ISBN 978-985-21-2319-8

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MENSTRUAL FUNCTION AND ITS DISORDERS

Minsk BSMU 2026

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА АКУШЕРСТВА И ГИНЕКОЛОГИИ
С КУРСОМ ПОВЫШЕНИЯ КВАЛИФИКАЦИИ И ПЕРЕПОДГОТОВКИ

С. А. Павлюкова, С. В. Жуковская

МЕНСТРУАЛЬНАЯ ФУНКЦИЯ И ЕЕ НАРУШЕНИЯ

MENSTRUAL FUNCTION AND ITS DISORDERS

Учебно-методическое пособие

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УДК 618.17-008.8(075.8)=111
ББК 57.16я73
П12

Рекомендовано Научно-методическим советом университета в качестве учебно-методического пособия 15.04.2026 г., протокол № 8

Р е ц е н з е н т ы: канд. мед. наук, доц., зам. директора по научной работе Республиканского научно-практического центра «Мать и дитя» И. В. Курлович; каф. акушерства и гинекологии Гродненского государственного медицинского университета

Павлюкова, С. А.

П12 Менструальная функция и ее нарушения = Menstrual function and its disorders : учебно-методическое пособие / С. А. Павлюкова, С. В. Жуковская. – Минск : БГМУ, 2026. – 48 с.

ISBN 978-985-21-2319-8.

Изложены основные сведения о нейрогуморальной регуляции менструального цикла, этиологии, патогенезе, классификации нарушений менструальной функции, клинических проявлениях, диагностике, дифференциальной диагностике, методах лечения и профилактики аменореи, дисменореи, аномальных маточных кровотечений.

Предназначено для специальности «Лечебное дело» медицинского факультета иностранных учащихся по учебной дисциплине «Акушерство и гинекология».

УДК 618.17-008.8(075.8)=111
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Учебное издание

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На английском языке

Ответственная за выпуск Л. Ф. Можейко
Переводчики С. А. Павлюкова, С. В. Жуковская
Компьютерная вёрстка Н. М. Федорцовой

Подписано в печать 15.07.26. Формат 60×84/16. Бумага писчая «Марафон Бизнес». Ризография. Гарнитура «Times». Усл. печ. л. 2,79. Уч.-изд. л. 2,8. Тираж 38 экз. Заказ 415.

Издатель и полиграфическое исполнение: учреждение образования «Белорусский государственный медицинский университет». Свидетельство о государственной регистрации издателя, изготовителя, распространителя печатных изданий № 1/187 от 24.11.2023. Ул. Ленинградская, 6, 220006, Минск.

ISBN 978-985-21-2319-8

ABBREVIATIONS

AFC — antral follicle count
AMH — anti-müllerian hormone
AUB — abnormal uterine bleeding
COCs — combined oral contraceptives
COX2 — cyclooxygenase-2
FHA — functional hypothalamic amenorrhea
FSH — follicle-stimulating hormone
GnRH — gonadotropin-releasing hormone
HMB — heavy menstrual bleeding
HPA-axis — hypothalamus-pituitary-adrenal axis
HPO-axis — hypothalamus-pituitary-ovarian axis
LH — luteinizing hormone
NSAIDs — nonsteroidal anti-inflammatory drugs
PCOS — polycystic ovarian syndrome
PID — pelvic inflammatory disease
POI — premature ovarian insufficiency
SHBG — sex hormones binding globulin
SPRM — selective progesterone receptor modulators
TSH — thyroid-stimulating hormone

MOTIVATIONAL CHARACTERISTIC OF THE SUBJECT

Theme of the seminar: "Menstrual function and its disorders". The material is apprehended according to the thematic seminar plan for specialty 1-79 01 01 "General Medicine" of the Faculty of Medicine for International Students in the academic discipline "Obstetrics and Gynecology".

Problem review. The menstrual cycle is a complex, rhythmic biological process that serves as a vital sign of female reproductive health. Orchestrated by the hypothalamic-pituitary-ovarian (HPO) axis, the cycle relies on precise feedback loops involving gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and progesterone. For medical students and clinicians, a thorough understanding of this physiological regulation is not merely academic — it is the cornerstone of diagnosing and managing a vast array of gynecologic and systemic conditions. When the HPO axis functions correctly, it facilitates ovulation and prepares the endometrium for potential pregnancy. However, disruptions in this delicate endocrine symphony manifest as menstrual disorders that affect millions of women globally, influencing physical health, psychological well-being, and socioeconomic status.

Menstrual disorders, ranging from the absence of menses to debilitating pain and excessive bleeding, are among the most common reasons women of reproductive age seek medical care. These disturbances are not trivial annoyances but are frequently indicative of underlying pathology, such as endocrine disorders, coagulopathies, or anatomic abnormalities.

Amenorrhea, the absence of menstruation, serves as a critical diagnostic signal. Whether primary (failure to reach menarche) or secondary (cessation of previously established regular or irregular menstrual cycles), amenorrhea often points to severe dysfunction within the HPO axis, anatomical obstructions, or other underlying issues such as thyroid disorders or hyperprolactinemia. Beyond its reproductive implications, prolonged hypoestrogenic amenorrhea poses significant long-term health risks, particularly regarding bone mineral density and cardiovascular health.

Dysmenorrhea, or pathologically painful menstruation, represents a pervasive yet often ignored public health issue. As detailed in subsequent sections, it affects a vast proportion of the female population — estimated prevalence ranging between 50 % and 90 % worldwide. While often dismissed as a "normal" part of womanhood, severe dysmenorrhea is a leading cause of recurrent absenteeism from school and work, resulting in billions of dollars in lost productivity annually. Furthermore, secondary dysmenorrhea can be the first presenting symptom of progressive conditions like endometriosis, where delayed diagnosis can lead to chronic pelvic pain and infertility.

Heavy menstrual bleeding (HMB), formerly known as menorrhagia, affects approximately one-third of women at some point during their reproductive lives. It is a primary cause of iron-deficiency anemia globally, contributing to fatigue, cognitive impairment, and decreased physical performance. The etiology of HMB is diverse, ranging from structural causes like uterine fibroids and polyps to non-structural causes like coagulopathies and ovulatory dysfunction. In low-resource settings, the burden of HMB is compounded by limited access to menstrual hygiene products and medical management, exacerbating social stigma and gender inequality.

Therefore, the collective impact of these disorders on global female health is profound. Menstrual disturbances are associated with a significantly decreased quality of life and increased rates of anxiety and depression. By mastering the physiology of the menstrual cycle and recognizing the pathophysiology behind its disturbances, clinicians can move beyond symptom management. Early and accurate intervention allows for the preservation of fertility, the prevention of long-term sequelae such as anemia and osteoporosis, and a substantial improvement in the daily lives of patients. Thus, competence in this area is essential for any provider involved in the primary or specialty care of women.

Total duration of the lesson: 6 hours.

Aim of the lesson: provide detailed information concerning physiology of the menstrual cycle; etiology, pathogenesis, diagnosis (including differential diagnosis), treatment and prevention of such common menstrual cycle disturbances as amenorrhea, dysmenorrhea and heavy menstrual bleeding.

Goals of the lesson:

1. Study neurohormonal regulation of a normal menstrual cycle.
2. Learn up-to-date classification of menstrual cycle disturbances such as dysmenorrhea, amenorrhea and heavy menstrual bleeding.
3. Study etiology, pathogenesis, diagnosis (including differential diagnosis), treatment and prevention of dysmenorrhea.
4. Study etiology, pathogenesis, diagnosis (including differential diagnosis), treatment and prevention of amenorrhea.
5. Study etiology, pathogenesis, diagnosis (including differential diagnosis), treatment and prevention of abnormal uterine bleeding in different periods (adolescence, reproductive period, peri- and menopause).

Basic knowledge requirements. For successful learning a student must revise earlier studied material in:

– human anatomy: anatomy of central nervous system (hypothalamus, pituitary gland), female reproductive tract;

– normal physiology of central nervous system (hypothalamus, pituitary gland, thyroid gland, ovaries, adrenals);

– biological and bioorganic chemistry: structure and functions of hormones and other biologically active substances involved in menstrual cycle regulation.

Control questions on related disciplines:

1. Normal menstrual cycle and its regulation.
2. Classification of menstrual cycle disturbances: amenorrhea, dysmenorrhea and heavy menstrual bleeding.
3. Etiology, pathogenesis, diagnosis (including differential diagnosis), treatment and prevention of dysmenorrhea.
4. Etiology, pathogenesis, diagnosis (including differential diagnosis), treatment and prevention of amenorrhea.
5. Etiology, pathogenesis, diagnosis (including differential diagnosis), treatment and prevention of abnormal uterine bleeding.

Control questions on the topic of the class:

1. Describe the involvement of HPO-axis in the regulation of menstrual cycle.
2. Describe etiology, pathogenesis, current classification, approach to diagnosis (including differential diagnosis), treatment and prevention of dysmenorrhea.
3. Describe etiology, pathogenesis, current classification, approach to diagnosis (including differential diagnosis), treatment and prevention of amenorrhea.
4. Describe etiology, pathogenesis, current classification, approach to diagnosis (including differential diagnosis), treatment and prevention of abnormal uterine bleeding.

NORMAL MENSTRUAL CYCLE AND ITS REGULATION

The ***normal menstrual cycle*** is a finely coordinated cyclic process of stimulating and inhibiting effects that lead to the release of one mature egg and associated with physiological changes in the body under hormonal effect. Various factors involved in the regulation of this process, including hormones, paracrine, and autocrine factors, are identified so far.

The most noticeable aspect of the female reproductive system is ***menstruation***, or the visible manifestation of cyclic physiologic uterine bleeding due to shedding of the endometrium, which occurs alongside a series of coordinated hormonal shifts. First menstruation, also known as ***menarche***, typically starts around puberty with a median age of 12.4.

The regulation of the menstrual function passes through a complex neurohumoral path. According to modern concepts, cyclic changes in the body of a woman are related to the implementation menstrual function and occur with the obligatory participation of 5 levels of regulation. Each of them is regulated by the structures located above according to the mechanism of positive and negative feedback.

Menstrual cycle. The menstrual cycle is a highly regulated physiological process in which the coordinated release of hormones from the hypothalamus, pituitary gland, and ovaries produces a mature oocyte and prepares the endometrium for blastocyst implantation.

According to the International Federation of Gynecology and Obstetrics (FIGO), normal menstrual cycles should have consistent frequency, regularity, duration, and volume of flow.

Normality of menstrual cycle:

1. 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.

2. Menstrual duration is defined as bleeding lasting 3–8 days, while bleeding beyond 8 days is considered prolonged menses.

3. The volume of menstrual flow is equal 30–80 mL per cycle and classified as light, normal, or heavy. No defined objective thresholds separate these classifications, as they are often impractical in clinical settings. heavy menstrual bleeding is defined as blood loss exceeding 80 mL per cycle, based on weighed menstrual products. 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.

4. Menstrual regularity is defined by the variation in cycle duration from one cycle to the next and average duration is 28 days with fluctuation from 24 to 38 days. 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.

5. Ovulation is one of the parameter of normal menstrual cycle. It means that should be 2 phases and ovulation. Anovulatory cycle (even regular) is abnormal.

Menstrual cycle includes simultaneous changes in the ovaries (ovarian cycle) and the uterus (uterine cycle).

Ovarian cycle consists of the development and maturation of a follicle, ovulation and formation of corpus luteum and its degeneration.

Thus, the ovarian cycle consists of: 1) recruitment of groups of follicles; 2) selection of dominant follicle and its maturation; 3) ovulation; 4) corpus luteum formation, degeneration of the corpus luteum.

Ovarian cycle has 2 phases, regulated by hormones released from the hypothalamus and pituitary gland:

– follicular phase: production and maturation of a dominant follicle;

– luteal phase: formation and degeneration of the corpus luteum.

The follicular phase begins from the first day of menses until ovulation. The development of ovarian follicles (folliculogenesis) begins at the last days of menstrual cycle before the release of mature follicle during ovulation (Fig. 1).

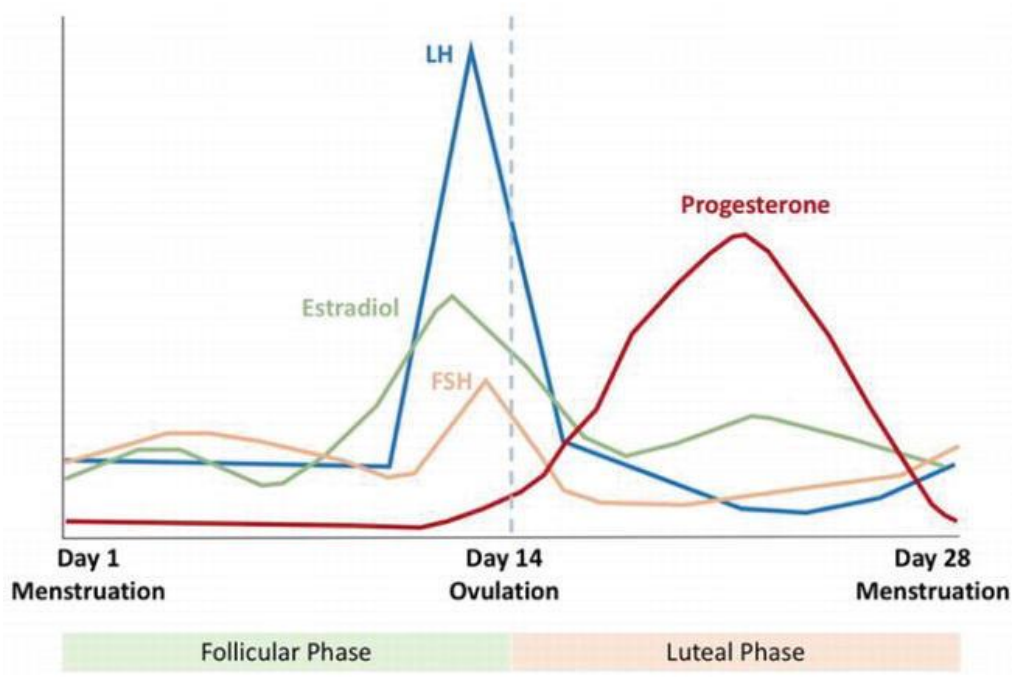


Fig. 1. Ovarian cycle: hormonal changes

Recruitment of groups of follicles or preantral phase is a process of development and differentiation of the cohort of the growing follicles which takes about 85 days and spreads over 3 ovarian cycles. The initial recruitment and growth of primordial follicles are not under the control of any hormone. After a certain stage (2–5 mm) the growth and differentiation of primordial follicles are

under the control of FSH. Unless the follicles are rescued by FSH at this stage, they undergo ***atresia*** (Fig. 2). Predominant change in the oocyte includes enlargement to the size of the follicle. The oocyte becomes surrounded by an acellular barrier of glycoprotein produced by the follicular cells (zona pellucida). The flattened outer single layer pregranulosa cells become cuboidal and multilayered (granulosa cells). Through channels (gap junctions) between the granulosa cells and the oocyte nutrition to the oocyte is maintained. There is noticeable beginning of differentiation of the theca interna layer of ovarian stroma surrounding the follicle. The granulosa cells now acquire *FSH receptors*.

