Pathophysiology, Diagnosis, and Treatment of Amenorrhoea

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Introduction

Amenorrhoea means absence of menstrual bleeding. It is a clinical sign rather than a disease by itself. The original essay correctly identified pregnancy, hypothalamic-pituitary signaling, ovarian function, uterine anatomy, stress, weight change, exercise, and hormonal disorders as important, but it mixed primary and secondary amenorrhoea, used a single six-month definition, and referred to the "hypothalamus adrenal gland axis," which is not the reproductive pathway that governs menstruation. The relevant pathway is the hypothalamic-pituitary-ovarian axis. Gonadotropin-releasing hormone from the hypothalamus stimulates pituitary luteinizing hormone and follicle-stimulating hormone, which regulate ovarian steroid production and ovulation. The endometrium responds to estrogen and progesterone. Menstruation occurs when a prepared endometrium sheds after hormone withdrawal, provided the uterus and outflow tract are anatomically capable of bleeding.

Amenorrhoea can therefore arise from pregnancy or lactation, developmental anomalies, hypothalamic suppression, pituitary disease, ovarian insufficiency, chronic anovulation, endocrine disorders, medication, or acquired uterine injury. Diagnosis should locate the level of dysfunction and identify conditions that need urgent treatment. It should not begin with the assumption that all amenorrhoea reflects "low hormone secretion." Some patients have low estrogen, some have normal estrogen with chronic anovulation, some have high gonadotropins, and others have anatomical obstruction. The clinical history, pregnancy test, examination, and targeted laboratory tests define the mechanism (American Society for Reproductive Medicine, 2024; Klein et al., 2019).

Primary and Secondary Amenorrhoea

Primary amenorrhoea is the absence of menarche by an age or developmental threshold at which evaluation is expected. Current practice commonly begins evaluation when menstruation has not occurred by age fifteen or within approximately three years of breast development, with earlier evaluation when secondary sexual characteristics are absent, genital anatomy is abnormal, or symptoms suggest endocrine or genetic disease. Secondary amenorrhoea occurs when a person who previously menstruated stops having periods. A common threshold is absence for three months in someone with previously regular cycles or six months in someone with irregular cycles. Definitions vary slightly among guidelines, so clinicians interpret them together with age, cycle history, and

symptoms.

This distinction guides the differential diagnosis. Primary amenorrhoea raises particular questions about puberty, chromosomes, gonadal development, Müllerian structures, and outflow obstruction. Secondary amenorrhoea more often involves pregnancy, hypothalamic suppression, polycystic ovary syndrome, hyperprolactinemia, thyroid disease, primary ovarian insufficiency, medication, or acquired uterine causes. The categories overlap; for example, a person with a congenital gonadal disorder may present before or after limited spontaneous menstrual function.

Normal Hypothalamic-Pituitary-Ovarian Physiology

Reproductive function depends on pulsatile secretion of gonadotropin-releasing hormone, or GnRH, from the hypothalamus. GnRH stimulates the anterior pituitary to release luteinizing hormone, or LH, and follicle-stimulating hormone, or FSH. FSH supports ovarian follicle development and estradiol production, while the mid-cycle LH surge triggers ovulation in an ovulatory cycle. After ovulation, the corpus luteum produces progesterone. If pregnancy does not occur, progesterone and estradiol fall and the endometrium sheds.

The system is regulated through feedback. Estradiol usually suppresses hypothalamic and pituitary activity but produces positive feedback before ovulation, helping generate the LH surge. Inhibins from the ovary also affect FSH. Energy availability, stress signals, prolactin, thyroid function, illness, and medications can alter this axis. Menstrual bleeding is therefore the visible outcome of a coordinated endocrine and anatomical process.

Pregnancy: The First Diagnosis to Exclude

Pregnancy is the most common physiological cause of secondary amenorrhoea in reproductive-age patients and should be excluded early, even when contraception is reported or the patient believes pregnancy is impossible. Human chorionic gonadotropin maintains the corpus luteum during early pregnancy, sustaining progesterone and the endometrium. Menstrual shedding does not occur because the hormonal environment is organized to support gestation.

