Etiology and management of amenorrhea in adolescent and young adult women

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In this article, we will review the etiology and management of amenorrhea in adolescent and young adult women, beginning with the diagnostic work-up and followed by etiologies organized by system. Most cases of amenorrhea are caused by dysfunction of the hypothalamic-pituitary-ovarian (HPO) axis, which is the major regulator of the female reproductive hormones: estrogen and progesterone. We begin by reviewing hypothalamic etiologies, including eating disorders and relative energy deficiency in sport. Then, pituitary causes of amenorrhea are reviewed, including hyperprolactinemia, empty sella syndrome, Sheehan's syndrome and Cushing's syndrome. Next, ovarian causes of amenorrhea are reviewed, including polycystic ovarian syndrome and primary ovarian insufficiency. Finally, other etiologies of amenorrhea are discussed, including thyroid disease, adrenal disease and reproductive tract anomalies. In conclusion, there is a wide and diverse range of causes of amenorrhea in adolescents that originate from any level of the HPO axis, as well as anatomic and chromosomal etiologies. Treatment should be focused on the underlying cause. Preservation of bone density and risk of fractures should be discussed with amenorrheic patients since many causes of amenorrhea can result in decreased bone density and may be irreversible.

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Introduction

The median age of menarche (first menstrual period) has remained relatively stable over the past 30 years, with the first menstrual period occurring between 12 and 13 years for the majority of girls in developed countries, with some variability depending on race.[1] In the National Health and Nutrition Survey III, the mean age of menarche was 12.1 years for black girls, 12.2 years for Mexican-American girls, and 12.7 years for white girls.[2] Menarche typically occurs 2-3 years after thelarche (breast budding, the first sign of puberty in girls), commonly at Tanner stage IV of breast development. Ninety-eight percent of females will have had menarche by 15 years old.[1] Thus, primary amenorrhea is defined as absence of menarche by 15 years old. Secondary amenorrhea is defined as the cessation of regular menses for 3 months or the cessation of irregular menses for 6 months. Oligomenorrhea is defined as irregular menstrual cycles >35 days apart, although in adolescents the definition may be extended to include cycles that last longer than 45 days until 2-3 years after menarche.

Most cases of amenorrhea are caused by dysfunction of the hypothalamic-pituitary-ovarian (HPO) axis, which is the major regulator of the female reproductive hormones: estrogen and progesterone. Gonadotropin releasing hormone (GnRH) is released in a pulsatile fashion from the hypothalamus at the onset of puberty, which triggers the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary. LH and FSH bind to receptors in the ovaries and lead to the release of estrogen and progesterone. During the menstrual cycle, estrogen and progesterone are released in fluctuating concentrations with low levels of estrogen and progesterone in the follicular phase and high estrogen and progesterone levels in the luteal phase. The follicular phase ends with ovulation and the luteal phase ends with either menstruation or fertilization.

The average length of the menstrual cycle is 28 days, although it can vary from 21 to 45 days in adolescent girls and 21−35 days in adult women.[3] Dysfunction at any point in the HPO axis can lead to

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menstrual abnormalities and amenorrhea. Hypogonadotropic hypogonadism is a form of hypogonadism (low estrogen/progesterone levels) that is caused by low levels of hormones that stimulate the ovaries, including GnRH, LH and FSH. Hypergonadotropic hypogonadism results from abnormal function of ovaries in females with decreased estrogen and progesterone levels, despite high or normal GnRH, LH and FSH. Outside of the HPO axis, amenorrhea can be caused by abnormalities in thyroid or adrenal hormones, or anatomic abnormalities in the female reproductive organs including the uterus, cervix, vagina or hymen. Pregnancy must also be excluded in all cases of amenorrhea.