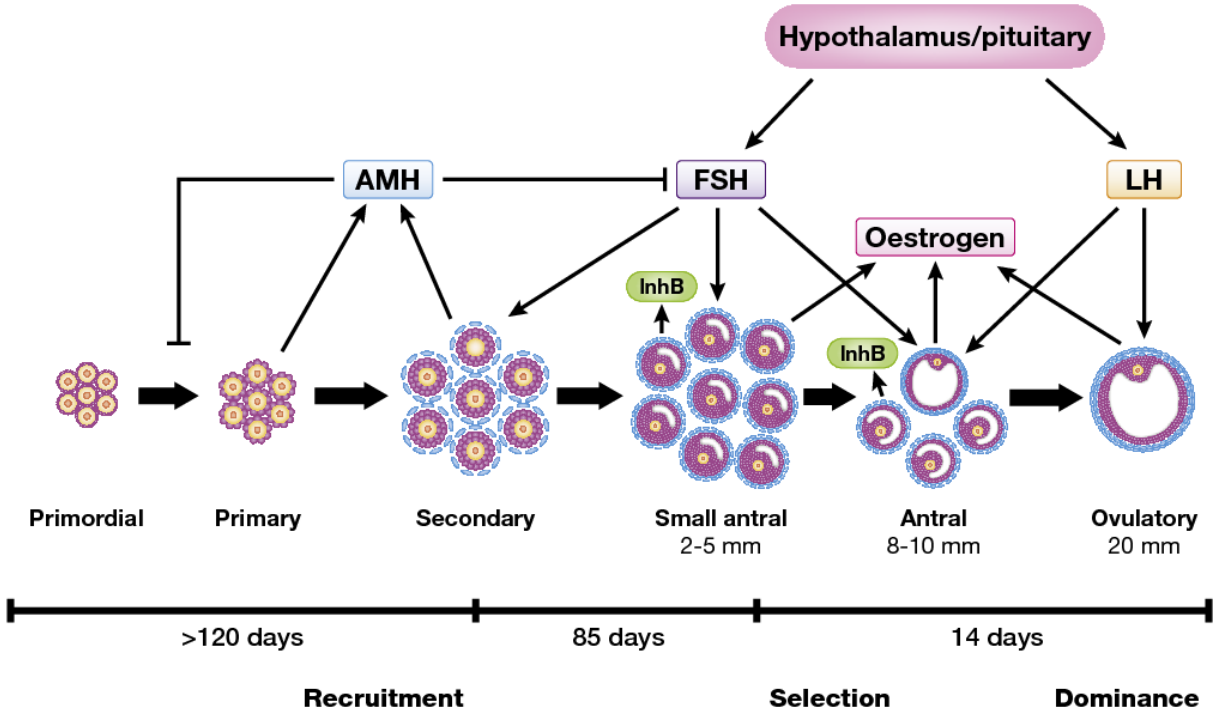


Fig. 2. Recruiting, selection, and ovulation of dominant follicle

During the follicular phase, FSH is responsible for recruitment among those follicles that remain available. Between days 5 and 7 of the cycle, follicular selection normally occurs, to allow only one follicle, the dominant follicle to ovulate and the rest to experience atresia. Anti-müllerian hormone (AMH), which is secreted in the granular layer, also participates in the selection of dominant follicle. On day 8 of the cycle, the dominant follicle promotes its own growth, suppressing the maturation of the other ovarian follicles.

During the follicular phase, estradiol plasma levels are higher along with the growth of the number of granulosa cells and the growth of the dominant follicle. FSH receptors are found exclusively in the cell membrane of granulosa cells. The increase in FSH during the late luteal phase induces its own FSH receptors and eventually increases the secretion of estradiol by the granulosa cells by transforming androstenedione, which diffuses from the theca cells (Fig. 3).

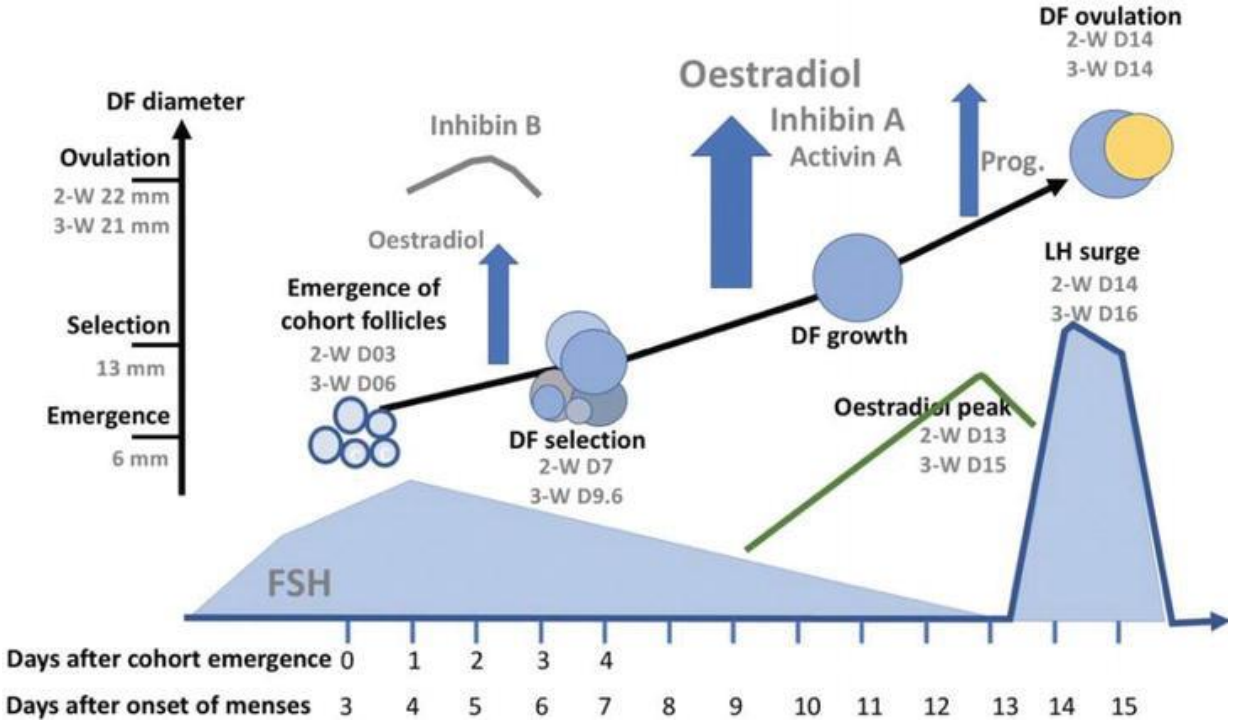


Fig. 3. Scheme of follicular and gonadotropins, steroids, and inhibins changes during follicular phase of menstrual cycle

It is important to point out that the increase in the numbers of receptors of FSH is due to an increase in the population of granulosa cells and not to an increase of the concentration of receptors of FSH on them. The increase in estradiol secretion also upregulates their own receptors, increasing the total of estradiol receptors (ER) in the granulosa cells. On the other hand, in the presence of estradiol, FSH stimulates the formation of LH receptors in the same cells, which allows the secretion of small amounts of progesterone and 17-hydroxyprogesterone (17 OHP) that would exert positive feedback on the pituitary gland. Already sensitized by the increase of estrogen, thus allowing the release of luteinizing hormone (LH) and achieve its peak. FSH also stimulates many steroidogenic enzymes such as aromatase and 3β-hydroxysteroid dehydrogenase (3β-HSD).

There are other signaling pathways that impact the differentiation of theca cells, the circadian clock genes, androgens, and estrogens and theca-associated vascular, immune and fibroblast cells, as well as the cytokines and matrix factors that play key roles in follicle growth.

Differently from granulose cells, LH receptors are localized at theca cells during all of the stages of menstrual cycle. LH receptors stimulate granulosa's cells. LH stimulates the production of androstenedione and at a lesser level the production of testosterone at the theca cells. Androstenedione is then transported to the cells of granulosa where it is aromatized, and finally, it becomes estradiol 17-β-hydroxysteroid dehydrogenase type I. This is known as *the hypothesis of two cells and two gonadotropins of the regulation of synthesis on the ovary* (Fig. 4).

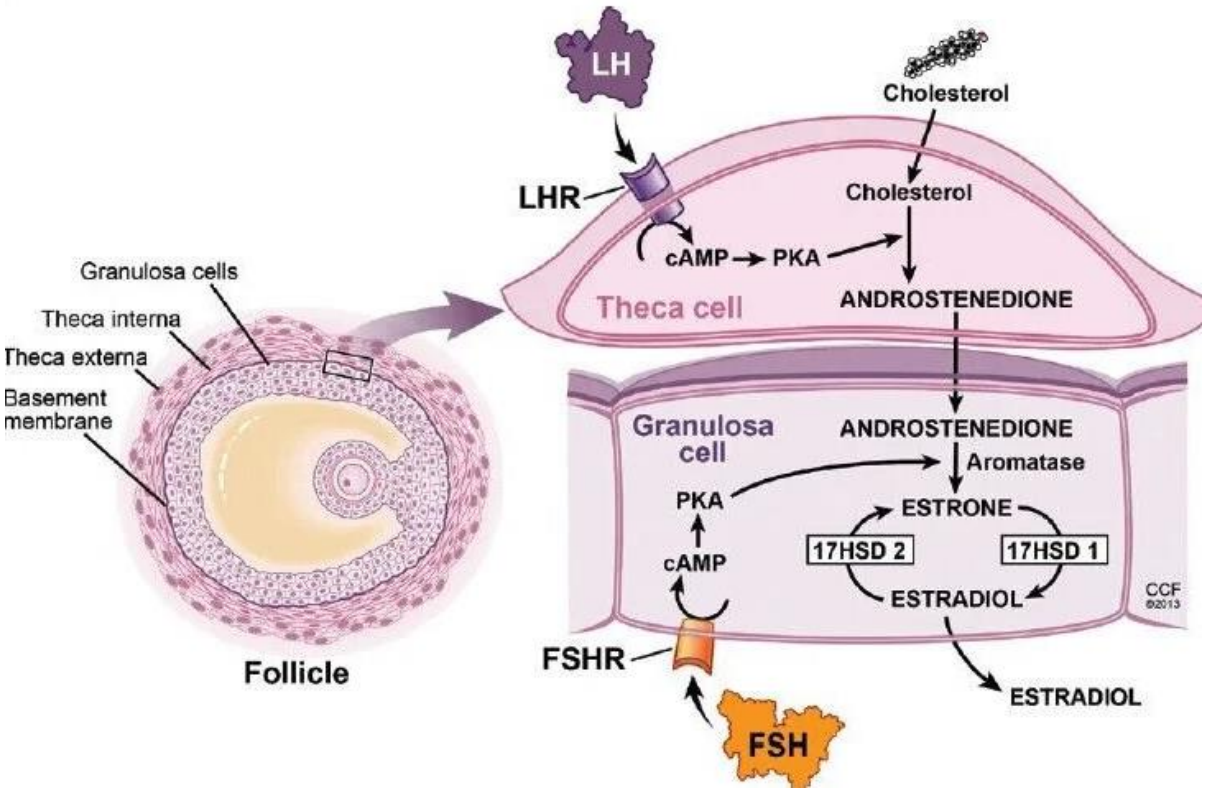


Fig. 4. Two cells and two gonadotropins theory, on the regulation and the synthesis of estrogens at the ovary

The normal follicular phase is divided in two stages: early and middle, and late.

Early follicular phase (days 1–4): it begins with the first day of menstruation. Follicular recruitment occurs due to the elevation of FSH, as a consequence of the *decrease in estradiol, progesterone, and inhibin A released by the corpus luteum of the previous cycle*, allowing the number of LH receptors to increase in the cells of the teak and the granulosa. The plasma levels of estradiol remain low at this stage.

Medium follicular phase (days 5–7): as the recruitment and growth of follicles induced by FSH progress, estradiol increases progressively. The follicle that achieves the highest number of FSH receptors may aromatize more estradiol and become *the dominant follicle*. The other follicles, with fewer receptors for FSH, undergo atresia. For estrogen synthesis, it is necessary for the thecal cells to produce androgens, under the stimulus of LH, and for these to diffuse to the granulosa cells. Simultaneously, two glycoproteins, *activin* and *inhibin*, are produced in the theca and granulose, with local actions. Inhibin B exerts a negative pituitary feedback effect, where it potentiates the effect of estradiol and inhibits the synthesis and release of FSH. This would be a mechanism to achieve dominance giving an advantage to the follicle that has greater development. The estrogen take-off marks the successful establishment of the dominance of a follicle.

The dominant follicle develops its internal theca and increases receptivity to LH, which stimulates the production of androgens by degrading molecules of

cholesterol to progesterone and from this to dehydroepiandrosterone, androstenedione, and testosterone. At the end of this phase, the granulosa-theca complex of the dominant follicle has almost complete functionality to enter the late follicular phase.

Late follicular phase (days 8–12): is characterized by the elevation of estrogens from the dominant follicle, reaching its maximum values between 40 and 50 hours, before an elevation of FSH that precedes the ovulatory peak of LH. This preovulatory follicle reaches an average diameter of 20 mm. The follicular fluid is increased in amount. The fluid contains estrogens, FSH, trace amount of androgen, prolactin, oocyte maturation inhibitor, luteinization inhibitor, inhibin which acts centrally to inhibit FSH, proteolytic enzymes, plasmin, etc.

The fully mature Graafian follicle just prior to ovulation is composed of the following structures from outside inward (Fig. 5):

a) theca externa;

b) theca interna;

c) membrana granulosa (limitans);

d) granulosa cell layer;

e) discus proligerus in which the ovum is incorporated with cells arranged radially (corona radiata);

f) antrum containing vesicular fluid.

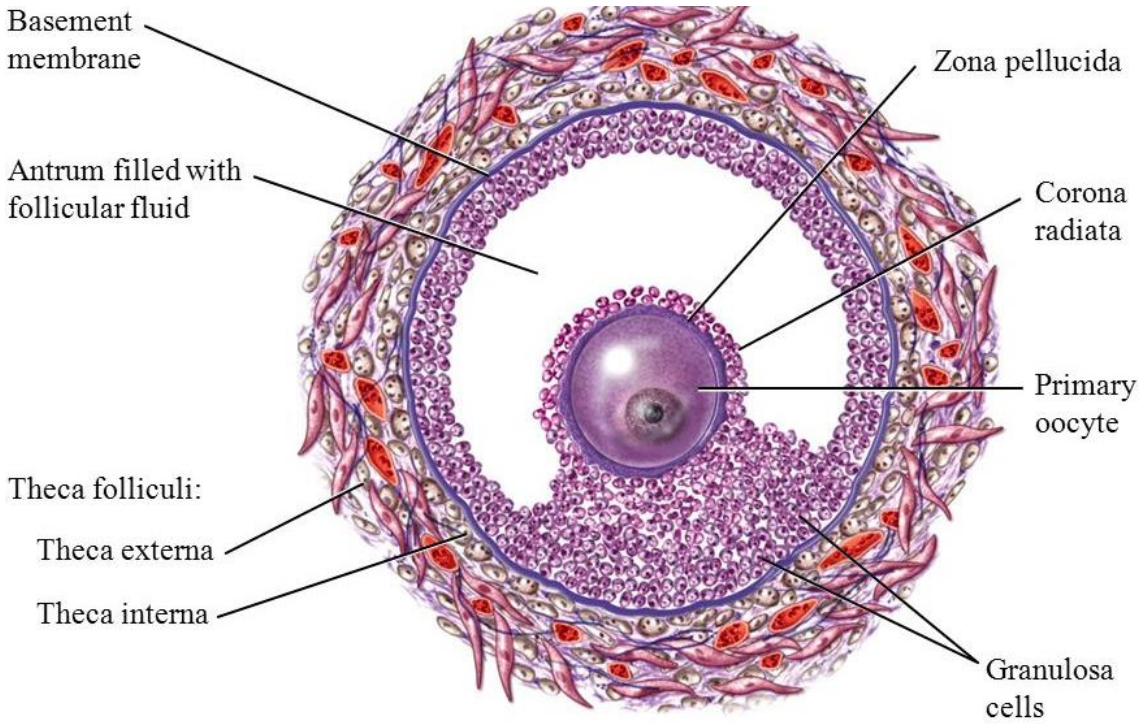


Fig. 5. Mature (Graafian) follicle

Ovulation. The dominant follicle, shortly before ovulation reaches the surface of the ovary. The cumulus becomes detached from the wall, so that the ovum with the surrounding cells (corona radiata) floats in the follicular fluid. The oocyte completes the first meiotic division with extrusion of the first polar

body which is pushed to the perivitelline space. The follicular wall near the ovarian surface becomes thinner. The point of the dominant follicle closest to the ovarian surface where the rupture occurs is called a "stigma." The stigma develops as a conical projection which penetrates the outer surface layer of the ovary and persists for a while (30–120 seconds) as a thin membrane. The cumulus escapes out of the follicle by a slow oozing process, taking about 60–120 seconds along with varying amount of follicular fluid. The stigma is soon closed by a plug of plasma.