A urine or serum pregnancy test is usually the first investigation. If pregnancy is present, the clinical question changes from amenorrhoea evaluation to determining gestational location and viability when symptoms indicate a problem. Severe one-sided pelvic pain, shoulder pain, syncope, or bleeding can signal ectopic pregnancy and requires urgent assessment. Amenorrhoea should therefore never be evaluated as a routine endocrine problem before pregnancy-related emergencies are considered.

Lactational Amenorrhoea

Breastfeeding can suppress ovulation through prolactin and altered hypothalamic GnRH pulsatility. Frequent exclusive or nearly exclusive breastfeeding is more likely to maintain amenorrhoea, particularly in the first months postpartum. The lactational amenorrhoea method can provide contraception only when specific criteria are satisfied, typically including amenorrhoea, full or nearly full breastfeeding, and less than six months since delivery. Once any criterion is no longer met, pregnancy risk increases and another contraceptive method is needed if pregnancy is not desired.

The return of ovulation can precede the first postpartum menstrual period, so absence of bleeding is not a guarantee of infertility outside established contraceptive criteria. Postpartum history should include breastfeeding pattern, delivery complications, hemorrhage, headaches, vision change, and symptoms of pituitary dysfunction.

Functional Hypothalamic Amenorrhoea

Functional hypothalamic amenorrhoea occurs when GnRH pulsatility is suppressed without a structural lesion. Low energy availability, weight loss, restrictive eating, excessive exercise, psychological stress, chronic illness, or combinations of these factors can contribute. LH and FSH are usually low or inappropriately normal, estradiol is reduced, and other causes must be excluded. The condition is sometimes associated with the female athlete triad or broader concept of relative energy deficiency in sport.

The word “functional” does not mean harmless or imaginary. Prolonged hypoestrogenism can reduce bone mineral density, impair fertility, and affect cardiovascular and psychological health. Treatment emphasizes restoring adequate energy intake, reducing excessive energy expenditure when relevant, treating disordered eating, and addressing stress. Weight alone is an incomplete measure; someone can have low energy availability without appearing underweight. Hormonal medication may produce scheduled bleeding without correcting the underlying energy deficit, so management should target the cause.

Polycystic Ovary Syndrome

Polycystic ovary syndrome, or PCOS, is a common cause of irregular cycles and secondary amenorrhoea. It involves variable combinations of ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology after exclusion of alternative disorders. The name is misleading because ovarian “cysts” are not required in every diagnostic framework, and the follicles seen on ultrasound are not the same as pathological ovarian cysts (Teede et al., 2023).

Patients may have acne, hirsutism, scalp hair thinning, weight concerns, insulin resistance, infertility,

or no visible androgen-related symptoms. Chronic anovulation can expose the endometrium to prolonged estrogen without regular progesterone, increasing the risk of endometrial hyperplasia. Management depends on goals and may include lifestyle support, treatment of metabolic risk, combined hormonal contraception, cyclic progestogen, antiandrogen therapy with reliable contraception, or ovulation induction when pregnancy is desired.

Hyperprolactinemia

Elevated prolactin can inhibit GnRH and cause amenorrhoea or oligomenorrhoea. Physiological causes include pregnancy and breastfeeding. Medications, particularly some antipsychotics, antidepressants, antiemetics, and other dopamine-modifying drugs, can raise prolactin. Pituitary adenomas and hypothyroidism are additional causes. Galactorrhea may occur, but its absence does not exclude hyperprolactinemia.

A prolactin result should be interpreted in context because stress, laboratory conditions, macroprolactin, and medication can affect levels. Persistent significant elevation may require pituitary imaging after secondary causes are reviewed. Headache, visual-field change, or neurological symptoms increase concern for a mass. Dopamine agonists are effective for many prolactinomas, but treatment should be individualized according to size, symptoms, fertility goals, and specialist guidance.

Thyroid Disease

Both hypothyroidism and hyperthyroidism can disrupt menstrual regularity. Hypothyroidism may increase thyrotropin-releasing hormone and prolactin, altering GnRH signaling, while broader metabolic changes also affect ovarian function. Symptoms can include fatigue, temperature intolerance, weight change, constipation or diarrhea, palpitations, tremor, skin change, or neck swelling, but mild disease may have few signs.

