

Pathophysiology, Diagnosis, and Treatment of Amenorrhoea

Posted on May 24, 2018

View this essay online:

<https://academic-master.com/pathophysiology-diagnosis-and-treatment-of-amenorrhoea/>

Introduction

Amenorrhoea is the absence or abnormal cessation of menstrual bleeding and should be understood as a clinical sign rather than a disease by itself. Normal menstruation depends on coordinated function of the hypothalamus, pituitary gland, ovaries, endometrium, and genital outflow tract. Gonadotropin-releasing hormone from the hypothalamus stimulates the pituitary to release luteinizing hormone and follicle-stimulating hormone; these hormones regulate ovarian follicle development, ovulation, and production of estradiol and progesterone. When pregnancy does not occur, withdrawal of ovarian hormones allows a prepared endometrium to shed. Amenorrhoea can therefore result from pregnancy, lactation, altered hypothalamic signaling, pituitary disease, chronic anovulation, ovarian insufficiency, thyroid or prolactin disorders, medication, congenital anatomy, or acquired uterine injury. The diagnostic task is to locate the disrupted level of the reproductive system rather than assume that every case reflects low hormone production. Current evaluation relies on menstrual and pubertal history, pregnancy testing, targeted examination, serum hormone patterns, and imaging when anatomy or pituitary disease needs clarification (American Society for Reproductive Medicine, 2024).

Primary, Secondary, and Physiological Amenorrhoea

Primary amenorrhoea describes failure to begin menstruation by the expected developmental age, while secondary amenorrhoea occurs after menstrual cycles have previously begun. The 2024 American Society for Reproductive Medicine committee opinion recommends evaluation when menstruation has not occurred by age fifteen in a person with normal secondary sexual development, with earlier investigation when pubertal development is absent, genital anatomy appears abnormal, or other signs suggest endocrine or genetic disease. Secondary amenorrhoea is commonly evaluated after three months without menses in someone whose cycles were previously regular or after a longer interval, often six months, when cycles were already irregular. These thresholds guide clinical attention rather than functioning as rigid rules detached from symptoms. Pregnancy remains the first diagnosis to exclude in a reproductive-age patient with secondary amenorrhoea because

contraception can fail and ovulation may occur unexpectedly. Lactation can also suppress ovulation through prolactin-mediated changes in hypothalamic GnRH pulsatility, especially during frequent breastfeeding in the early postpartum period.

The distinction between primary and secondary forms helps organize the differential diagnosis but does not create two completely separate disease lists. Congenital conditions, gonadal dysfunction, hypothalamic suppression, pituitary disorders, and endocrine disease can appear in either category depending on severity and timing. Primary amenorrhoea raises particular questions about chromosomal development, ovarian function, Müllerian structures, and outflow obstruction. Secondary amenorrhoea more commonly involves pregnancy, polycystic ovary syndrome, functional hypothalamic amenorrhoea, hyperprolactinemia, thyroid disease, primary ovarian insufficiency, medication, or acquired uterine injury. Physiological absence of menstruation can occur during pregnancy, breastfeeding, and before menarche, while hormonal contraceptives can intentionally reduce or eliminate withdrawal bleeding. Amenorrhoea during appropriately used hormonal contraception does not mean blood is accumulating in the uterus. Evaluation must therefore begin with context: age, prior cycle pattern, sexual activity, contraception, pregnancy possibility, weight and exercise changes, medications, chronic illness, stress, and associated symptoms.

Major Endocrine and Ovarian Causes

Functional hypothalamic amenorrhoea occurs when GnRH pulsatility is suppressed without a structural lesion, often in association with low energy availability, restrictive eating, significant weight loss, intensive exercise, psychological stress, chronic illness, or a combination of factors.

Gonadotropins are typically low or inappropriately normal and estradiol is reduced. The term “functional” does not mean harmless or imaginary. Prolonged hypoestrogenism can impair bone mineral density, fertility, and genitourinary health, while the underlying energy deficit may signal disordered eating or relative energy deficiency in sport. Treatment therefore targets nutritional adequacy, excessive energy expenditure, psychological stress, and any eating disorder rather than merely producing withdrawal bleeding with hormones. Weight by itself is an incomplete marker because a person can have low energy availability at a body weight that appears normal. Restoration of physiological reproductive signaling is more meaningful than creating an artificial monthly bleed while the underlying energy imbalance continues (Gordon et al., 2017).