Physiology of ovulation:

1. **LH surge:**

– peak level of estrogen (200 and 450 pg/mL) for 24–48 hours in the preovulatory follicle results in LH surge from the anterior pituitary (positive feedback) (Fig. 1);

– the increase in LH occurs *34–36 hours before ovulation* and is a very reliable predictor (trigger) of ovulation;

– this LH surge is responsible for the luteinization of granulosa cells that stimulates the synthesis of progesterone and also estradiol, synthesis of prostaglandins;

– the LH increase resumes the second meiotic division and the chromosomal reduction in the oocyte with the release of the first polar corpuscle.

2. **FSH surge:** preovulatory rise of 17 OHP facilitates the positive feedback action of estrogen to induce FSH surge that result in increase in plasminogen activator, plasminogen, plasmin and helps lysis of the wall of the follicle.

Follicle rupture is also due to the following factors:

1. Prostaglandins induce the hyperemia and edema that result from increased blood flow and vascular permeability.

2. Protease activity (collagenases and plasminogen activator) leads to the degradation of the follicular layers and wall.

3. Plasmin helps in detaching the cumulus cell-enclosed oocyte from the granulosa cells, which initiates the process of extrusion of the oocyte and cumulus.

Luteal phase. This phase is always constant and lasts 12–14 days after ovulation. The granulosa cells acquire a vacuolated appearance and a characteristic yellow color due to the concentration of a carotenoid called *lutein* and the incorporation of fat drops. The luteinized cells combine with the newly formed theca-lutein cells together with the surrounding stroma; thus, originates the transitory endocrine organ that secretes progesterone, known as *the corpus luteum*.

8–9 days following ovulation, at the time when implantation is expected, the corpus luteum attains a size of about 1–2 cm and reaches its secretory peak, maximum vascularization is reached, and the capillaries invade the granulosa cell layers in response to the secretion of angiogenic factors, both from the granulosa and from the theca cells, in harmony with the maximum levels of plasma progesterone and estradiol (Fig. 6).

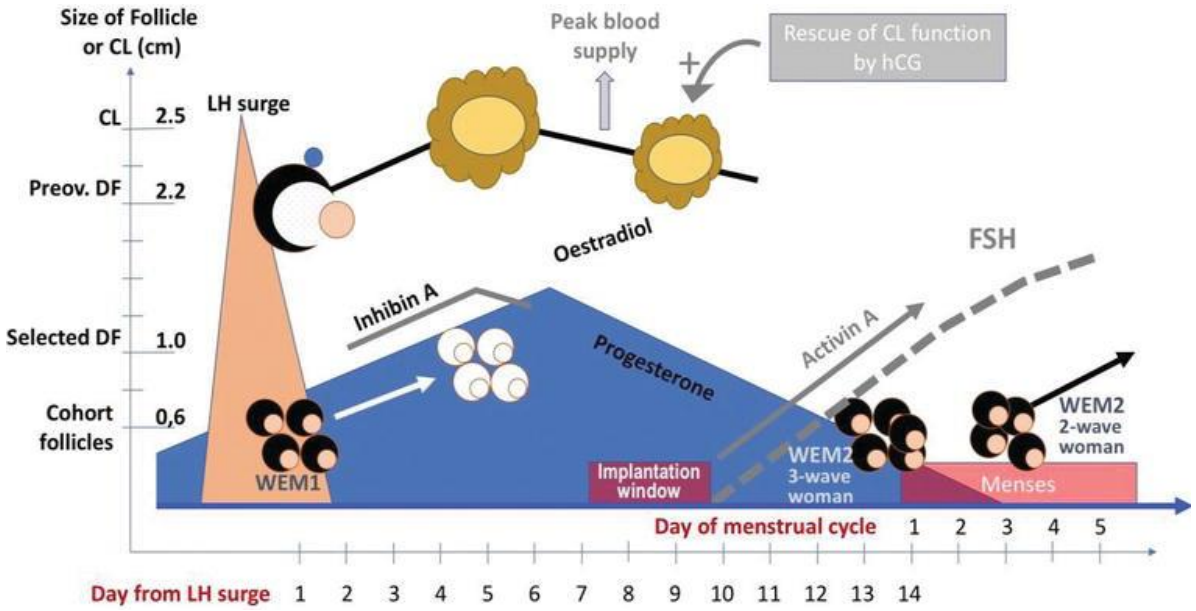


Fig. 6. Scheme of follicular and hormonal changes during luteal phase

Hormonal changes for formation and maintenance of corpus luteum:

1. FSH in presence of high level of estrogen induces LH receptors in the granulosa cells of the dominant follicle.

2. LH surge causes luteinization of the granulosa cells and progesterone secretion. LH secretion stimulates the function of corpus luteum.

3. Adequate folliculogenesis in the preovulatory phase with increased estradiol and of 17-OHP is essential for adequate corpus luteum formation.

The function of the corpus luteum decreases on the day 22–23 of cycle, unless chorionic gonadotropin appears due to an eventual pregnancy. If pregnancy does not occur, the corpus luteum undergoes luteolysis. Under the action of estradiol and prostaglandins, it forms a scar tissue called *corpus albicans*. Corpus luteum has a life span of about **12–14 days**. The cause of degeneration of corpus luteum in an infertile cycle is associated with prostaglandin F2α which has a luteolytic action, through the synthesis of endothelin-1 that inhibits steroidogenesis and stimulates the release of a growth factor, the tumor necrosis factor alpha, oxytocin, and vasopressin and produces a luteotropic effect through an autocrine/paracrine mechanism. Estradiol is also considered to have luteolytic effect. The role of prolactin is not clear.

Uterine cycle. The endometrium (the epithelium of the uterine cavity) consists of ciliated epithelium, glands, stroma and blood vessels. There are two anatomical layers — basal zone (stratum basalis) and the superficial functional zone.

Basal zone of the endometrium contacts with the myometrium. It consists of stromal cells which stain deeply and are compactly placed. The base of the endometrial glands extends into the layer. The zone is supplied by the basal arteries. After shedding of the superficial part during menstruation, the regeneration of all the components occurs from this zone. It measures about 1 mm. Functional zone is under the influence of fluctuating cyclic ovarian

hormones (estrogen and progesterone). The endometrial changes during an ovulatory cycle has been divided into four stages: menstruation; regenerative phase; proliferative phase; secretory phase (Fig. 7).

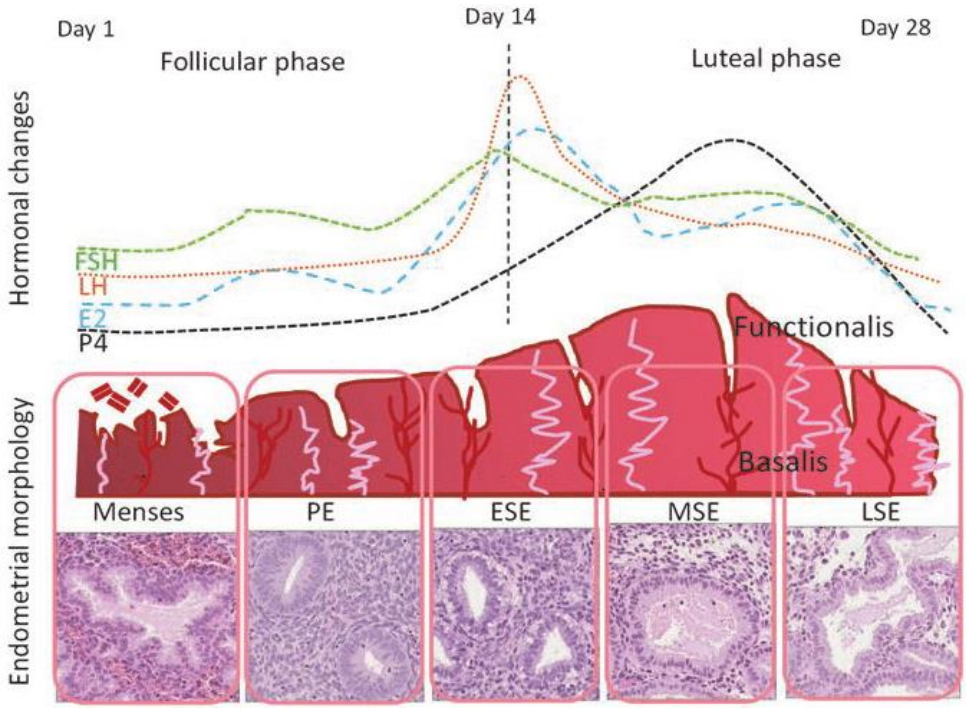


Fig. 7. The endometrial changes during menstrual cycle. PE — proliferative phase, narrow glands with pseudo stratification of nuclei; ESE — early secretory phase, subnuclear vacuoles and reduced proliferation; MSE — mid-secretory phase, dilated glands with secretion in the lumen, stroma is loose, glands tortuous, and only perivascular pseudo decidualization can be observed; LSE, late secretory phase, smaller glands and noticeable decidualization.

Menstruation is a phenomenon of repeated tissue injury and repair that is a fine balance between proliferation, decidualization, inflammation, hypoxia, apoptosis, hemostasis, vasoconstriction and repair and regeneration.

Regenerative phase of the endometrium starts even before the menstruation ceases and is completed 2–3 days after the end of menstruation. The cubical surface epithelium is derived from the gland lumina and stromal cells. New blood vessels grow from the stumps of the old one. The glands and the stromal cells are regenerated from the remnants left in the basal zone. The glands are lined by the cubical epithelium and lie parallel to the surface. The stromal ground substance re-expands. The thickness averages 2 mm.

Proliferative phase (5–14th day) is characterized by hypertrophy and proliferation of glands, increase in stromal matrix, and elongation of terminal arterioles to the endometrial lumen. A gradient of angiogenic factors is released from the endometrial epithelium by estradiol. Estrogen also upregulates the progesterone receptors that orchestrate the environment during the secretory phase. The thickness measures about 3–4 mm.

Secretory phase begins on day 15 and ceases 5–6 days prior to menstruation. The changes of the components are due to the combined effects of estrogen and

progesterone. The endometrium contains receptors for progesterone which are induced by estrogen. The surface epithelium becomes more columnar and ciliated at places. The glands increase in size. The lining epithelium become taller. There is appearance of vacuoles due to secretion of glycogen between the nuclei and the basement membrane. This is called subnuclear vacuolation, which is the earliest (36–48 hours) evidence of progesterone effect (ovulation). The subnuclear vacuolation persists until about 21st day of cycle. The intracellular secretion then enters the gland lumina on the way to the uterine cavity pushing the nuclei back towards the basement membrane. The effect is a saw-toothed glandular epithelium. The fluid has got nutritive value for any fertilized ovum reaching the uterus during that time. The glands become corkscrew-shaped. The blood vessels undergo marked spiraling. The stromal cells become swollen, large and polyhedral and after the 21st day tend to collect more superficially around the neck of the glands. The deeper spongy layer is composed of convoluted glands, coiled arterioles and comparatively few stromal cells in edematous stroma. The thickness of the endometrium reaches its highest (6–8 mm).

The endometrial growth ceases 5–6 days prior to menstruation in an infertile cycle due to dehydration of the glands. The regressive changes in the endometrium are pronounced 24–48 hours prior to menstruation. There is marked spiralling of the arteries and the withdrawal of hormones estrogen and progesterone causes intense spasm of the spiral arterioles at the basal part. These two lead to stasis and tissue anoxemia. There is infiltration of leucocytes and monocytes in the stroma.

Menstruation is essentially degeneration and casting off the endometrium prepared for a pregnancy. Regression of corpus luteum with fall of estrogen and progesterone results in retrogressive changes in the endometrium:

– the degenerative changes are predominantly of vascular origin (stasis of blood and spasm of the arterioles lead to *tissue ischemia* due to decreased blood flow);

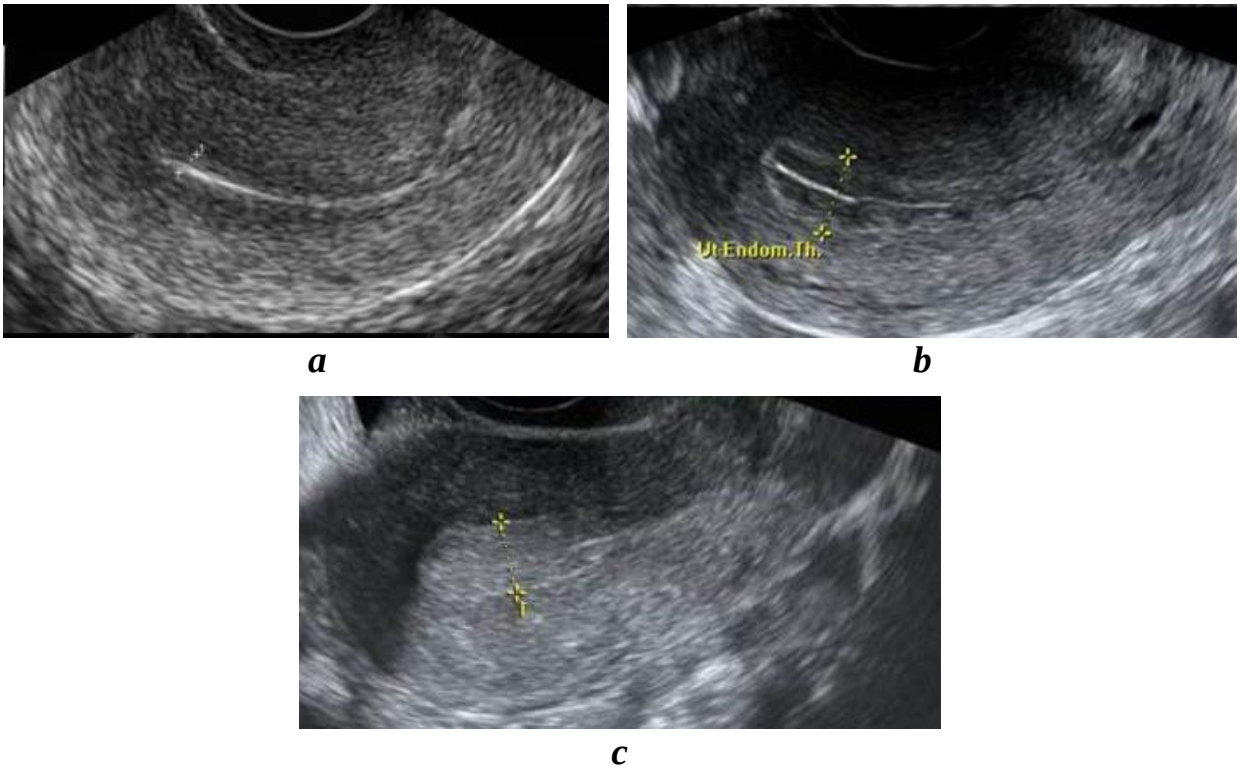
– after the fall of serum steroids concentrations, *matrix metalloproteinases* play a key role in the onset of menstrual bleeding in the endometrium, by inducing the degradation of the extracellular matrix of this mucosa;

– endometrial prostaglandins cause contractions of the uterine smooth muscle and detachment of degraded tissue (the release of prostaglandins may appear due to instability of the lysosomal membranes in the endometrial cells.

Menstrual flow is composed of detachment of endometrial tissue, red blood cells, inflammatory exudates, and proteolytic enzymes. 2 days after the start of menstruation and while the shedding of the endometrium still occurs, the estrogen produced by the new growing follicles begins to stimulate the regeneration of the superficial layers of the endometrium. The estrogen secreted by the growing follicles causes a long constriction of the vessel facilitating the formation of a veil over endometrial vessels.

