]

According to Sherman et al., the percent agreement was 34.9% and that agreement between panelists at a cut point of complex hyperplasia and more severe versus simple hyperplasia or less severe was 88.0%. By comparison, current study is in agreement at least partially that panel assessment can change the original impressions about endometrial biopsy. The researcher of the current study believed that the utilization of various systems of classifying pathologies of endometrial biopsies is the cause behind lack of total agreement between original diagnosis and current panel assessment. In other words, it seems that the utilization of the most recent WHO classification system for classifying endometrial lesions must be emphasized among Iraqi pathologist and that the older 1994 WHO system and other older versions dealing with endometrial pathology should be ignored.[97]

Indeed, the recommendation to review the old version of WHO classification of endometrial lesion was based on research work in which inter-observer variation was very obvious. In 2009, Izadi-Mood et al.[98] conducted an investigation involving a cohort of 100 endometrial curettage specimens diagnosed with either endometrial hyperplasia or well-differentiated adenocarcinoma, which were subjected to blind review by five pathologists. The primary objective of this study was to assess the intra- and interobserver reproducibility, and the authors concluded that revisions to the World Health Organization classification pertaining to endometrial hyperplasia and precancerous lesions are warranted.

A recent comprehensive systematic review was conducted by McCoy et al. in 2024, focusing on the factors correlated with interobserver variability among pathologists in the diagnosis of endometrial hyperplasia (99). In the aforementioned investigation, studies that met the eligibility criteria and reported on pathologist-specific variables or professional practices that affect interobserver variability in the diagnosis of EH, utilizing either the World Health Organization (WHO) classifications of 2014 or 2020, or the endometrioid intraepithelial neoplasia (EIN) classification system, were incorporated; it was determined that interobserver variability was significantly pronounced even among specialist gynecological pathologists in the majority of the studies.[99]

The pronounced inclination of the panel to diminish the significance of lesions, a discovery that is almost unequivocally detached from the parameters employed for the classification of endometrial hyperplasia (EH) or the nomenclature utilized, constitutes a significant apprehension in the diagnostic process of endometrial biopsy.[97]

A report published in 2006 found that a pathology panel frequently downgraded diagnoses of AH to less severe categories, although only 7% of biopsies were reclassified as Negative.[100] Skov et al.[101] reported significant lack of agreement among 6 European experts in the interpretation of 128 consecutive curettages originally reported as EH. In another study focusing exclusively on the reproducibility of AH diagnoses, a 3-member pathology panel agreed unanimously with the original diagnosis of AH in only 15% of specimens.[100]

To the best of our knowledge, this is the first Iraqi report raising the issue of inter-observer variability in categorizing endometrial biopsies and highlighting the role of panel diagnosis approach in downgrading the over-estimated rate of endometrial hyperplasia without atypia diagnosis. Another point of strength in the current study is the inclusion of a relatively large sample size of benign endometrial lesions enhancing the power of statistics of this academic work.Probably, the most important limitation of the current study is being a single center study in which only cases in Al-Najaf province.

6. CONCLUSIONS AND RECOMMENDATIONS

6.1. Conclusions

1. Proliferative endometrium is under diagnosis to a negligible extent.
2. Significant underestimation of disordered proliferative endometrium.
3. There is substantial overestimation of endometrial hyperplasia without atypia which may lead unnecessary close follow up and or medical and surgical therapeutic interventions.

6.2. Recommendations

1. Careful handling of endometrial sampling and adequate material are recommended to avoid overestimation and/or under estimation of particular endometrial pathology.
2. The conduction of a future study comparing the results of endometrial sampling to those of hysterectomy results to evaluate the reliability of endometrial sampling in defining endometrial pathology.
3. A larger sample size and multiple centers study is needed to validate the results of the present study.

ACKNOWLEDGEMENTS

Thanks Allah whose will and guide, enabled me to complete this thesis.

The completion of this project could not have been accomplished without the support of my supervisor

Professor Dr. Rihab Hameed. I would like to take this opportunity to express my profound gratitude and deep regard to her, for her exemplary guidance, valuable feedback and constant encouragement throughout the duration of the project.

Deep thanks and appreciations are to be expressed to Dr. Azhar Naji Mohammed Hassan Alnajim for her help in accomplishing this thesis.

