

AMENORRHEA

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1. Core Definition and Clinical Presentation

Amenorrhea is defined clinically as the absence of menstrual bleeding, or menses, during the reproductive years. This state is specifically characterized by the failure of menstruation to occur within the chronological time frame spanning from the onset of puberty until the beginning of menopause, excluding periods of physiological cessation such as pregnancy, lactation, or the immediate post-partum phase. It is crucial to understand that amenorrhea is not a primary disease itself, but rather a profound symptom reflecting underlying dysfunction within the intricate hormonal, anatomical, or genetic regulatory systems governing the female reproductive axis, primarily the hypothalamic-pituitary-ovarian (HPO) axis.

The establishment of the menstrual cycle relies on a complex feedback loop involving the hypothalamus releasing gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These gonadotropins, in turn, act upon the ovaries, prompting ovulation and the cyclical production of estrogen and progesterone. When any component of this regulatory cascade fails--whether due to congenital anomaly, acquired pathology, or significant external stressors--the endometrial lining fails to proliferate and shed, resulting in amenorrhea. Identifying the precise point of failure is paramount for effective diagnosis and treatment planning, distinguishing between central regulatory issues, primary ovarian failure, or structural impediments.

Clinically, the presentation of amenorrhea varies widely depending on its etiology and classification. Patients may present with additional signs related to underlying hormonal imbalances, such as hirsutism, acne, galactorrhea, or symptoms suggestive of hypoestrogenism, including hot flashes and vaginal dryness. Furthermore, significant alterations to physical or cognitive wellness, including severe emotional stress, intense athletic training, or conditions like anorexia nervosa, are recognized causative factors capable of disrupting the delicate homeostatic balance required for regular menstruation, necessitating a holistic approach to patient evaluation.

2. Classification: Primary Amenorrhea

Primary amenorrhea refers specifically to the state where menses have never begun following the period of pubescence. Traditionally, this diagnosis is applied when a young woman has reached the age of 15 or 16 and has not yet experienced menarche, regardless of the presence of secondary sexual characteristics (such as breast development or pubic hair). An alternative and sometimes more urgent diagnostic criterion is the absence of menses by age 13 in the complete absence of any secondary sexual characteristics, suggesting a profound developmental delay or

congenital abnormality that requires immediate investigation.

The etiology of primary amenorrhea is often related to genetic abnormalities or congenital anatomical defects. Common genetic causes include Turner Syndrome (45,XO karyotype), which involves ovarian dysgenesis leading to premature ovarian failure, or variations in sex development (VSDs) such as androgen insensitivity syndrome (AIS) or Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome), where the uterus or upper vagina fails to develop properly. Anatomical defects can also involve obstructions, such as an imperforate hymen or transverse vaginal septum, which prevent the outflow of menstrual blood despite normal hormonal function, sometimes leading to cyclical pelvic pain.

Identifying primary amenorrhea necessitates a systematic diagnostic approach focused on distinguishing between delayed puberty, anatomical obstructions, or underlying hormonal or genetic syndromes. Initial evaluations involve a detailed history, physical examination, hormone assays (FSH, LH, TSH, Prolactin), and often genetic testing (karyotyping). Early diagnosis is vital, particularly in cases of genetic or structural anomalies, not only for providing necessary reproductive health counseling but also for addressing associated long-term health risks, such as potential bone density issues or psychological distress related to delayed development or the inability to conceive.

3. Classification: Secondary Amenorrhea

Secondary amenorrhea is diagnosed when a woman who previously had regular menstrual cycles experiences a cessation of menses. This state is recognized following the absence of menstruation for a duration of six consecutive months, or the equivalent of three previously established cycle lengths, in the absence of pregnancy, lactation, or menopause. Secondary amenorrhea is significantly more common than primary amenorrhea and typically arises from acquired conditions that disrupt the HPO axis or endometrial function, making pregnancy the single most frequent cause that must be ruled out immediately during diagnosis.

Beyond pregnancy, the causes of secondary amenorrhea are diverse, frequently stemming from hypothalamic, pituitary, ovarian, or uterine pathology. Hypothalamic dysfunction, often termed Functional Hypothalamic Amenorrhea (FHA), is a prevalent non-organic cause characterized by decreased GnRH pulse frequency due to excessive physical stress, rapid or significant weight loss, or profound psychological distress. The source content exemplifies this when noting, "Tina's sudden amenorrhea in her late twenties when she was not sexually active concerned her gynecologist," suggesting a non-pregnancy-related, possibly stress or lifestyle-induced, cessation of menses.

Other major causes of secondary amenorrhea include endocrine disorders such as Polycystic Ovary Syndrome (PCOS), which leads to chronic anovulation and irregular cycles, and premature

ovarian insufficiency (POI), where the ovaries cease functioning before age 40. Uterine causes, such as Asherman's syndrome (intrauterine adhesions following dilation and curettage or infection), also result in secondary amenorrhea by rendering the endometrium unresponsive to hormonal stimulation, despite normal ovarian function. Because the underlying causes dictate the long-term prognosis, a thorough differential diagnosis is essential to prevent complications such as infertility and hypoestrogenic bone loss.