The endometrial changes that occur can be visualized with sonography. The endometrium in the early prolipherative phase is thin (3–5 mm thickness), linear and echogenic (Fig. 8, *a*). The late prolipherative phase (preovulatory phase) is characterized by thickening of the endometrium and trilaminar appearance and

refers to three refractive lines: 1) central thin, echogenic line; 2) darker echolucent rim in the middle; 3) surrounding echogenic basilar layer. The size of the endometrium is between 6 and 9–11 mm thick (Fig. 8, *b*). Secretory phase is associated with thick, hyperechoic, homogenous endometrium appearance (Fig. 8, *c*).



a ***b***

c

Fig. 8. Types of endometrium in transvaginal ultrasound

Cervix. The mucous secreting glands of the endocervix are affected by the changes in steroid hormone concentration. Immediately after menstruation, the cervical mucous is scant and viscous. During the late follicular phase, under the influence of rising estradiol levels, the cervical mucous becomes clear, copious and elastic. The quantity of cervical mucous increases 30 fold compared to the early follicular phase. The stretchability or elasticity of the cervical mucous can be evaluated between two glass slides and recorded as the spinnbarkeit. If examined under the microscope, the cervical mucous will display a characteristic ferning or palm-leaf arborization appearance. After ovulation, as progesterone levels rise, the cervical mucous once again becomes thick, viscous and opaque and the quantity produced by the endocervical cells decreases.

Vagina. The changes in hormonal levels of estrogen and progesterone also have characteristic effects on the vaginal epithelium. During the early follicular phase, exfoliated vaginal epithelial cells have vesicular nuclei and are basophilic. During the late follicular phase, and the influence of the rising estradiol level, the vaginal epithelial cells display pyknotic nuclei and are acidophilic. As progesterone rises during the luteal phase, the acidophilic cells decrease in number and are replaced by an increasing number of leukocytes.

DYSMENORRHEA

Dysmenorrhea, defined clinically as painful menstruation, is a highly prevalent condition worldwide affecting between 50 % and 90 % of adolescent females and women of reproductive age. Approximately 45 % of patients experiencing these symptoms will initially seek care from a primary care physician and from a gynecologist.

The condition is associated with a reduced quality of life, significant absenteeism, and a significantly increased risk for both depression and anxiety. Up to half of patients with dysmenorrhea report missing school or work at least once due to debilitating symptoms, while 10 % to 15 % experience recurrent absences during their menstrual cycles. While symptoms tend to persist throughout the reproductive years, their severity may diminish over time, particularly following childbirth.

PATHOGENESIS

Dysmenorrhea is classified into two **subtypes**: primary and secondary.

Primary dysmenorrhea is characterized by painful menstruation in the absence of any identifiable pelvic pathology, therefore being purely functional in nature. The underlying pathophysiology is presented in Fig. 9.

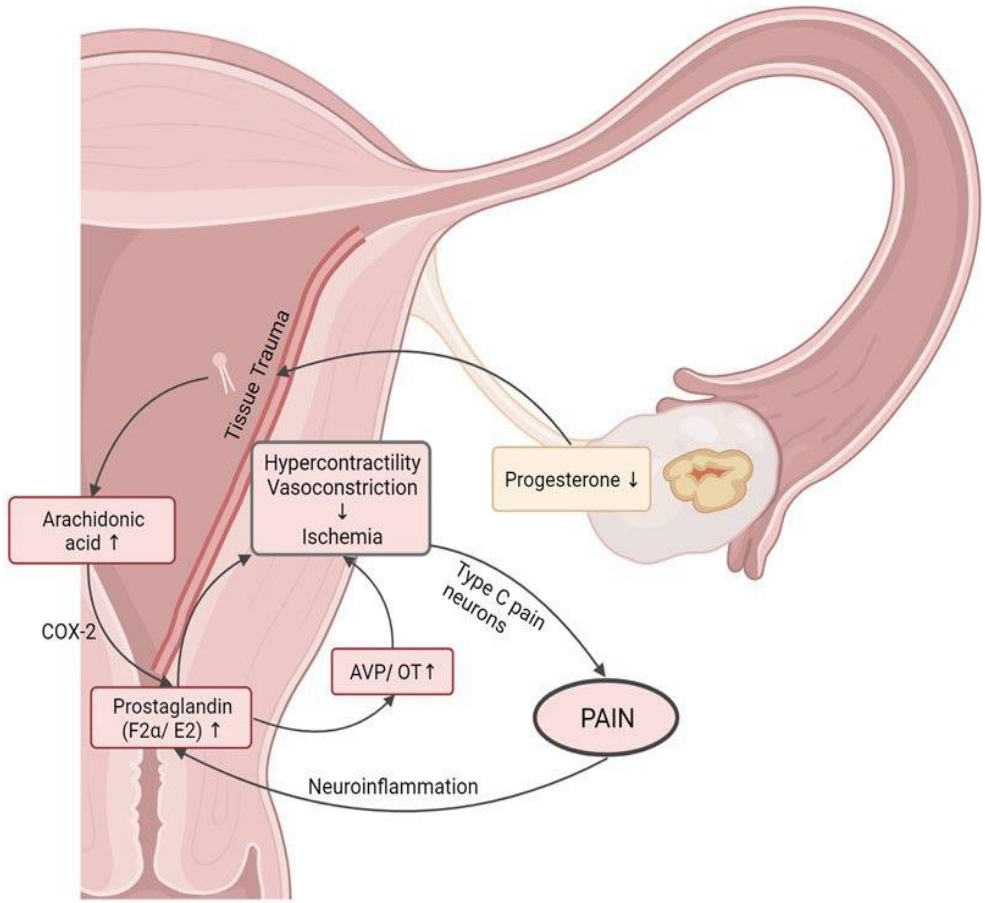


Fig. 9. Pathogenesis of primary dysmenorrhea

The decrease in progesterone happening before menstruation due to regressing corpus luteum triggers endometrial tissue trauma, which results in increased production of arachidonic acid, in turn leading to elevated levels of cyclooxygenase-2 (COX-2), which mediated synthesis of prostaglandins F2a and E2. These pro-inflammatory mediators lead to uterine hypercontractility and vasoconstriction, which provokes tissue ischemia and, through specific type C pain neurons evoke the feeling of pain. Pain, consequently, supports the "vicious cycle" via neuroinflammation.

In contrast, **secondary dysmenorrhea** is caused by underlying pelvic pathology or a specific medical condition, representing approximately 10 % of all dysmenorrhea cases. Endometriosis is the leading etiology of secondary dysmenorrhea both in adolescents and women of reproductive age. Other potential causes include pelvic masses (ovarian tumors, etc.), pelvic inflammatory disease (PID), and both congenital or acquired anatomic abnormalities, such as Müllerian anomalies, uterine fibroids, adenomyosis and other gynecological diseases.

Obviously, secondary dysmenorrhea isn't a specific nosologic and diagnostic entity, but just a symptom of underlying conditions requiring thorough differential diagnosis (Table 1).

Table 1

Differential diagnosis of secondary dysmenorrhea

Pathology	Characteristic signs and symptoms
Endometriosis	Pain closely connected with menstrual cycle phases (increasing before and during menstruation); painful intercourse, urination or bowel movements; infertility
Adenomyosis (uterine endometriosis)	Heavy bleeding during menstruation often accompanied by blood clots; pain with intercourse; abdominal tenderness; increased uterus which is tender on palpation
Ovarian tumors	Chronic pain of low or moderate intensity that doesn't vary with menstrual cycle; acute intense pain in case of ovarian rupture or torsion; palpable abdominal mass
Uterine polyps	Irregular and/or heavy menstrual bleeding; infertility in case of large polyps, especially blocking the fallopian tubes entrance
Uterine fibroids	Heavy, prolonged menstrual bleeding; constipation or difficulty emptying the bladder in case of large fibroids; palpable abdominal masses
Pelvic inflammatory disease (PID)	Diffuse abdominal pain; fever; vaginal discharge with foul odor; painful intercourse; possible bleeding after intercourse
Congenital obstructive uterine malformations	Primary amenorrhea; pain is cyclic but not accompanied by uterine discharge due to obstruction
Pelvic adhesions	History of prior surgical interventions; infertility; bowel obstruction and/or painful bowel movements; pain changes with change in position
Cervical stenosis	History of prior surgical interventions involving cervix; amenorrhea; infertility

Risk Factors

Several ***factors*** are associated with an increased risk of dysmenorrhea, especially primary, including:

– age under 30 years;
– body mass index (BMI) below 20 kg/m^2;
– tobacco use and “vaping”;
– early menarche (prior to age 12);
– prolonged menstrual cycles;
– heavy menstrual bleeding;
– history of sexual abuse and other psychological disturbances.

The condition also correlates with nulliparity, premenstrual syndrome, and a history of pelvic inflammatory disease.

Conversely, ***protective*** factors include advancing age, higher parity, regular physical activity, and the use of oral contraceptives.

Clinical Presentation

Dysmenorrhea typically manifests as cramping lower abdominal pain that coincides with the onset of menses and persists for 8 to 72 hours. This pain is frequently associated with most common systemic symptoms, such as: nausea, vomiting, diarrhea, headaches, muscle cramps, lumbago, fatigue, sleep disturbances.

Research indicates that nearly half (47 %) of the women affected experience moderate pain, while 17 % rate their pain as severe on a standard visual analogue scale (Fig. 10).

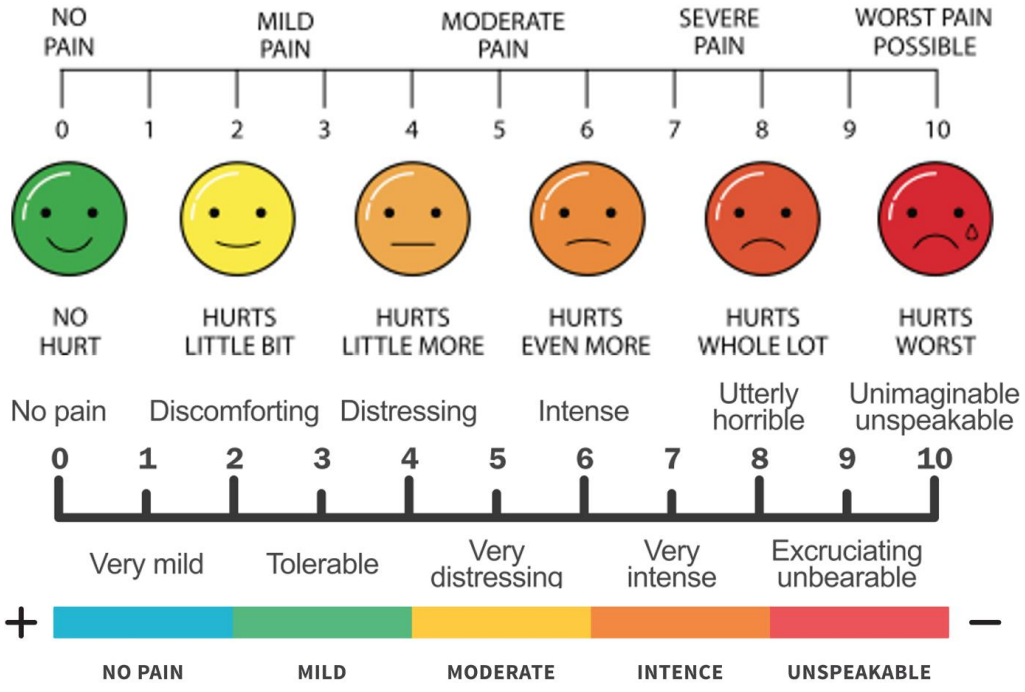


Fig. 10. Visual analogue scale of pain perception

Primary dysmenorrhea generally presents 6 to 12 months after menarche, coinciding with the establishment of ovulatory cycles, and characteristically recurs with each subsequent cycle.

Conversely, **secondary dysmenorrhea** may present immediately upon menarche or develop later in the reproductive years. Clinical features suggestive of a secondary etiology include a change in the nature of the pain, progressive worsening of symptoms, abnormal uterine bleeding, vaginal discharge, and dyspareunia (painful intercourse).

DIAGNOSIS

The diagnostic evaluation should initiate with a comprehensive history, encompassing medical, gynecologic, menstrual, family, and surgical backgrounds. For example, a family history of dysmenorrhea may point toward endometriosis, whereas prior pelvic surgery raises suspicion for adhesions.

It is crucial to establish whether the pain is temporally associated with menstruation and to document any non-prescription or prescription treatments the patient has previously utilized.

Clinicians must elicit symptoms carefully, as patients and even medical professionals frequently normalize menstrual pain: according to the statistics, nearly two-thirds of patients with complaints of severe menstrual pain are dismissed with reassurance that no pathology exists and this dismissal is particularly prevalent among adolescents.

Consequently, significant diagnostic delays are common, averaging 5.4 years for adolescents and 1.9 years for adults. In cases of secondary dysmenorrhea, the latency period between symptom onset and surgical confirmation can extend from four to 11 years, which greatly impedes treatment and leads to significant decrease of the quality of life. **Diagnostic steps** for dysmenorrhea evaluation include:

1. Thorough evaluation of patient's complaints and history.
2. Pelvic bimanual examination (performed rectally in a non-sexually-active patient).
3. Pelvic ultrasound examination.
4. Infectious screening for sexually transmitted diseases (in sexually active patients).
5. Additional diagnostic procedures if indicated (hysteroscopy, laparoscopy, etc.).

TREATMENT AND PREVENTION

Empiric therapy is indicated if the patient's history aligns with primary dysmenorrhea or secondary dysmenorrhea attributed to endometriosis. In case of secondary dysmenorrhea caused by other underlying conditions (PID, adhesions, etc.) treatment must be tailored specifically to cure this condition or at least minimise its impact.

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute the first-line pharmacologic treatment for primary dysmenorrhea, demonstrating superior efficacy compared with both placebo and acetaminophen. The mechanism of action involves the inhibition of prostaglandin synthesis. To maximize efficacy, NSAIDs should be started one to two days prior to the expected onset of menses and continued on a scheduled basis during the first two to three days of flow, which corresponds to the peak of prostaglandin release. Evidence suggests no significant difference in safety or analgesic efficacy among various NSAIDs, including COX-2 inhibitors. Commonly utilized regimens include

– ***ibuprofen***: loading dose of 800 mg, then 400 to 800 mg every eight hours;

– ***naproxen*** (loading dose of 500 mg, then 250 to 500 mg every 12 hours).

These medications are available over the counter and are cost-effective. Additionally, NSAIDs offer the concurrent benefit of reducing menstrual flow in case of heavy menstrual bleeding.

Although NSAIDs are established as effective agents, approximately 20 % of patients experience little to no symptomatic relief.

Hormonal therapy is considered a first-line intervention for NSAID-resistant dysmenorrhea and may be utilized as monotherapy or as an adjunct to NSAID therapy for patients not seeking immediate conception. These agents alleviate symptoms by inducing endometrial atrophy and suppressing cyclooxygenase-2 expression and subsequent prostaglandin synthesis. Beyond analgesia, hormonal therapies provide ancillary clinical benefits, including the management of HMB, premenstrual dysphoria, acne, and hirsutism. Furthermore, they are associated with the preservation of bone mineral density and a reduction in the risk of endometrial, ovarian, and colorectal malignancies.

Combined estrogen-progestin oral contraceptives (COCs) are effective in both adolescent and adult populations with primary dysmenorrhea, resulting in significant reductions in pain severity and analgesic requirements. For patients with contraindications to estrogen, progestin-only pills are a viable alternative.

Alternative hormonal delivery systems are also appropriate for management:

– transdermal patches;

– vaginal rings;

– subdermal progestin implants;

– depot medroxyprogesterone acetate injections;

– and the levonorgestrel-releasing intrauterine system (LNG-IUS).

The LNG-IUS is at least as effective as, if not superior to, oral contraceptives for treating primary dysmenorrhea and secondary dysmenorrhea related to endometriosis. However, in some countries, including the Republic of Belarus, the use of LNG-IUS is not widely implemented in the adolescent population due to precautions of potential negative impact on their future fertility (which doesn’t have substantial scientific evidence).

When selecting a hormonal regimen, secondary benefits against potential contraindications must be carefully balanced.