Thyroid-stimulating hormone is commonly included in the initial laboratory evaluation of amenorrhoea. Treating the thyroid disorder can restore cycles in some patients. Thyroid testing is important because menstrual dysfunction may be the presenting feature of a systemic endocrine disease rather than a primary ovarian problem.

Primary Ovarian Insufficiency

Primary ovarian insufficiency refers to loss or marked reduction of ovarian function before age forty. It may be spontaneous, genetic, autoimmune, iatrogenic after chemotherapy or radiation, surgical, or unexplained. Patients can present with amenorrhoea, irregular cycles, infertility, hot flashes, sleep disturbance, vaginal dryness, or no obvious estrogen-deficiency symptoms. FSH is elevated because

the pituitary increases stimulation when ovarian feedback is inadequate.

Primary ovarian insufficiency is not identical to permanent menopause. Intermittent ovarian activity and occasional spontaneous pregnancy can occur. Diagnosis has implications for bone, cardiovascular health, fertility, and emotional wellbeing. Evaluation may include repeat gonadotropins, genetic testing such as karyotype or *FMR1* premutation analysis in appropriate patients, and assessment for autoimmune disease. Hormone replacement is often recommended until the usual age of natural menopause unless contraindicated, with fertility counseling tailored to the individual (Nelson, 2009).

Gonadal Dysgenesis and Turner Syndrome

Turner syndrome is a chromosomal condition involving complete or partial absence or structural abnormality of one X chromosome. Gonadal dysgenesis can lead to insufficient estrogen and primary amenorrhoea. Other features may include short stature, cardiac abnormalities, renal differences, hearing problems, and characteristic physical findings, although presentation is variable. Mosaic forms can have partial spontaneous puberty or menstruation.

A patient with primary amenorrhoea, absent or incomplete secondary sexual development, or short stature may need chromosomal evaluation. Management extends beyond menstruation and includes cardiovascular surveillance, growth and pubertal treatment, reproductive counseling, and assessment of associated conditions.

Müllerian Agenesis and Outflow Anatomy

Müllerian agenesis, also called Mayer-Rokitansky-Küster-Hauser syndrome, involves congenital absence or underdevelopment of the uterus and upper vagina in a person with typical ovarian function and a 46,XX karyotype. Secondary sexual characteristics usually develop because the ovaries produce estrogen, but menstruation cannot occur because functional endometrium is absent. This presentation differs physiologically from ovarian failure.

Other anatomical causes include imperforate hymen, transverse vaginal septum, and cervical obstruction. Obstruction can produce cyclic pelvic pain and accumulation of menstrual blood. Physical examination and pelvic imaging help distinguish absent structures from blocked outflow. Sensitive communication is crucial because the diagnosis can affect identity, sexual function, fertility options, and emotional health.

Androgen Insensitivity Syndrome

Complete androgen insensitivity syndrome can present with primary amenorrhoea in a person with a 46,XY karyotype, testes that produce anti-Müllerian hormone, absent uterus, typical breast

development, and sparse or absent pubic and axillary hair. The external phenotype is female because tissues cannot respond normally to androgens. This condition should be distinguished from Müllerian agenesis, in which a 46,XX person has functioning ovaries and normal androgen responsiveness.

Diagnosis requires careful endocrine, genetic, and anatomical evaluation. Discussion of gonadal management, malignancy risk, hormone therapy, sexuality, and disclosure should be individualized and led by experienced multidisciplinary teams. Outdated or stigmatizing language should be avoided.

Asherman Syndrome and Acquired Uterine Causes

Intrauterine adhesions can develop after uterine instrumentation, postpartum procedures, infection, or surgery and may reduce or eliminate menstrual bleeding. Asherman syndrome is an important acquired anatomical cause of secondary amenorrhoea, especially when the history includes curettage after pregnancy or uterine surgery. Gonadotropins and ovarian hormones may be normal because the problem lies in the endometrial cavity.