Polycystic ovary syndrome is another 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 term can be misleading because visible ovarian “cysts” are not required in every diagnostic framework, and ultrasound findings alone should not establish the diagnosis, particularly in adolescents (Teede et al., 2023). Hyperprolactinemia can also suppress GnRH and may result from pregnancy, breastfeeding, medications, hypothyroidism, or a pituitary adenoma. Galactorrhea may occur but is not required. Thyroid disease can disrupt menstruation through direct metabolic effects and altered hypothalamic-

pituitary signaling. Primary ovarian insufficiency, defined by marked loss of ovarian function before age forty, typically produces elevated FSH and low estrogen and may be genetic, autoimmune, treatment-related, surgical, or unexplained. Unlike permanent menopause, intermittent ovarian activity and occasional spontaneous pregnancy can still occur.

Anatomical, Genetic, and Acquired Causes

Primary amenorrhoea with normal breast development requires careful evaluation of reproductive anatomy. Müllerian agenesis, or Mayer-Rokitansky-Küster-Hauser syndrome, involves congenital absence or underdevelopment of the uterus and upper vagina in a person with functioning ovaries and a typical 46,XX karyotype. Estrogen allows secondary sexual characteristics to develop, but menstruation cannot occur because functional uterine endometrium is absent. Complete androgen insensitivity syndrome can present differently: a person with a 46,XY karyotype has testes producing anti-Müllerian hormone, an absent uterus, breast development, and reduced or absent pubic and axillary hair because tissues do not respond normally to androgens. Turner syndrome and other forms of gonadal dysgenesis may lead to insufficient ovarian estrogen and primary amenorrhoea, often alongside features such as short stature or cardiovascular, renal, or hearing differences. Sensitive, multidisciplinary counseling is essential because these diagnoses can affect fertility, sexual function, identity, and long-term health as well as menstrual bleeding.

Outflow obstruction and acquired uterine injury can also prevent visible menstruation even when ovarian hormone production continues. An imperforate hymen, transverse vaginal septum, or cervical obstruction may produce cyclic pelvic pain because menstrual blood cannot exit normally. Pelvic examination and imaging help distinguish obstruction from absence of uterine structures. In secondary amenorrhoea, intrauterine adhesions known as Asherman syndrome can develop after uterine instrumentation, postpartum procedures, infection, or surgery. In these cases gonadotropins and ovarian hormones may remain normal because the problem lies within the uterine cavity. Saline infusion sonography or hysteroscopy can evaluate suspected adhesions, and hysteroscopy can also permit treatment. Structural pituitary or hypothalamic disease is less common but important when amenorrhoea accompanies severe headache, visual-field loss, excessive thirst, multiple pituitary-hormone deficits, or a history of significant postpartum hemorrhage, cranial radiation, trauma, or infiltrative disease.

Clinical Evaluation and Diagnostic Testing

A structured history is the foundation of evaluation. Clinicians should ask about age at breast development and menarche, previous cycle regularity, pregnancy possibility, contraception, breastfeeding, weight change, eating patterns, exercise, stress, medications, chronic disease, headaches, vision changes, galactorrhea, hot flashes, vaginal dryness, acne, hirsutism, pelvic pain, and prior uterine procedures. Family history may reveal delayed puberty, early ovarian insufficiency,

genetic conditions, or endocrine disease. Physical examination can assess growth, blood pressure, thyroid findings, pubertal development, signs of androgen excess, galactorrhea, and evidence of estrogen deficiency. Pelvic examination or ultrasound is used selectively when anatomy must be clarified and should be performed with consent and trauma-informed communication. Primary amenorrhoea and secondary amenorrhoea often require different emphasis, but neither should be investigated through a routine one-size-fits-all panel that ignores the patient's history and clinical context.

After pregnancy testing, common initial laboratory measurements include FSH, estradiol, prolactin, and thyroid-stimulating hormone, with LH and androgen testing added when clinically useful. High FSH with low estradiol suggests ovarian insufficiency, whereas low or inappropriately normal gonadotropins with low estradiol are more consistent with hypothalamic or pituitary suppression. Persistent prolactin elevation prompts review of pregnancy, medications, thyroid function, and possible pituitary pathology. Pelvic ultrasound can determine whether the uterus is present, evaluate endometrial thickness, and examine the ovaries, while pituitary MRI is reserved for clinically justified cases such as significant hyperprolactinemia or neurological features. A progestin-withdrawal test can sometimes provide information about estrogen effect and outflow patency, but it has limitations and does not replace modern hormone assays or imaging. The purpose of testing is to answer specific physiological questions efficiently rather than order every available reproductive hormone at once.