Nonpharmacologic and integrative approaches shouldn't be used as first-line therapy due to their low efficacy, but they might serve as useful adjuncts to standard medical treatment or as monotherapy when first-line agents are contraindicated or refused by the patient.

Physical activity has been shown to attenuate both the severity and duration of pain in primary dysmenorrhea: scientific data indicates that exercise sessions lasting 45 to 60 minutes, performed at least three times weekly, can significantly alleviate menstrual pain in patients with moderate to severe symptoms, regardless of the exercise intensity. While exercise may be less effective than NSAIDs in reducing pain intensity or menstrual flow, its broad health benefits warrant its inclusion in patient counseling as a viable therapeutic option.

High-frequency transcutaneous electrical nerve stimulation demonstrates some efficacy in reducing pain associated with primary dysmenorrhea. Compared to placebo, this method slightly improves pain scores, extends the duration of relief, and lowers analgesic consumption.

Self-acupressure offers a low-risk intervention that may decrease pain intensity, duration, and analgesic requirements over a three-month interval, though it does not demonstrate comparable performance with NSAIDs. Both manual acupuncture and electroacupuncture appear effective in reducing pain compared to no treatment; however, evidence suggests they may not outperform sham acupuncture.

Behavioral interventions and pain management techniques, including progressive muscle relaxation, guided imagery, and biofeedback, aimed at enhancing coping strategies may alleviate spasmodic pain. However, the existing literature supporting these modalities is limited by small sample sizes and methodological shortcomings.

Current evidence is insufficient to recommend ***dietary supplements*** such as fenugreek, fish oil, ginger, valerian, vitamin B1, Zataria multiflora, or zinc sulfate for dysmenorrhea, nor does it support antioxidant use for endometriosis-associated pain.

Preventive strategies are generally aimed at eliminating risk factors mentioned above and at establishing a routine maintaining a better overall state of health:

– balanced diet;

– regular and adequate physical activity;

– work-life (or work-study) balance;

– interventions aimed at minimising stress levels, such as psychological techniques of mindfulness, meditation, cognitive-behavioral therapy, etc.

To sum up the information mentioned above, a step-by-step approach to dysmenorrhea management can be seen as following (Fig. 11):

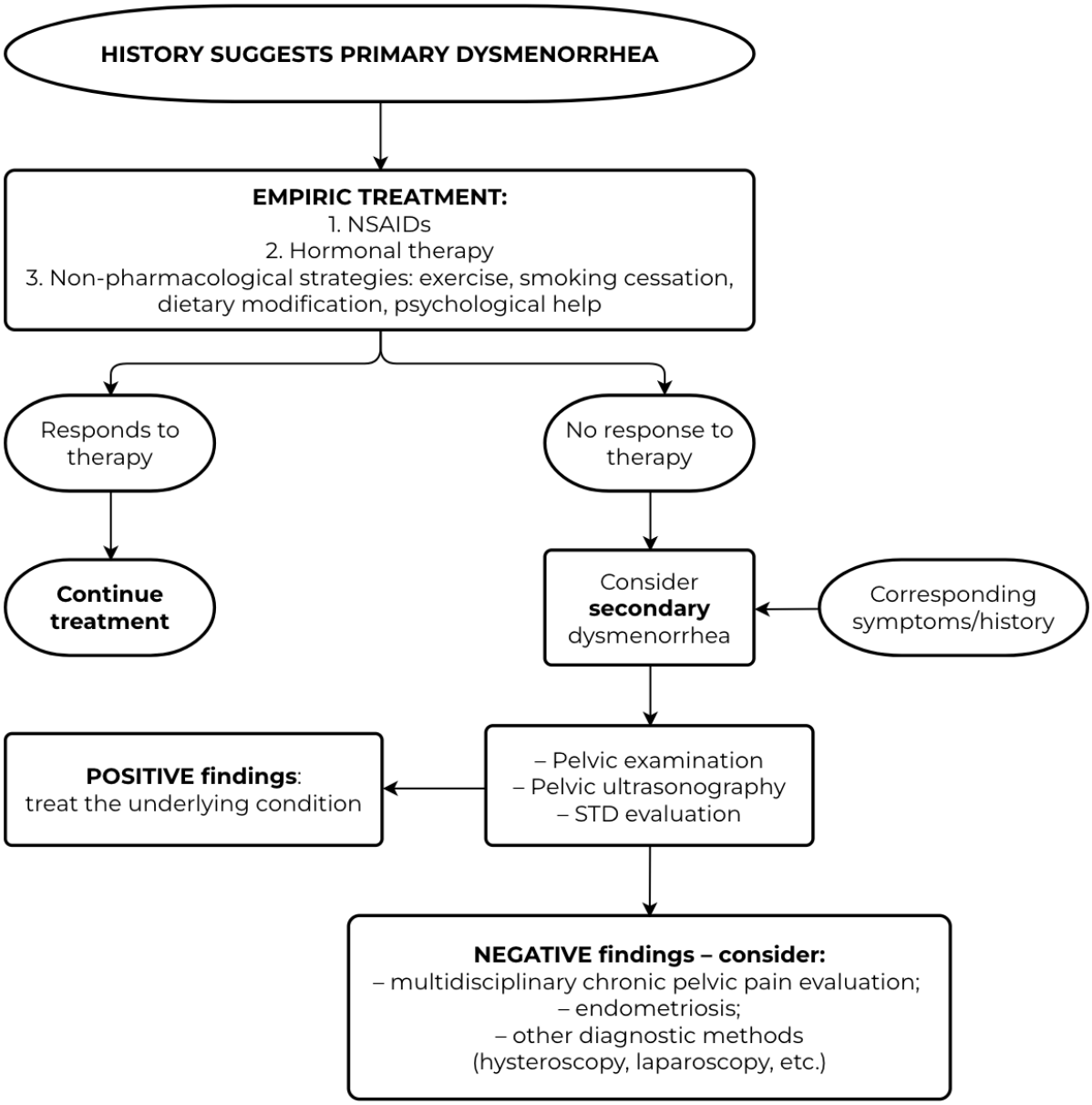


Fig. 11. Approach to dysmenorrhea management

AMENORRHEA

Amenorrhea — the absence of menstruations — is not a single disease itself but a cardinal symptom of underlying physiological or pathological disruptions within the HPO-axis. It is clinically categorized as

– **primary**: the absence of menarche by age 15 in the presence of normal secondary sexual characteristics;

– **secondary**: the cessation of established menses for at least 3 months in a woman with a history of previously regular cycles, or 6 months in those with previously irregular cycles.

Clinical significance of amenorrhea extends far beyond the absence of menstrual bleeding — it serves as a critical biomarker for a wide spectrum of health conditions and has profound implications for long-term female health.

The most immediate consequence of amenorrhea, particularly secondary amenorrhea, is infertility, as it signifies an interruption in the ovulatory cycle. However, the systemic impact is often more extensive. In cases of hypothalamic amenorrhea, often triggered by energy deficit (low body weight, excessive exercise, or nutritional stress), the body conserves energy by downregulating the reproductive axis. This state of hypoestrogenism has widespread effects. The most well-recognized is its detrimental impact on bone mineral density. Estrogen is crucial for bone remodeling; its deficiency accelerates bone resorption, leading to osteopenia or osteoporosis and a significantly increased risk of stress fractures, even in young women.

Conversely, amenorrhea resulting from anovulatory conditions like polycystic ovarian syndrome (PCOS) is characterized by a state of hyperandrogenism and insulin resistance. Here, the health risks are metabolic, including a markedly increased predisposition to type 2 diabetes mellitus, dyslipidemia, hypertension, and potentially endometrial hyperplasia due to unopposed estrogen stimulation of the endometrium. Other etiologies, such as premature ovarian insufficiency, induce an early menopausal state, conferring both the skeletal and cardiovascular risks associated with estrogen deficiency. Therefore, a thorough diagnostic workup of amenorrhea is imperative, not merely to address fertility concerns, but to identify and mitigate these associated long-term health risks to the metabolic, cardiovascular, and skeletal systems.

There are specific periods when amenorrhea is absolutely physiological and doesn't require any interventions. There **periods** include:

– prepuberty;

– pregnancy and breastfeeding;

– menopause.

The prevalence of pathological amenorrhea — not caused by pregnancy, lactation, or menopause — is approximately 3–4 % in general population. However, its prevalence in specific cohorts (female athletes, patients with eating disorders, infertile women) is considerably higher.

ETIOLOGY, PATHOGENESIS AND CLASSIFICATION

As was already mentioned, the requirements for normal menstrual function include five distinct **functional and structural components (**Fig. 12):

– supra-hypothalamic structures (limbic system, etc.);

– hypothalamus;

– anterior pituitary;

– ovaries;

– genital outflow tract (uterus, cervix, vagina).

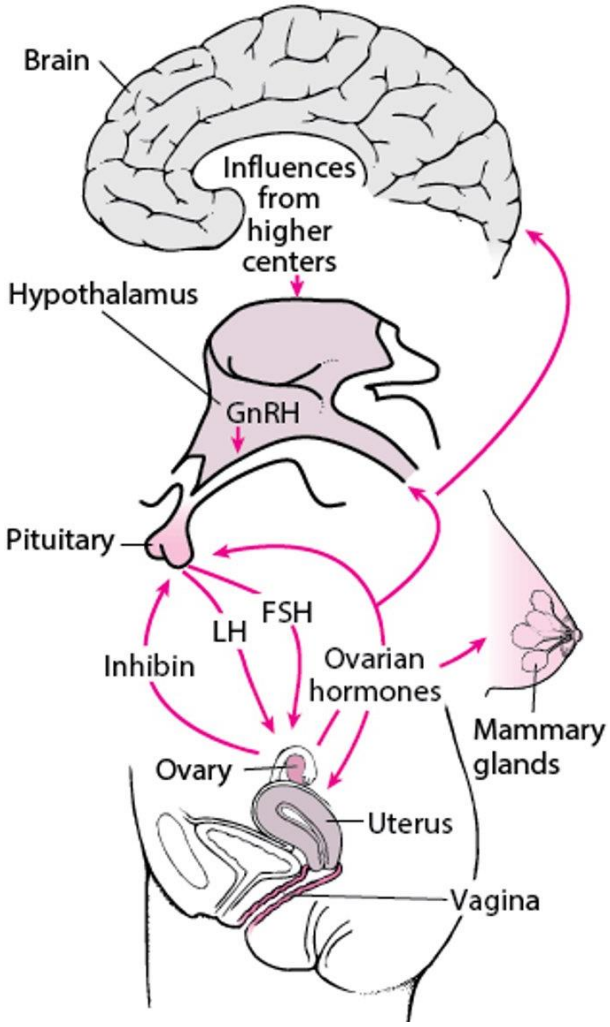


Fig. 12. Components involved in pathogenesis of amenorrhea

Therefore, pathologies in any of these components can lead to amenorrhea.

Although the spectrum of potential causes of amenorrhea is broad (Table 2), most cases are accounted for by **six conditions**:

– polycystic ovary syndrome (PCOS);

– hyperprolactinemia;

– thyroid dysfunction;

– hypogonadotropic and hypergonadotropic hypogonadism;

– structural anatomic abnormalities.

Other causes are less frequently encountered in a typical reproductive medicine practice.

Amenorrhea may also occur with sexual ambiguity or virilization, but usually, in these cases, amenorrhea is not the primary complaint. Sexual ambiguity or virilization should be evaluated as separate disorders, being mindful that amenorrhea is an important component of their presentation.

Table 2

Etiology of primary amenorrhea

Level	Reasons	Prevalence, %
Hypothalamus	Constitutional delay of puberty Functional hypothalamic amenorrhea Isolated GnRH-deficiency Inflammatory and/or infiltrative disease Infections Tumors Ionizing radiation Traumatic brain injury	10–21
Pituitary gland	Hyperprolactinemia Tumors Inflammatory and/or infiltrative disease Infections Traumatic brain injury, including surgical interventions GnRH-receptor mutation	1–4
Ovaries	Primary ovarian insufficiency Gonadal dysgenesis Gonadal agenesis Polycystic ovary syndrome Enzymatic deficiency FSH or LH receptor mutation	24–52
Genital outflow tract	Congenital abnormalities in Müllerian ducts development Congenital defect of urogenital sinus development	15–43
Other	Thyroid disease Adrenal disease Complete androgen insensitivity Medications	2–8

Among the **medications** that induce amenorrhea and disrupt normal menstrual cycle are:

– antipsychotics;
– anticonvulsants;
– several tricyclic antidepressants;
– medications used for chemotherapy, especially cyclophosphamide;
– steroid hormones, especially androgens;
– GnRH agonists;
– drugs of abuse (heroin, cocaine and other stimulants).

Obviously, the most common group of causes of primary amenorrhea (up to 52 %) is the group of ovarian pathology, closely followed in prevalence by such anatomical abnormalities as outflow tract pathologies, mostly due to congenital malformations such as Müllerian agenesis, imperforate hymen and other obstructive anomalies (vaginal septae, cervical atresia, etc.). The prevalence of other disorders (thyroid, adrenal, etc.) is quite low in the group of primary amenorrhea.

The causes of secondary amenorrhea remain largely the same, however, with a slightly different structure regarding prevalence (Table 3).

Table 3

Etiology of secondary amenorrhea

Level	Reasons	Prevalence, %
Hypothalamus	Functional hypothalamic amenorrhea Inflammatory or infiltrative disease Infection Tumor Radiation Traumatic brain injury	35
Pituitary gland	Hyperprolactinemia Pituitary tumors Pituitary infarction Space-occupying lesions Inflammatory and infiltrative disorders Radiation/surgery Infection	17
Ovaries	Polycystic ovary syndrome Premature ovarian insufficiency Ovarian tumors	40
Genital outflow tract	Cervical stenosis (acquired) Intrauterine synechiae (acquired)	7
Other	Thyroid disease Adrenal disease Complete androgen insensitivity Medications	1

As is demonstrated in the table above, ovarian reasons still contribute the most to the etiology and pathogenesis of secondary amenorrhea, with PCOS and premature ovarian insufficiency among the leading causes, closely followed by functional hypothalamic amenorrhea.

According to current worldwide statistics, the majority of all amenorrhea cases are accounted for by such conditions as polycystic ovary syndrome (PCOS), functional hypothalamic amenorrhea, premature ovarian insufficiency, hyperprolactinemia, thyroid dysfunction, and structural anatomic abnormalities.

PCOS is the most prevalent endocrine cause of anovulatory infertility and secondary amenorrhea worldwide. Its pathophysiology is multifactorial, characterized by a vicious cycle of androgen excess and insulin resistance. In many patients, hyperinsulinemia decreases the production of sex hormone-binding globulin (SHBG) by the liver and acts synergistically with LH to stimulate ovarian theca cells to overproduce androgens. This hyperandrogenic environment disrupts the delicate feedback loops of the HPO axis, often resulting in persistently elevated LH levels and normal to low FSH levels. The imbalance arrests follicular development; follicles fail to reach dominance and ovulation does not occur. Without ovulation and the subsequent formation of a corpus luteum, progesterone

is not produced leading to menstrual cycle disruptions and endometrial hyperplasia due to a state of unopposed estrogenic influence.

Therefore, ***3 diagnostic criteria*** for PCOS include:

– ***specific morphology on ultrasound*** when one of the ovaries (or each) contains 20 and more antral follicles or its volume exceeds 10 ml;

– ***clinical or biochemical hyperandrogenism:*** clinical hyperandrogenism usually presents with acne, hirsutism (excessive growth of terminal hairs in androgen-dependent zones such as above upper lip, on the chin, around the nipples, on the abdomen and inner parts of the thighs) and visceral adiposity. Biochemical hyperandrogenic state is diagnosed by increased levels of common and free testosterone which can be measured directly or counted as "free androgen index";

– ***menstrual cycle disruption:*** oligo- or amenorrhea, with oligomenorrhea meaning prolonged intervals between menstrual cycles (more than 38 days) and/or fewer than 10 menstruations per year.

To diagnose PCOS, any 2 of the 3 criteria must be present.