Saline infusion sonography or hysteroscopy can evaluate the cavity, with hysteroscopy allowing direct visualization and treatment. Fertility and pregnancy risks depend on the extent of adhesions and response to treatment.

Pituitary and Hypothalamic Structural Disease

Amenorrhoea may result from pituitary tumors, infiltrative disorders, severe postpartum hemorrhage causing pituitary injury, cranial radiation, trauma, or hypothalamic lesions. These conditions are less common than pregnancy, PCOS, functional hypothalamic amenorrhoea, or hyperprolactinemia but may be medically urgent.

Symptoms such as persistent severe headache, visual-field loss, excessive thirst and urination, unexplained fatigue, adrenal insufficiency, or multiple pituitary hormone deficits require broader evaluation. Imaging should be ordered for a clinical reason rather than routinely in every case.

Medication and Contraceptive Effects

Hormonal contraception can intentionally reduce or stop withdrawal bleeding. Progestin-only methods, hormonal intrauterine devices, implants, injections, and continuous combined contraceptives commonly alter bleeding. Amenorrhoea in this setting may be expected and is not evidence that blood is “building up.” Pregnancy should still be excluded when clinically relevant, particularly if doses were missed or the method is overdue.

Other medications can affect prolactin, ovarian function, weight, or hypothalamic signaling. A complete medication history should include prescriptions, over-the-counter products, supplements, anabolic steroids, opioids, chemotherapy, and gender-affirming hormones where relevant. Patients should not stop essential medication without discussing alternatives with a clinician.

Chronic Disease and Systemic Illness

Chronic kidney disease, liver disease, inflammatory disorders, poorly controlled diabetes, celiac disease, severe infection, and other systemic illnesses can disrupt reproductive function through energy imbalance, inflammation, altered hormone metabolism, or pituitary effects. Menstrual changes may therefore signal broader illness.

Clinical history should include gastrointestinal symptoms, weight change, chronic pain, medication, fatigue, exercise, sleep, and symptoms outside the reproductive system. Treatment of the underlying condition may restore menstruation, but reproductive and bone health sometimes require parallel management.

History and Physical Examination

A structured history identifies age at thelarche and menarche, previous cycle pattern, sexual activity and pregnancy possibility, contraception, weight change, diet, exercise, stress, medications, chronic illness, headaches, visual symptoms, galactorrhea, hot flashes, vaginal dryness, acne, hirsutism, pelvic pain, and previous uterine procedures. Family history can reveal early menopause, delayed puberty, genetic disease, or endocrine disorders.

Physical examination may include growth pattern, body mass index while avoiding overreliance on it, blood pressure, thyroid examination, signs of androgen excess, estrogen status, galactorrhea, and pubertal development. Pelvic examination or ultrasound may be appropriate depending on age, consent, symptoms, and whether anatomy needs clarification. Evaluation should be trauma-informed and avoid unnecessary invasive examination.

Initial Laboratory Evaluation

After pregnancy testing, common initial laboratory tests include FSH, LH, estradiol, prolactin, and thyroid-stimulating hormone. Androgen testing may be added for hirsutism, acne, or virilization. Results are interpreted as a pattern. High FSH with low estradiol suggests ovarian insufficiency; low or inappropriately normal gonadotropins with low estradiol suggest hypothalamic or pituitary causes; hyperprolactinemia directs evaluation toward medication, pregnancy, thyroid disease, or pituitary pathology.

No single laboratory panel is appropriate for every patient. Primary amenorrhoea with absent uterus requires different testing from a previously menstruating athlete after weight loss. The goal is not to order every hormone at once but to answer specific diagnostic questions efficiently.

Pelvic Ultrasound and Other Imaging

Pelvic ultrasonography can determine whether the uterus is present, assess endometrial thickness, examine ovaries, and identify structural abnormalities. Ovarian morphology can support a PCOS diagnosis in appropriate patients, but ultrasound alone should not diagnose PCOS. In adolescents, multifollicular ovaries can be physiologic and create overdiagnosis.