4. Etiological Factors and Pathophysiology

The pathophysiology of amenorrhea can be broadly categorized based on the anatomical level of the HPO axis disruption. Hypothalamic disorders represent a highly common category, often driven by functional factors. In Functional Hypothalamic Amenorrhea (FHA), the body interprets energetic stress (e.g., low caloric intake combined with high energy expenditure) or severe emotional stress as a hostile environment unsuitable for reproduction. This leads to the suppression of GnRH release, which subsequently causes low FSH and LH levels, ultimately leading to ovarian dormancy and estrogen deficiency. This adaptive suppression is reversible once the underlying physical or psychological stressors are mitigated.

Pituitary causes typically involve conditions that disrupt the normal synthesis or release of gonadotropins. Hyperprolactinemia, often caused by pituitary adenomas (prolactinomas), is a key example, as elevated prolactin levels inhibit GnRH secretion, leading to anovulation and amenorrhea. Less common pituitary etiologies include severe systemic illness or infiltrative diseases. Ovarian failure, conversely, involves a primary defect at the end-organ level, such as POI, where the ovaries prematurely run out of follicles or become resistant to gonadotropin stimulation. In these cases, the pituitary attempts to compensate by drastically increasing FSH and LH secretion, resulting in high gonadotropin levels coupled with low estrogen.

The role of cognitive wellness and severe emotional stressors as causative factors cannot be overstated, particularly in secondary amenorrhea. Psychological distress impacts the limbic system and subsequent hypothalamic function via the stress hormones, like cortisol. Chronic elevation of cortisol can directly inhibit GnRH pulsatility, effectively putting the reproductive system on hold. Furthermore, conditions such as anorexia nervosa or bulimia directly cause amenorrhea through malnutrition and extreme leanness, leading to insufficient energy availability necessary for reproductive maintenance. Therefore, treatment protocols must often address these underlying psychological and behavioral alterations alongside hormonal deficiencies.

5. Diagnostic Workup and Management

The diagnostic investigation of amenorrhea is stepwise, beginning with the exclusion of the most common cause: pregnancy. Following this, the workup aims to determine the level of dysfunction--

whether it is uterine, ovarian, pituitary, or hypothalamic. Initial hormonal assessments typically include quantitative beta-hCG, TSH (to exclude thyroid disease), and Prolactin levels. If these initial screening tests are normal, further testing usually involves measuring FSH and LH levels to categorize the amenorrhea as hypogonadotropic (low gonadotropins, suggesting hypothalamic/pituitary failure) or hypergonadotropic (high gonadotropins, suggesting primary ovarian failure).

A standard procedure in the evaluation of secondary amenorrhea is the Progesterone Withdrawal Test (or challenge test). This involves administering a progestin for several days; withdrawal bleeding suggests that the patient possesses sufficient estrogen and a responsive uterus, pointing toward anovulation (often due to PCOS or FHA). Failure to bleed necessitates further investigation, potentially involving an estrogen-progesterone challenge to confirm the presence of a uterus and rule out Asherman's syndrome. Pelvic imaging, typically via ultrasound, is essential for identifying anatomical abnormalities in primary amenorrhea or assessing ovarian morphology (e.g., polycystic ovaries) in secondary amenorrhea.

Management is entirely dependent upon the specific etiology and the patient's primary goals (e.g., restoring fertility versus preventing long-term complications). For FHA, lifestyle modification focusing on stress reduction, nutritional rehabilitation, and moderation of exercise intensity is the first line of therapy, aiming to restore endogenous menstrual function. In cases of estrogen deficiency (such as POI or persistent FHA), Hormone Replacement Therapy (HRT) is often instituted to prevent the long-term sequelae of hypoestrogenism, particularly osteoporosis. For conditions like PCOS, management focuses on regulating cycles and addressing hyperandrogenism, often using combined oral contraceptives or insulin-sensitizing agents like metformin.

6. Psychological and Long-Term Implications

The long-term implications of untreated amenorrhea are significant, extending far beyond fertility concerns. The primary concern is the consequence of prolonged hypoestrogenism, which leads to accelerated bone loss, potentially resulting in osteopenia or severe osteoporosis, dramatically increasing the risk of fragility fractures later in life. This risk is particularly high in cases of FHA and POI, where estrogen production is severely compromised. Appropriate monitoring of bone mineral density via DXA scans and timely initiation of estrogen replacement are critical preventative measures.

Psychologically, the experience of amenorrhea, particularly when associated with conditions like eating disorders, athletic pressures, or unexplained hormonal dysfunction, can induce significant distress, anxiety, and depression. The disruption of a fundamental aspect of reproductive health often leads to feelings of inadequacy, body image concerns, and worry about future fertility.

Therefore, the management plan frequently requires a multidisciplinary team approach, integrating endocrinology or gynecology with psychological counseling or psychiatric support to address the cognitive and emotional factors contributing to or resulting from the condition.

For women desiring fertility, the prognosis depends heavily on the underlying cause. While amenorrhea due to FHA is generally reversible with lifestyle changes, requiring patience and support, conditions involving primary ovarian failure (POI) often require advanced reproductive technologies, such as oocyte donation. The clinical management of amenorrhea thus mandates not only addressing the immediate physiological symptoms but also providing comprehensive education and empathetic support regarding the patient's reproductive potential and long-term health maintenance.

7. Further Reading

[Amenorrhoea \(Wikipedia\)](#)

[Amenorrhea: Symptoms and Causes \(Mayo Clinic\)](#)

[Turner Syndrome \(National Center for Biotechnology Information\)](#)

[Polycystic Ovary Syndrome \(Mayo Clinic\)](#)