Functional hypothalamic amenorrhea (FHA) is a form of hypogonadotropic hypogonadism caused by the suppression of the HPO axis in the absence of anatomic or organic disease.

It is typically triggered by a state of energy deficit relative to expenditure, often seen in the context of

– ***excessive exercise***;

– ***restrictive eating disorders*** such as anorexia nervosa;

– ***chronic psychological stress***.

These stressors activate the hypothalamic-pituitary-adrenal axis (increasing cortisol) and alter metabolic signals (reducing leptin and increasing ghrelin). These metabolic and stress signals inhibit the hypothalamic pulsatile secretion of gonadotropin-releasing hormone (GnRH). The disruption in GnRH pulsatility leads to diminished pituitary secretion of LH and FSH, resulting in low serum estradiol levels, anovulation, and the cessation of menses.

Premature ovarian insufficiency (POI) is defined as the loss of ovarian activity before the age of 40. It is characterized by the depletion of the ovarian follicular pool or follicular dysfunction (gonadotropin resistance). Etiologies range from genetic defects (e.g., Turner syndrome mosaicism, Fragile X premutation) and autoimmune disorders to endometriosis and iatrogenic causes like chemotherapy, surgically diminished ovarian reserve after removal of ovarian tumors, etc. In POI, the ovaries fail to produce adequate estrogens and inhibin B. The loss of negative feedback inhibition on the pituitary gland results in the hallmark laboratory finding of hypergonadotropic hypogonadism (elevated FSH and LH). Consequently, the endometrium lacks the estrogenic stimulation necessary for proliferation, leading to amenorrhea.

In case of **hyperprolactinemia** elevated serum prolactin levels induce amenorrhea through direct suppression of the hypothalamic secretion of GnRH. Whether caused by a prolactin-secreting pituitary adenoma, medication effects (e.g., dopamine antagonists), or other physiologic factors, excess prolactin inhibits

the pulsatile secretion of GnRH. This inhibition is crucial because normal menstrual function requires precise GnRH pulses to stimulate pituitary release of LH and FSH. The suppression of gonadotropins results in a state of hypogonadotropic hypogonadism, preventing folliculogenesis and ovulation, thereby causing amenorrhea.

Both **hypothyroidism** and **hyperthyroidism** can disrupt the menstrual cycle, though mechanisms vary:

– in case of ***hypothyroidism***, increased levels of thyrotropin-releasing hormone stimulate the pituitary thyrotrophs but can also cross-stimulate lactotrophs, leading to secondary hyperprolactinemia. As described above, high prolactin suppresses GnRH pulsatility. Additionally, hypothyroidism alters the metabolism of sex steroids and decreases SHBG, leading to feedback disruptions that lead to anovulation;

– excess of thyroid hormones in ***hyperthyroidism*** increases SHBG levels, which increases total estradiol levels but decreases its bioavailable fraction. The sustained high levels of LH and estradiol seen in thyrotoxicosis disrupt the mid-cycle LH surge necessary for ovulation, leading to oligomenorrhea or amenorrhea.

Amenorrhea caused by **structural defects** can be congenital or acquired, occurring despite a potentially normal functioning HPO axis:

– ***congenital conditions*** such as Müllerian agenesis (Mayer–Rokitansky–Küster–Hauser syndrome, Fig. 13) involve the absence of the uterus and upper vagina, but normal ovarian function and secondary sexual characteristics. Imperforate hymen or transverse vaginal septae are outflow tract obstructions where menstruation occurs (cyclic pain is common), but blood is mechanically prevented from exiting the body (cryptomenorrhea);

– ***acquired conditions*** such as Asherman syndrome involves the formation of intrauterine adhesions (synechiae) and fibrosis, typically following surgical procedures (e.g., dilation and curettage) or infection. These adhesions obliterate the endometrial cavity or block the cervical outflow tract. Even with normal ovarian hormonal signaling, the damaged endometrium is unable to proliferate and shed, resulting in secondary amenorrhea.

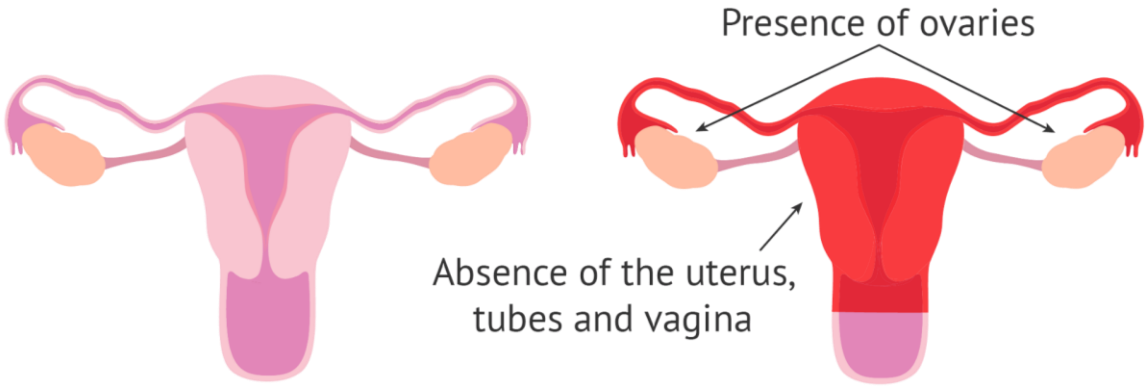


Fig. 13. Schematic representation of Mayer–Rokitansky syndrome in comparison with a normally developed uterus

DIAGNOSTIC CONSIDERATIONS

In case of **primary amenorrhea** the initial workup involves the following (Fig. 14):

– ***clinical assessment***: a detailed history (including family history, the course of pregnancy and birth, neonatal and later development, etc.), physical examination, including an assessment of the external, internal genitalia and breasts;

– key ***hormonal tests***: serum FSH and estradiol to identify most common causes;

– interpreting ***clinical signs*** such as breast development (according to Tanner scale) suggests prior estrogen action, while its absence points to delayed puberty and requires further investigation;

– ***pelvic ultrasound*** performed to assess the anatomy of reproductive tract and rule out congenital malformations leading to amenorrhea;

– ***karyotyping*** in case of supposed genetic causes.

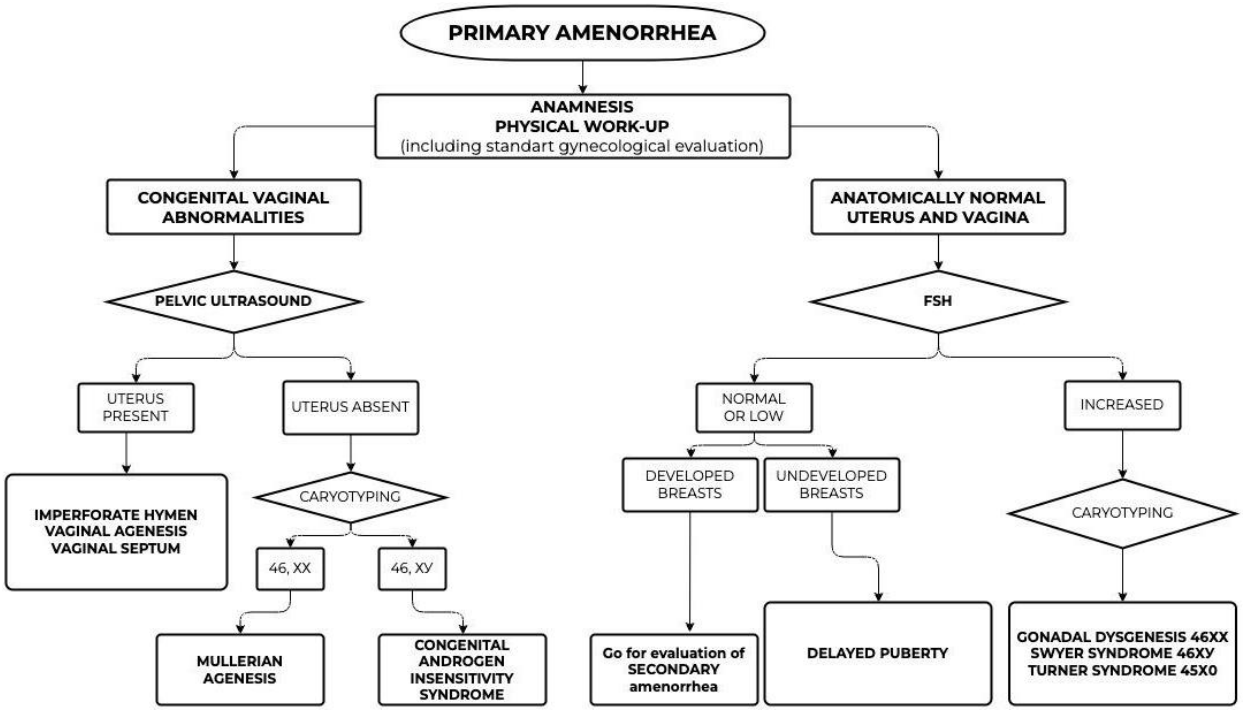


Fig. 14. Diagnostic steps in case of primary amenorrhea

In case of **secondary amenorrhea** the initial workup involves the following (Fig. 15):

– ***serum human chorionic gonadotropin*** in sexually active patients to rule out potential pregnancy;

– ***clinical assessment*** focused on family history, significant voluntary or involuntary weight changes (loss or gain), presence of acute or chronic stress, eating disorders and eating patterns (vegetarianism, veganism, etc.), exercise patterns, prior surgeries, signs of possible endocrine disorders, medications, etc.;

– ***physical examination*** including general evaluation, examination per speculum and bimanual gynecologic examination in sexually active patients (replaced by rectal-abdominal exam in non-sexually active females);

– ***hormonal assessment***: FSH, LH, AMH, TSH, prolactin, estradiol;

– ***pelvic ultrasound*** additionally focused on antral follicles count assessment.

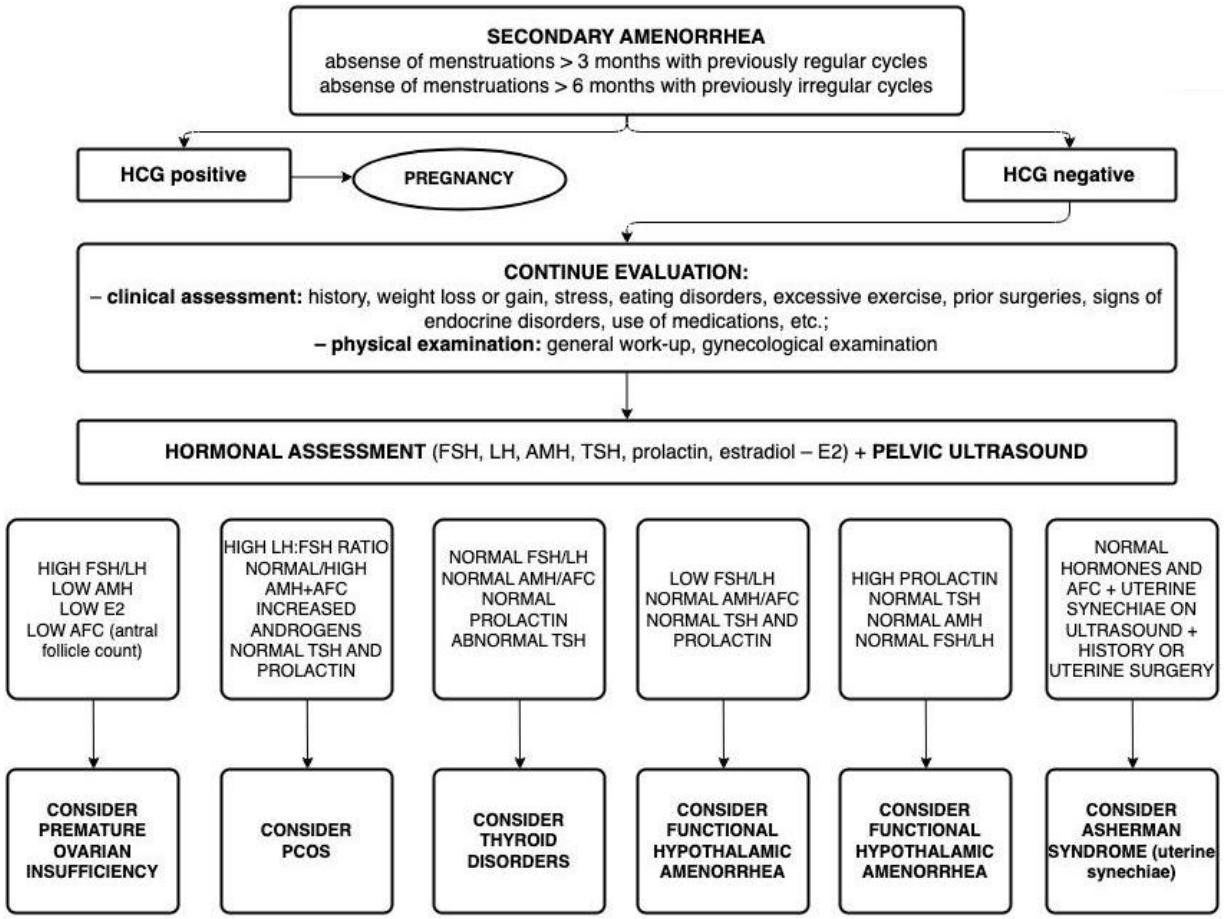


Fig. 15. Diagnostic steps in case of secondary amenorrhea

MANAGEMENT

Management of amenorrhea is strictly guided by the underlying etiology, with goals ranging from restoration of ovulatory cycles and fertility to symptom management and protection of long-term health (e.g., bone density which is compromised in case of estrogen deficiency).

Treatment for **PCOS** is tailored to the patient's reproductive goals and metabolic profile and includes:

– ***lifestyle modification:*** first-line therapy involves controlled weight loss and adequate exercise, which improves insulin sensitivity and can restore spontaneous ovulation in many patients;

– ***combined oral contraceptives (COCs):*** for patients not seeking immediate pregnancy, COCs are the mainstay of treatment as they efficiently regulate menstrual cycle, protect the endometrium from hyperplasia (by providing progestin to balance estrogen influence), and suppress ovarian androgen production;

– ***ovulation induction:*** for patients seeking pregnancy, letrozole (an aromatase inhibitor) is currently the first-line agent to induce ovulation, with clomiphene citrate as an alternative;

– ***metformin:*** this insulin-sensitizing agent may be used as an adjunct to improve metabolic parameters and restore ovulatory cycles, particularly in patients with insulin resistance.

In **functional hypothalamic amenorrhea** the primary goal is reversing the underlying energy deficit or stressor to restore hypothalamic GnRH pulsatility which can be achieved due to:

– ***psychotherapy*** and ***behavioral modification:*** treatment focuses on increasing caloric intake, reducing exercise intensity, and managing psychological stress (e.g., in cognitive behavioral therapy), in many cases help of a mental health specialist is required (psychiatrist, psychotherapist, etc.);

– ***hormonal replacement therapy:*** if psychotherapy lifestyle changes do not restore menstruation after 6 months, or if bone mineral density is compromised, transdermal estradiol with cyclic progesterone is greatly preferred over oral contraceptives because transdermal estrogen does not suppress IGF-1 (a bone-trophic hormone) as oral ethinylestradiol does, offering better bone protection;

– ***ovulation induction:*** for infertility, pulsatile GnRH therapy (where available) or gonadotropin injections can induce ovulation, though these carry a risk of multiple gestation.

In **premature ovarian insufficiency** ovarian function is unlikely to return spontaneously, therefore management focuses on hormone replacement therapy and health maintenance.

– ***hormonal replacement therapy:*** unless contraindicated, physiologic doses of estrogen and progesterone are required at least until the natural age of menopause (approximately till age 50–51) to mitigate vasomotor symptoms and prevent osteoporosis and decrease the risk of cardiovascular disorders. The hormonal replacement dosage is typically higher than that used for postmenopausal women due to higher estrogen requirements;

– ***fertility***: spontaneous pregnancy is rare, while oocyte donation (donor eggs) with in vitro fertilization is the most successful option for achieving pregnancy.