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الخلاصة

مقدمة: من المعروف جيدًا أن تفسير خزعات بطانة الرحم بين أخصائيي علم الأمراض أمرٌ صعب. حتى عام ٢٠٠٨، كان تشخيص فرط تنسج بطانة الرحم من خلال أخذ عينات من بطانة الرحم يمثل تحدياتٍ كبيرةً نظرًا للاختلافات التشخيصية الكبيرة التي تتأثر بكفاية العينة وتفسير الخصائص النسيجية الموجودة.

هدف الدراسة:دراسة مراجعة لمدة ثلاث سنوات لتقييم انتشار التشخيص غير المقدر والمبالغ فيه لبطانة الرحم التكاثرية وبطانة الرحم التكاثرية المضطربة وفرط تنسج بطانة الرحم دون خلل نمطي بين النساء حول سن اليأس مع نزيف الرحم غير الطبيعي وفقًا لأحدث تحديث في معايير التشخيص.

المواد وطرق العمل: في هذه الدراسة المقطعية الرصدية، تم جمع 178 عينة نسيجية مغلفة بالفورمالين ومغطاة بالبارافين (FFPE) وشرائح ملطخة بالهيماتوكسيلين والإيوزين بأثر رجعي من مريضات عراقيات يعانين من نزيف رحمي غير طبيعي يعانين من فرط تنسج بطانة الرحم دون خلل في النسيج، وبطانة رحم تكاثرية مضطربة وبطانة رحم تكاثرية.

النتائج: كشفت التشخيصات الأصلية لبطانة الرحم أن 40.4% من الحالات (72 من أصل 178) تم تشخيصها على أنها بطانة رحم تكاثرية، و3.4% (6 من أصل 178) على أنها بطانة رحم تكاثرية مضطربة، و56.2% (100 من أصل 178) على أنها فرط تنسج بطانة الرحم دون خلل نمطي. بلغ العدد الإجمالي للحالات التي تم تحليلها 178 حالة، وهو ما يمثل 100% من العينة. أظهرت تشخيصات لجنة علم الأمراض على مدى ثلاث سنوات أن 39.9% من الحالات (71 من أصل 178) شُخِّصت على أنها بطانة رحم تكاثرية، و24.2% (43 من أصل 178) على أنها بطانة رحم تكاثرية مضطربة، مع دلالة إحصائية (Sig.) قدرها 0.01، و36.0% (64 من أصل 178) على أنها فرط تنسج بطانة الرحم دون خلل نمطي، مع دلالة إحصائية قدرها 0.03. أما بالنسبة لبطانة الرحم التكاثرية، فقد سُجِّل نقصان ثابت في التقدير بنسبة 1.1% على مدى فترة الثلاث سنوات و 2.8 % لعام 2023 (p=0.01)، دون ملاحظة أي زيادة في التقدير. في المقابل، يُظهر فرط تنسج بطانة الرحم دون خلل نمطي مبالغة كبيرة، بنسبة 20.2% خلال فترة الثلاث سنوات، و23.5% في عام 2021، و28.5% في عام 2022، و11.2% في عام 2023، وجميعها ذات دلالة إحصائية (p=0.01). يُظهر اضطراب بطانة الرحم التكاثرية مبالغة ضئيلة في التقدير (0.6%) في تحليل الثلاث سنوات و1.4% عام 2023، دون ملاحظة أي نقص في التقدير. تشير البيانات إلى اتجاهات ثابتة من نقص التقدير في بطانة الرحم التكاثرية والمبالغة في التقدير في فرط تنسج بطانة الرحم دون خلل نمطي، مع دلالة إحصائية في معظم الحالات.

الاستنتاجات: لا يُشخص فرط تنسج بطانة الرحم التكاثرية بشكل كافٍ إلى حدٍ يُذكر؛ ولكن هناك مبالغة كبيرة في تقدير فرط تنسج بطانة الرحم دون خلل نمطي، مما قد يؤدي إلى متابعة دقيقة غير ضرورية أو تدخلات علاجية طبية وجراحية

وزارة التعليم العالي والبحث العلمي المجلس العراقي للاختصاصات الطبية

طيف اضطرابات بطانةالرحم التكاثرية وفرط تنسج بطانةالرحم دون خلل في النمطية لدى النساء حول سن اليأس. دراسة مراجعة نسيجية مرضية امتدت لثلاث سنوات

اطروحه

مقدمه الى المجلس العراقي للاختصاصات الطبية - كجزء من متطلبات الحصول على درجة زميل المجلس العراقي للاختصاصات الطبية في اختصاص النسيج المرضي

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استاذة واستشارية في النسيج المرضي

2025 A.D. **1446 A.H.**