Pituitary magnetic resonance imaging is indicated when significant persistent hyperprolactinemia or other pituitary features are present. Hysteroscopy evaluates suspected intrauterine adhesions. Bone-density assessment may be appropriate after prolonged hypoestrogenism, particularly with functional hypothalamic amenorrhoea or ovarian insufficiency.

The Progesterone Withdrawal Test

Historically, clinicians used a progestin challenge to assess whether endogenous estrogen had prepared the endometrium and whether the outflow tract was patent. Withdrawal bleeding after progestin suggests sufficient estrogen and an intact outflow tract, often consistent with chronic anovulation. No bleeding may reflect low estrogen, endometrial damage, or outflow obstruction.

The test has limitations and is not a substitute for a complete evaluation. Modern hormone assays and ultrasound often provide more direct information. The original essay describes estrogen and progesterone testing as if restoration of bleeding automatically identifies the disease. A response helps localize physiology but does not by itself establish the final diagnosis.

Consequences of Prolonged Amenorrhoea

The health implications depend on the mechanism. Prolonged estrogen deficiency can reduce bone density and contribute to genitourinary symptoms. Chronic anovulation with continued estrogen exposure can increase the risk of endometrial hyperplasia. Amenorrhoea can also signal infertility, but absence of menstruation does not always mean conception is impossible. Ovulation may occur unpredictably in conditions such as primary ovarian insufficiency and during recovery from hypothalamic amenorrhoea.

Psychological effects include anxiety about fertility, body image, sexual development, or an underlying diagnosis. These concerns deserve direct support. Menstruation should not be presented as the only marker of femininity or health, especially for people with congenital differences, gender

diversity, or medically induced amenorrhoea.

Treatment Principles

Treatment targets the underlying cause and the patient's goals. Pregnancy receives obstetric care; PCOS management addresses cycle protection, hyperandrogenism, metabolic health, and fertility as needed; functional hypothalamic amenorrhoea requires restoration of energy availability and reduction of contributing stress; hyperprolactinemia may require medication or management of a causative drug; thyroid disease is treated specifically; primary ovarian insufficiency often requires hormone replacement and fertility counseling; and structural lesions may need surgical management.

Simply producing menstrual bleeding is not always equivalent to correcting the disorder. Conversely, a patient using hormonal contraception may be healthy without monthly bleeding. Clinical goals include bone health, endometrial protection, fertility planning, symptom control, cardiovascular and metabolic risk, and psychological wellbeing.

When Amenorrhoea Requires Prompt Evaluation

Amenorrhoea with severe pelvic pain, positive pregnancy test and pain or bleeding, syncope, neurological symptoms, sudden virilization, significant headache or visual change, severe weight loss, or symptoms of adrenal or pituitary failure deserves urgent assessment. Primary amenorrhoea with an obstructive anomaly can produce painful blood accumulation. Rapid virilization may indicate an androgen-secreting tumor. These conditions are uncommon but important not to miss.

Routine evaluation is also appropriate when menstruation has not begun by expected developmental thresholds or has stopped for the defined interval, even without pain. Early assessment can protect bone, fertility, and general health and can reduce uncertainty.

Conclusion

Amenorrhoea is the absence of menstruation caused by disruption at one or more levels of the reproductive system. The principal regulatory pathway is the hypothalamic-pituitary-ovarian axis, not a hypothalamic-adrenal axis. Pregnancy should be excluded first in reproductive-age patients with secondary amenorrhoea. Subsequent evaluation distinguishes hypothalamic suppression, pituitary disease, PCOS and other chronic anovulatory states, primary ovarian insufficiency, thyroid and prolactin disorders, medication effects, congenital anatomy, and acquired uterine disease.

The original distinction between "primary" and "secondary" forms is useful, but modern thresholds are more precise than a universal six-month rule. Diagnosis requires history, targeted examination, pregnancy testing, hormone patterns, and imaging when indicated. Treatment should restore

underlying health and protect bone, endometrium, fertility, and wellbeing rather than merely force a monthly bleed. Persistent amenorrhoea merits medical evaluation because the menstrual pattern can provide important information about reproductive and systemic health (Gordon et al., 2017; Melmed et al., 2011).

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