In **hyperprolactinemia** treatment depends on the cause (adenoma vs. medication) and size of the tumor:

– ***dopamine agonists:*** cabergoline or bromocriptine are the first-line treatments for prolactinomas as they decrease the volume of the tumor and prolactin levels, thereby restoring GnRH pulsatility and ovulation;

– ***medication adjustment:*** in case of drug-induced hyperprolactinemia, the offending agent should be stopped or switched to a non-hyperprolactinemic alternative if clinically feasible;

– ***surgery:*** transsphenoidal resection of pituitary prolactin-secreting adenoma is reserved for patients resistant to medical therapy or those with compressive symptoms (e.g., visual field defects) due to large tumors and symptoms not relieved by agonists.

Restoration of euthyroid status in amenorrheic patients with **thyroid disorders** usually corrects the menstrual disturbance.

– for ***hypothyroidism:*** levothyroxine replacement therapy normalizes TSH and prolactin levels, restoring normal feedback loops;

– for ***hyperthyroidism:*** treatment with thioamides (methimazole or propylthiouracil), radioactive iodine, or surgery to control thyrotoxicosis allows SHBG and sex steroid levels to normalize, leading to the resumption of regular cycles.

In case of **structural anatomic abnormalities** management is primarily surgical:

– for ***imperforate hymen or transverse vaginal septum*** surgical incision or resection of the obstruction relieves the hematocolpos (blood filling the vagina due to obstructed outflow) and allows for normal menstrual outflow;

– for ***Asherman syndrome*** hysteroscopic removal of adhesions is performed to restore the uterine cavity. Postoperatively, high-dose estrogen therapy is often prescribed to stimulate endometrial regrowth, sometimes with the insertion of a balloon catheter to prevent adhesion recurrence;

– Müllerian ***agenesis*** treatment focuses on creating a functional vagina for allowing sexual activity, either through non-surgical dilation (primary approach) or surgical vaginoplasty. As these women have fully functional ovaries, they don't need hormonal treatment and in case of pregnancy-planning they can undergo in vitro fertilisation programs with surrogacy.

ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding (AUB) is defined as uterine bleeding occurring in reproductive-aged women that is abnormal in the parameters of regularity, frequency, volume, or duration. AUB is a common condition that significantly impacts the quality of life. Up to one-third of women will experience AUB in their life, with irregularities most commonly occurring at menarche and perimenopause.

CLASSIFICATION

AUB terminology and classification have evolved to promote clarity and uniformity in diagnosis. Revisions to AUB terminology were first published in 2007, followed by updates from the International Federation of Obstetrics and Gynecology (FIGO) in 2011 and 2018. FIGO System 1 established more defined descriptive terms nongestational AUB based on the frequency, regularity, duration, and volume of flow. The nonspecific terminology of menorrhagia, metrorrhagia, and oligomenorrhea was also replaced with the terms heavy menstrual bleeding characterized by bleeding > 80 mL or heavy enough to interfere with a patient's qualify of life, intermenstrual bleeding (cyclical or random spontaneous bleeding between menstrual periods) and breakthrough

bleeding on hormone medication. FIGO System 2 (2018) introduced **PALM-COEIN**, which categorizes AUB into structural (polyp, adenomyosis, leiomyoma, malignancy/hyperplasia) and nonstructural (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, not otherwise classified) etiologies.

AUB can also be divided into acute and chronic bleeding.

Acute AUB is excessive bleeding that requires immediate intervention to prevent further blood loss. In patients with acute AUB and menarche within the last year, consider anovulatory bleeding due to immaturity of the hypothalamic-pituitary-gonadal axis.

Chronic AUB is refered to irregularities in menstrual bleeding for most of the previous 6 months.

Historical terminology is no longer recommended by FIGO:

– menorrhagia or hypermenorrhea: abnormally high volume menstrual bleeding (now termed heavy menstrual bleeding);

– metrorrhagia: abnormal bleeding between menstrual periods (now termed intermenstrual bleeding);

– menometrorrhagia: heavy and/or prolonged, irregular menstruation;

– oligomenorrhea: infrequent menstruation with cycle intervals > 38 days;

– polymenorrhea: frequent menstruation with cycle intervals < 24 days;

– hypomenorrhea: light menstruation.

FIGO-AUB system 1: bleeding characteristics. *Frequency* (the number of days in the cycle interval):

– normal: 24–38 days;

– absent (amenorrhea): no bleeding days;

– infrequent (formerly oligomenorrhea): > 38 days;

– frequent (formerly polymenorrhea): < 24 days.

Regularity (variation between shortest and longest cycle menstrual cycle length):

– normal: ≤ 7–9 days (i.e., normal cycle length ± 4 days);

– irregular: ≥ 8–10 days.

Duration (the length of menstruation):

– normal: ≤ 8 days;

– prolonged: > 8 days.

Volume (the amount of bleeding as described by the patient):

– normal;

– light menstrual bleeding (formerly hypomenorrhea);

– heavy menstrual bleeding (formerly hypermenorrhea or menorrhagia): excessive menstrual bleeding that interferes with quality of life.

Intermenstrual bleeding (bleeding between regular menstrual periods):

– normal: none;

– random: occurs unpredictably;

– cyclic: predictable bleeding during early, mid, or late cycle.

Unscheduled bleeding (breakthrough bleeding, endometrial bleeding that occurs on unexpected days while taking hormonal contraceptives):

– none: on hormonal contraceptives with no unscheduled bleeding;

– present.

PALM-COEIN FIGO system 2. The PALM-COEIN classification, established by FIGO, organizes the potential causes of AUB into the following structural and nonstructural categories (Fig. 16).

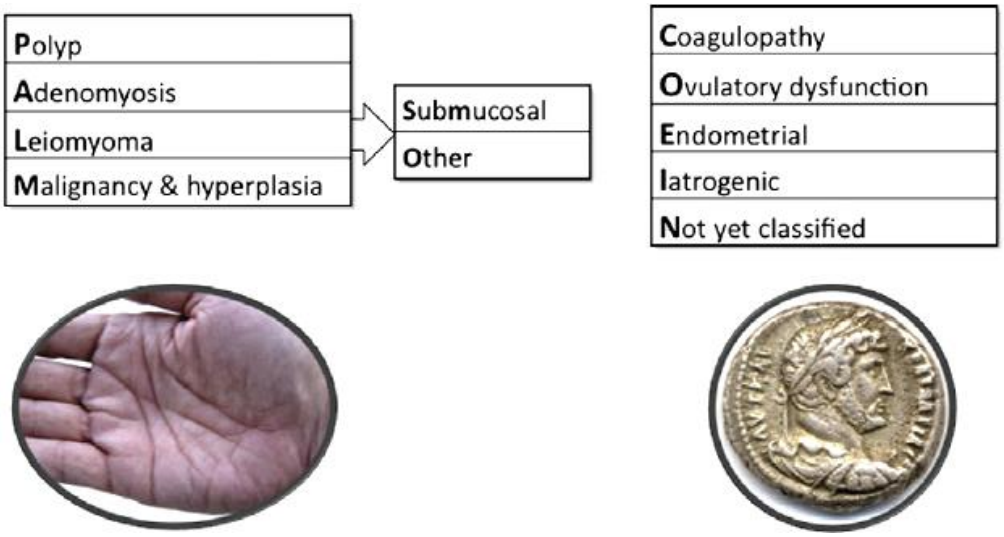


Fig. 16. The PALM-COEIN classification

Structural etiologies:

– **Polyp (P):** endometrial or endocervical polyps are focal outgrowths of tissue that may be asymptomatic or cause intermenstrual bleeding. While most are benign, they occasionally carry a malignancy risk.

– **Adenomyosis (A):** this condition involves the presence of endometrial tissue within the uterine muscle and is often associated with heavy, painful, or prolonged menstruation and may result in uterine enlargement.

– **Leiomyoma (L):** commonly known as fibroids, these benign smooth muscle tumors can lead to heavy or prolonged menstrual bleeding, particularly if large or submucosal. Many leiomyomas are asymptomatic.

– **Malignancy and hyperplasia (M):** these include endometrial hyperplasia and cancers, often presenting with unpredictable bleeding. Risk factors include prolonged estrogen exposure without opposition by progesterone.

Nonstructural etiologies:

– **Coagulopathy (C):** systemic bleeding disorders (von Willebrand disease).

– **Ovulatory dysfunction (O):** conditions like polycystic ovary syndrome (PCOS), hypothalamic disorders, or thyroid dysfunction can lead to infrequent, irregular, heavy, or prolonged bleeding due to inconsistent ovulation.

– **Endometrial disorders (E):** these involve localized issues in the endometrium's ability to control bleeding, possibly due to inflammation, infection, or vasoconstriction abnormalities.

– **Iatrogenic (I):** medications (hormonal contraceptives, anticoagulants, or tamoxifen) or surgical injury (Asherman syndrome) can induce abnormal bleeding.

– **Not otherwise classified (N):** rare or poorly understood causes comprise this group, including arteriovenous malformations, chronic endometritis, or cesarean scar defects.

PATHOPHYSIOLOGY

The pathophysiology of AUB is referred to multiple interaction between endocrine, immune, and vascular systems in the endometrium, where disruptions in these mechanisms can lead to irregularities in menstrual bleeding. Normal menstruation involves progesterone withdrawal at the end of the menstrual cycle, triggering a well-coordinated cascade of endometrial changes including epithelial and stromal apoptosis, inflammatory mediator release, and matrix metalloproteinase activation, which facilitate endometrial shedding and subsequent repair. Effective hemostasis requires spiral arteriole constriction, clot formation, and tissue regeneration. In individuals with AUB, these processes are dysregulated, leading to excessive or irregular bleeding.

In women experiencing AUB due to alterations in the ovarian production of steroids (AUB-O) or related to medication (AUB-I), the decline in progesterone levels occurs unpredictably. In AUB-O patients, irregular and heavy bleeding occurs due to the absence of cyclic sex steroid production. Anovulatory cases lead to continuous endometrial growth driven by estrogen, causing eventual necrosis and partial shedding as the thickened lining outgrows its blood supply. Oligo-ovulation can result in episodes of partial shedding and normal menses.

The main factor behind AUB-E is disruptions in the molecular and cellular processes that control the amount of blood shed during menstruation. Vasoconstriction may induce temporary tissue oxygen deficiency and trigger the stabilization of hypoxia-inducible factor 1, which orchestrates endometrial repair.

Structural causes like fibroids and adenomyosis further complicate the picture, disrupting myometrial contractility, paracrine signaling, and vascular function. For example, fibroids may induce excessive bleeding through mechanisms, e.g., increased endometrial surface area, altered angiogenesis, and impaired clotting factor expression. The precise mechanisms linking polyps to AUB have not been identified.

During menstruation, damage to blood vessels following endometrial injury leads to platelets binding to collagen within a damaged basement membrane, which triggers a cascade of events related to blood clot formation. Effective hemostasis is crucial in limiting menstrual blood loss during menstruation, and this mechanism is compromised in women with AUB linked to the clotting processes (AUB-C).

CLINICAL PRESENTATION

One of the following bleeding abnormalities described in the FIGO-AUB classification system 1 must be present:

– abnormal bleeding frequency, duration, regularity, and/or volume;

– intermenstrual bleeding;

– unscheduled bleeding.

Associated features. These vary depending on the underlying cause of AUB and can include:

– other menstrual cycle abnormalities, e.g., dysmenorrhea;

– abdominal and/or pelvic pain;

– postcoital bleeding;

– signs of anemia;

– signs of bleeding disorders;

– signs of hyperandrogenism;

– red flags for sexual assault;

– clinical features of sexually transmitted infections;

– clinical features of cervical cancer.

DIAGNOSIS

Clinical History. The clinical assessment of AUB involves a systematic evaluation to help identify underlying causes and assess the severity of bleeding. Hemodynamic stability should be ascertained first, with resuscitative measures performed in unstable patients with acute AUB, before obtaining a thorough history. In stabilized patients, the clinician should obtain a detailed history of patients who present with complaints related to menstruation and should include the following elements:

1. Menstrual history (age at menarche. last menstrual period, menses frequency, regularity, duration, the volume of flow; intermenstrual and postcoital bleeding).

2. Sexual and reproductive history (obstetrical history, fertility desire and subfertility, current contraception, history of sexually transmitted infections, PAP smear test).

3. Associated or systemic symptoms (weight loss, pain, discharge, bowel or bladder symptoms, signs/symptoms of anemia or history of a bleeding disorder, signs/symptoms or history of endocrine disorders).

4. Current medications.

5. Family history (e.g., coagulopathies, malignancy, endocrine disorders).

6. Social history.

Physical Examination. Clinicians should first assess for signs of hemodynamic instability, e.g., orthostatic hypotension or tachycardia.

The physical examination includes:

– vital signs, including blood pressure and body mass index;

– dermatologic indicators of anemia or of coagulopathies;

– tanner staging in adolescents;

– signs of endocrine disorders;

– abdominal exam to palpate for any pelvic or abdominal masses;

– pelvic exam.

Laboratory studies:

– β-human chorionic gonadotropin test (urine or serum): to rule out pregnancy;

– CBC and serum ferritin: to evaluate for anemia, thrombocytopenia, and iron deficiency;

– TSH;

– type and screen, crossmatch: in severe acute bleeding;

– prothrombin time, activated partial thromboplastin time, platelet count, and international normalized ratio: if a bleeding disorder is suspected and in all adolescents with heavy menstrual bleeding;

– age-appropriate cervical cancer screening;

– Chlamydia testing;

– additional laboratory tests: prolactin, gonadotropins (FSH, LH), diagnostic workup of bleeding disorders.

Imaging studies. Imaging is indicated for abnormalities detected during a bimanual examination or when symptoms persist despite initial treatment. Transvaginal and transabdominal ultrasound imaging modalities are preferred as first-line imaging for most patients when indicated and are particularly effective for identifying structural causes, e.g., polyps, adenomyosis, or leiomyomas. Transabdominal ultrasound may be more appropriate in the adolescent population.

Saline-infused sonohysterography may be considered to enhance the detection of intracavitary lesions by introducing sterile saline into the uterine cavity during transvaginal ultrasound; however, this method is not as useful for endometrial assessment if the endometrium was not well visualized on initial ultrasound. Magnetic resonance imaging (MRI) is typically reserved for cases with complex anatomy, leiomyomas, or adenomyosis. Diffusion-weighted imaging can improve diagnostic accuracy, particularly for differentiating benign and malignant lesions.

Endometrial sampling. Endometrial *biopsy* is indicated:

– in patients with AUB and increased risk of endometrial hyperplasia or cancer;

– all patients ≥ 45 years of age;

– patients < 45 years of age with persistent bleeding despite medical management, unopposed estrogen (e.g., due to obesity or PCOS), other risk factors for endometrial cancer (type 2 diabetes, tamoxifen therapy, Lynch syndrome).

Office-based endometrial biopsy is the first-line approach with hysteroscopic dilation and curettage recommended if office sampling fails, is inadequate, or cannot be performed. In patients with persistent symptoms following normal biopsy results, hysteroscopy should be performed as blind sampling may miss focal lesions.

Contraindications to endometrial sampling procedures include pregnancy, uncontrolled bleeding disorders, and acute pelvic infection.

Differential diagnosis for genital tract bleeding based on anatomic location include:

– **pregnancy and pregnancy-associated complications:** intrauterine pregnancy, spontaneous abortion, ectopic pregnancy, placenta previa;

– **vulva:** any benign growths or malignancy;

– **vagina:** vaginitis, benign growths, sexually transmitted infections, malignancy, trauma, foreign bodies;

– **cervix:** benign growths, sexually transmitted infections, malignancy;

– **fallopian tubes and ovaries:** pelvic inflammatory disease, malignancy;

– **urinary tract:** infections, malignancy;

– **gastrointestinal tract:** inflammatory bowel disease, Behçet syndrome.

TREATMENT

Treatment for AUB depends on factors such as the underlying cause and acuity of bleeding, fertility and contraceptive goals, comorbidities, treatment efficacy, adverse effects, and cost.