Treatment, Health Consequences, and Urgent Presentations

Treatment depends on the underlying mechanism and the patient's goals. Pregnancy receives appropriate obstetric care; functional hypothalamic amenorrhoea requires restoration of energy availability and management of contributing stress; PCOS treatment may address cycle protection, hyperandrogenism, metabolic risk, and fertility; hyperprolactinemia may require a dopamine agonist or adjustment of a causative medication; thyroid disease is treated specifically; and primary ovarian insufficiency often requires hormone replacement until approximately the usual age of natural menopause unless contraindicated. Structural lesions may require surgical management, while hormonal contraception may be continued without concern merely because it suppresses bleeding. Producing menstrual bleeding is not always equivalent to correcting the disease, and lack of monthly bleeding is not always harmful. Clinical goals include protection of bone and endometrium, symptom control, reproductive planning, cardiovascular and metabolic health, sexual wellbeing, and treatment of the systemic disorder responsible for the menstrual change.

The consequences of amenorrhoea depend on its cause. Prolonged estrogen deficiency can reduce bone density and contribute to vaginal or urinary symptoms, whereas chronic anovulation with continued estrogen exposure can increase the risk of endometrial hyperplasia. Fertility may be reduced, but absence of menstruation does not always mean pregnancy is impossible because

ovulation can occur unpredictably during recovery or in primary ovarian insufficiency. Psychological concerns about fertility, puberty, body image, or diagnosis deserve direct support and should not be minimized. Certain presentations require prompt assessment rather than routine follow-up: amenorrhoea with a positive pregnancy test and severe pelvic pain or bleeding may indicate ectopic pregnancy; sudden virilization can suggest an androgen-secreting tumor; severe headache or visual change raises concern for pituitary disease; and primary amenorrhoea with cyclic severe pain may reflect an obstructed outflow tract. Early evaluation can protect general, reproductive, and bone health while reducing unnecessary anxiety.

Conclusion

Amenorrhoea represents disruption of menstrual function at one or more levels of the hypothalamic-pituitary-ovarian and reproductive-anatomical system. The first step in reproductive-age patients with secondary amenorrhoea is to exclude pregnancy, after which the history, examination, and targeted tests help distinguish functional hypothalamic suppression, PCOS, hyperprolactinemia, thyroid disease, primary ovarian insufficiency, medication effects, congenital anatomy, pituitary disease, and acquired uterine causes. Primary amenorrhoea should be investigated by age fifteen when secondary sexual development is otherwise normal, with earlier evaluation when pubertal development or anatomy is abnormal. Current assessment relies particularly on pregnancy testing, FSH, estradiol, prolactin, TSH, and imaging selected for the clinical question. Treatment should address the underlying condition and protect bone, endometrial, metabolic, fertility, and psychological health rather than simply force a menstrual bleed. Menstrual patterns are therefore clinically useful signals, but interpretation always depends on physiology, anatomy, life stage, medications, and individual goals.

References

- American Society for Reproductive Medicine. (2024). Current evaluation of amenorrhea: A committee opinion. *Fertility and Sterility*, 122, 52–61.
- Gordon, C. M., Ackerman, K. E., Berga, S. L., Kaplan, J. R., Mastorakos, G., Misra, M., Murad, M. H., Santoro, N. F., & Warren, M. P. (2017). Functional hypothalamic amenorrhea: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, 102(5), 1413–1439.
- Klein, D. A., Paradise, S. L., & Reeder, R. M. (2019). Amenorrhea: A systematic approach to diagnosis and management. *American Family Physician*, 100(1), 39–48.
- Melmed, S., Casanueva, F. F., Hoffman, A. R., Kleinberg, D. L., Montori, V. M., Schlechte, J. A., & Wass, J. A. H. (2011). Diagnosis and treatment of hyperprolactinemia: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, 96(2), 273–288.

Nelson, L. M. (2009). Primary ovarian insufficiency. *New England Journal of Medicine*, 360, 606–614.

Teede, H. J., Tay, C. T., Laven, J. J. E., et al. (2023). Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertility and Sterility*.