Management of acute emergent abnormal uterine bleeding. For patients with severe AUB and hemodynamically unstable, emergent interventions include mechanical control with intrauterine tamponade using a balloon, Foley catheter, or gauze packing, high-dose medical interventions-intravenous (IV) or oral estrogen if not contraindicated, combined oral contraceptives (COCs), oral progestins, or IV tranexamic acids. Estrogen contraindications include migraine with aura, history of thromboembolic disease or thrombosis risk factors, hypertension, and congenital cardiac anomalies. In some cases, surgical procedures such as dilation and curettage, uterine artery embolization, or hysterectomy may be necessary.

Hospitalization is indicated for hemodynamically unstable patients or those with severe refractory bleeding despite outpatient management for 24 hours, including patients saturating > 1 pad in an hour or bleeding through a pad within 2 hours, hemoglobin level < 8 g/dL, or signs of hypovolemia or orthostatic hypotension.

Medical treatment depends on clinical stability and suspected etiology.

Hormonal: conjugated estrogen 25 mg IV every 4 to 6 hours for 24 hours or 35-μg high-dose COCs 3 times daily for 7 days, then once daily, tapered after bleeding cessation. Estrogen-containing treatments are contraindicated in patients at high risk for thrombosis. Progestin-only options include medroxyprogesterone 20 mg or norethindrone 20 mg 3 times daily for 7 days.

Nonhormonal: tranexamic acid 10 mg/kg IV up to 600 mg per dose or 1.5 g orally every 8 hours for 5 days, and NSAIDs are effective adjuncts.

Adjunctive measures: supportive treatments include antiemetics for hormonal therapy-induced nausea and iron supplementation for anemia.

Treatment of nonemergent abnormal uterine bleeding. Hemodynamically stable patients with severe bleeding can typically be managed with oral hormonal and nonhormonal therapies.

The effect of this therapy the following:

– suppresses endometrial development;

– reestablishes predictable bleeding patterns;

– decreases menstrual flow.

Hormonal options:

1. Levonorgestrel-releasing intrauterine system (LNG-IUD) 52-mg are the most effective types and comparable to hysterectomy in quality-adjusted life years and should be considered as part of first-line medical treatment for chronic AUB.

2. Estrogen-progestin oral contraceptives (COCs): monophasic 30 to 35 μg estrogen-containing COC daily with or without inert pills are effective for reducing blood loss and regulating ovulatory dysfunction.

3. Progestin-only therapy: continuous oral progestins, including medroxyprogesterone 5 to 10 mg, norethindrone 5 to 10 mg daily, or depot medroxyprogesterone 150 mg subcutaneously every 3 months reduce bleeding but often result in lower patient satisfaction.

Nonhormonal options. Tranexamic acid: Tranexamic acid 1.5 g orally every 8 hours for 5 days with menses.

NSAIDs: Ibuprofen 600 mg every 6 hours or 800 mg every 8 hours; naproxen 500 mg initially and repeat 3 to 5 hours later, then 250 to 500 mg twice daily; mefenamic acid 500 mg 3 times daily.

Various treatment strategies regarding PALM-COEIN classification is presented in Fig. 17.

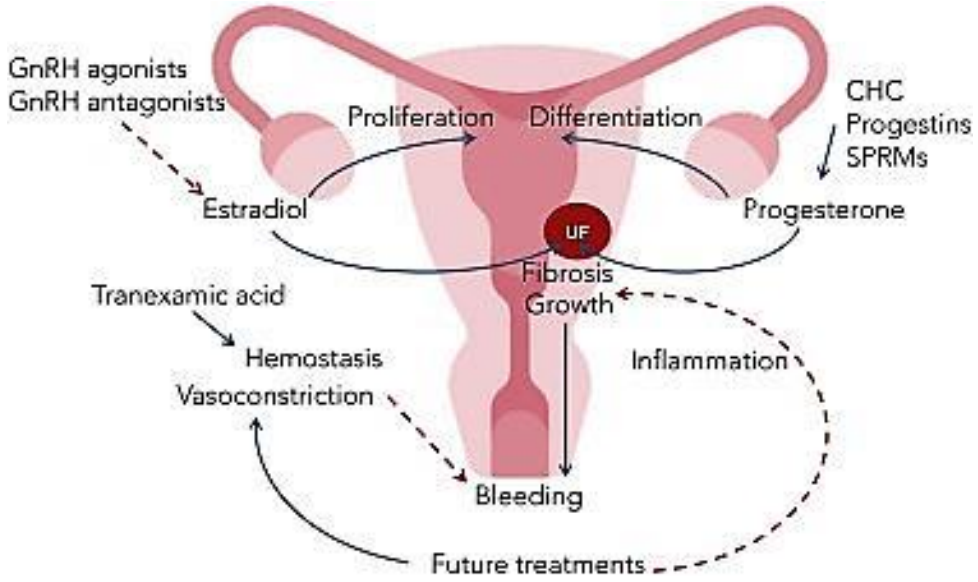


Fig. 17. Mechanisms of uterine bleeding and the main targets of medical treatments. CHC — estrogen-progestin oral contraceptives, SPRM — selective progesterone receptor modulators, UF — uterine fibroids

Long-term management and maintenance therapy include hormonal therapies, including COCs, oral or injectable progestins, and LNG-IUDs. Continuous or extended regimens can stabilize bleeding, and nonhormonal treatments can be used, including oral iron and dietary optimization for anemia.

Gonadotropin-releasing hormone (GnRH) agonists or antagonists suppress ovarian hormone production and cause amenorrhea: e.g., elagolix, relugolix. They are effective for fibroid-related bleeding. However, hypoestrogenic adverse effects (e.g., osteoporosis, menopausal symptoms) limit their use to 6 months. If long-term use is required, add-back therapy low-dose estrogen and progestin therapy may be given (estradiol 1 mg and norethisterone acetate 0.5 mg once daily).

GnRH antagonists do not induce an initial estradiol flare and rapidly and reversibly suppress gonadotropins and ovarian sex hormones, which reduces heavy bleeding within a few days. Oral GnRH antagonists are available, some of which are combined with estrogen and progestin as add-back therapy.

Selective progesterone receptor modulators (SPRM) impede cellular proliferation of leiomyoma cells. Use of ulipristal acetate is limited (short-term) due to potential adverse liver effects. Mifepristone has also been used for symptom relief.

Danazol (antigonadotropic effect) reduces menstrual blood loss (by causing endometrial atrophy) but is not frequently used because it has many androgenic adverse effects, which may be lessened by using lower doses or a vaginal formulation. To be effective, danazol must be taken continuously, usually for about 3 months. It is usually used only when other forms of therapy are contraindicated.

Surgical Management. Surgical management is recommended for patients unresponsive to medical management or required definitive treatment. Surgical management includes:

1. **Dilatation and curettage:** sharp endometrial curettage is an option for AUB treatment, especially in patients with endometrial hyperplasia or dilation of the uterine cavity.
2. **Hysterectomy** is a definitive treatment for patients who do not desire fertility conservation.
3. **Endometrial ablation** is a hysteroscopic destruction of the endometrial lining and an effective alternative to hysterectomy, equivalent to LNG-IUD for outcomes, although not recommended in those desiring fertility preservation.
4. **Hysteroscopic or laparoscopic myomectomy** is used for patients with uterine fibroids, depending on size, type, and patient goals.
5. **Hysteroscopic polypectomy** may be considered for endometrial polyp resection.
6. **Uterine artery embolization** is interventional radiology procedure in which bilateral uterine arteries are catheterized and blood flow is occluded with particulate material may be considered particularly for AUB due to leiomyomas, depending on size, type of fibroids.

TASKS FOR SELF-ASSESSMENT

TESTS

1. What is the term used for describing pathologically painful menstruation:

a) amenorrhea; c) dysmenorrhea;
b) oligomenorrhea; d) menorrhagia?

2. Primary dysmenorrhea is defined by presence of following:

a) cyclic pain related to menstruation with no underlying pathology;
b) acyclic pain non-related to menstruation with no underlying pathology;
c) cyclic pain related to menstruation with underlying uterine or ovarian pathology;
d) acyclic pain non-related to menstruation with no underlying pathology.

3. Secondary dysmenorrhea is defined by presence of following:

a) cyclic pain related to menstruation with no underlying pathology;
b) acyclic pain non-related to menstruation with no underlying pathology;
c) cyclic pain related to menstruation with underlying uterine or ovarian pathology;
d) acyclic pain non-related to menstruation with no underlying pathology.

4. What is the preferred group of medications in treatment of dysmenorrhea:

a) spasmolytic drugs;
b) non-steroidal anti-inflammatory drugs;
c) opioids;
d) vitamins?

5. Primary amenorrhea is diagnosed in case of following:

a) the absence of menarche by age 15 in the presence of normal secondary sexual characteristics;
b) the absence of menarche by age 10 in the presence of normal secondary sexual characteristics;
c) only amenorrhea caused by genetic causes;
d) amenorrhea after pregnancy.

6. Secondary amenorrhea is diagnosed in case of following:

a) absence of menstruation for 6 months and more in case of previously regular menstrual cycle and absence of menstruation for 12 months and more in case of previously irregular cycles;
b) absence of menstruation for 3 months and more in case of previously regular menstrual cycle and absence of menstruation for 6 months and more in case of previously irregular cycles;
c) absence of menstruation only in a female that previously had pregnancies and childbirth;
d) absence of menstruation only in case of menopause.

7. Amenorrhea caused by extreme weight loss, excessive physical exercises and chronic stress is most likely to be due to:

a) polycystic ovarian syndrome;
b) premature ovarian insufficiency;
c) functional hypothalamic amenorrhea;
d) Asherman syndrome.

8. Amenorrhea associated with clinical or laboratory signs of hyperandrogenism, chronic anovulation and increased number of follicles (20 and more) in the ovary is most likely caused by:

a) polycystic ovarian syndrome;
b) premature ovarian insufficiency;
c) functional hypothalamic amenorrhea;
d) Asherman syndrome.

9. Amenorrhea in case of Mayer–Rokitansky syndrome (Müllerian agenesis) is caused by:

a) congenital absence of both ovaries;
b) acquired cervical stenosis;
c) congenital absence of uterus;
d) post-inflammatory degeneration of endometrium.

10. In case of functional hypothalamic amenorrhea the most effective treatment to establish menstrual cycles would be:

a) combined oral contraceptives;
b) letrozole;
c) metformin;
d) hormonal replacement therapy including transdermal estrogen and progesterone.

11. Which of the following parameters is not characterizing AUB:

a) 24–38 days frequency;
b) bleeding > 80 mL;
c) intermenstrual bleeding;
d) breakthrough bleeding on hormone medication.

12. Which of the following characteristics is not associated with structural etiology in AUB:

a) polyp; c) myoma;
b) adenomyosis; d) endometrial disorders.

13. Ovulatory dysfunction as etiological function of AUB includes all following, except:

a) polycystic ovary syndrome;
b) hypothalamic disorders;
c) Asherman syndrome;
d) thyroid dysfunction.

14. What is an indication for endometrial biopsy:

a) all patients with AUB;
b) all patients ≥ 45 years of age;
c) all patient with AUB and obesity;
d) all patients < 35 years of age.

15. What is the preferred group of medications in treatment of acute emergent AUB:

a) spasmolytic drugs;
b) non-steroidal anti-inflammatory drugs;
c) vitamins;
d) combined oral contraceptives.

16. What is the preferred group of medications in treatment of chronic nonemergent AUB:

a) non-steroidal anti-inflammatory drugs;
b) vitamins;
c) combined oral contraceptives;
d) gonadotropin-releasing hormone agonists.

17. Nonhormonal treatment of AUB includes all following except:

a) vitamins;
b) combined oral contraceptives;
c) non-steroidal anti-inflammatory drugs;
d) tranexamic acid.

18. What is indication for endometrial ablation:

a) endometrial hyperplasia;
b) cervical hyperplasia;
c) uterine fibroids;
d) adenomyosis.

19. Uterine artery embolization is interventional radiology procedure for:

a) endometrial hyperplasia;
b) polyps;
c) uterine fibroids;
d) adenomyosis.

20. Long-term management of AUB includes all following except:

a) oral or injectable progestins;
b) spasmolytic drugs;
c) combined oral contraceptives;
d) gonadotropin-releasing hormone agonists.

Answers: 1 — c; **2** — a; **3** — c; **4** — b; **5** — a; **6** — b; **7** — c; **8** — a; **9** — c; **10** — d; **11** — a; **12** — d; **13** — c; **14** — b; **15** — d; **16** — c; **17** — b; **18** — a; **19** — c; **20** — b.

CLINICAL VIGNETTE

A 22-year-old female patient presents to a gynecology outpatient clinic with the chief complaint of no menstrual periods for the past 9 months. It is her first presentation for this issue. She reports having regular menses from menarche at age 13 until approximately 18 months ago, when her cycles became irregular and then stopped entirely. She is sexually active with one male partner and uses condoms inconsistently; a urine pregnancy test in the clinic is negative. She denies any history of pelvic pain, galactorrhea, or symptoms of hyperandrogenism (hirsutism, acne).

The patient is a professional long-distance runner. She reports that her training intensity increased significantly about 2 years ago in preparation for national competitions. Concurrently, she began following a strict, self-prescribed vegetarian diet to "improve performance and leanness." She describes a high level of academic stress due to studies. She notes a voluntary weight loss of approximately 10 kg (from over the past 6 months, and currently her BMI is 18.3 kg/m^2. She feels fatigued, often cold, and has noticed a decreased interest in sexual activity.

General examination.

Physical examination: vital signs — BP 102/68 mm Hg, HR 52 bpm, temp 97.8 °F, respiratory rate 14/min; neck: no thyromegaly or masses; cardiovascular: bradycardic, regular rhythm, no murmurs; abdomen: soft, non-tender, no organomegaly.

Organs and systems: neurological: no headaches or visual changes; gastrointestinal — no nausea/vomiting, normal bowel habits; cardiovascular — occasional lightheadedness, no palpitations; musculoskeletal — one past stress fracture (tibia, 1 year ago); psychiatric — endorsing significant stress and symptoms of mild anxiety.

Pelvic exam: normal external genitalia, vaginal mucosa appears mildly atrophic, cervix nulliparous, uterus small and anteverted, non-tender, adnexa without masses.

Laboratory and imaging studies. Pregnancy test (urine and serum): negative. Hormonal panel: low estradiol (< 20 pg/mL), low FSH (3.0 mIU/mL), low LH (2.5 mIU/mL), normal prolactin (12 ng/mL), normal TSH (1.8 mIU/mL), normal free thyroxine. Progestin challenge test: negative (no withdrawal bleed after a 10-day course of oral medroxyprogesterone acetate). Pelvic ultrasound: uterus is small in size with a thin endometrial lining (3 mm). Ovaries are normal in volume but with no dominant follicles or cysts. DEXA scan (bone density): Reveals low bone mineral density for age (Z-score of –1.8 at the lumbar spine).

Questions:

1. What is the most likely primary diagnosis?
2. What are the key pathophysiological and diagnostic criteria for this condition?
3. What is the strategy of management for this patient?

Answers:

1. ***Functional hypothalamic amenorrhea***, likely due to a combination of energy deficit (from excessive exercise and inadequate caloric intake) and psychological stress.

2. ***Criteria:*** a diagnosis of exclusion characterized by hypogonadotropic hypogonadism (low or inappropriately normal FSH/LH in the setting of low estradiol) in the absence of other organic causes (e.g., pituitary tumor, thyroid dysfunction, hyperprolactinemia). It is directly linked to suppression of the hypothalamic GnRH pulse generator due to stressors such as low energy availability (weight loss, excessive exercise), psychological stress, or a combination thereof. A negative progestin challenge test confirms hypothalamic-pituitary suppression.

3. ***Strategy of management:***

– a multidisciplinary approach focused on behavioral modification to reverse the causative factors: psychotherapy, nutritional counseling;

– estrogen-progestin replacement (transdermal estrogen in combination with cyclic progestin) to protect bone health while the underlying causes are addressed;

– regular follow-up to monitor weight, menstrual recovery, and bone density.

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