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Diagnostic work-up

Diagnosis begins with a thorough history and physical examination. In patients with otherwise normal development, initial work-up should include a pregnancy test, serum LH, FSH, thyroid-stimulating hormone (TSH), free thyroxine, estradiol and prolactin levels. If these tests are normal, a progestin challenge should be considered to trigger a withdrawal bleed. If the patient has a normal withdrawal bleed in response to progestin, the differential diagnosis includes hypothalamic amenorrhea, chronic disease, celiac disease and polycystic ovary syndrome (PCOS). If the patient does not experience a withdrawal bleed with a progestin challenge and estradiol levels are low, possibilities include hypothalamic amenorrhea, anorexia nervosa, chronic disease or a pituitary lesion. Elevated levels of TSH and a low free thyroxine are consistent with hypothyroidism, and low TSH and high free thyroxine with hyperthyroidism. In patients with elevated prolactin levels, the differential diagnosis includes a prolactinoma, idiopathic hyperprolactinemia, a central nervous system tumor, medications or pregnancy. A repeat prolactin level should be performed and magnetic resonance imaging of the brain should be considered, particularly if the patient is displaying signs or symptoms of increased intracranial pressure, such as headache, vomiting or diplopia.[4]

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Patients with low FSH and LH or normal levels that have evidence of disordered eating, excessive exercise or poor nutritional status, may have functional hypothalamic amenorrhea. In patients with low FSH and LH, constitutional delay of puberty or, rarely, primary gonadotropin-releasing hormone deficiency, should also be considered. In patients with elevated FSH levels, the differential diagnosis includes primary ovarian insufficiency (POI), Turner syndrome, radiation, chemotherapy, autoimmune oophoritis and Fragile X carrier status. Further workup would include: karyotype, fragile x mental retardation 1 (FMR1) testing, and screening for thyroid and adrenal autoantibodies, celiac disease and other autoimmune disorders.[5]

In patients with signs of androgen excess such as severe acne, hirsutism, male pattern baldness, or clitoromegaly, considerations include PCOS, late onset congenital adrenal hyperplasia (CAH), and androgen secreting tumors. A work-up for these conditions includes: pregnancy test, FSH, LH, TSH, free thyroxine, prolactin, sex-hormone binding globulin (SHBG), and androgen levels including total and free testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS) and morning 17 hydroxyprogesterone.[5] For severely elevated testosterone levels, >150 ng/dL, or DHEAS

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level >700 ug/dL, evaluation for an ovarian or adrenal tumor is required. For those patients with mildly or moderately elevated androgen levels, who meet the diagnostic criteria for PCOS, screening for metabolic syndrome should also be performed, including a Hemoglobin A1C (HbA1C), fasting glucose, 2 h glucose tolerance test and lipid levels. For patients with 17 hydroxyprogesterone levels >200 ng/dL, an adrenocorticotropic hormone (ACTH) stimulation test should be performed to evaluate for non-classic CAH. Additionally, in patients with signs or symptoms of acromegaly, an IGF-1 level should be performed, and in patients with signs or symptoms of Cushing's syndrome, cortisol excess should be evaluated.[4]

In cases of primary amenorrhea, if there is concern for an external or internal genital anomaly, a pelvic ultrasound is indicated. If the uterus is absent, consider androgen insensitivity, 46XY disorders, or agenesis of the uterus (MRKH). If the uterus is absent and there are signs of virilization on examination, consider 5-alpha reductase deficiency, partial androgen insufficiency and intersex conditions. Follow up labs include: testosterone levels, estradiol, LH, FSH, karyotype, and possibly pelvic MRI. Pelvic ultrasound can also be diagnostic for imperforate hymen, transverse vaginal septum, vaginal agenesis and agenesis of the cervix.[5]

Etiology

Hypothalamic causes of amenorrhea

Hypothalamic dysfunction can lead to hypogonadotropic hypogonadism via abnormal GnRH levels. Functional hypothalamic amenorrhea, also known as functional hypothalamic GnRH deficiency, accounts for approximately 35% of cases of secondary amenorrhea.[6] It results from a decrease in GnRH secretion from the hypothalamus leading to abnormal FSH and LH levels and low estradiol, which lead to impaired folliculogenesis and anovulation.[7] It can result from a variety of etiologies including emotional and illness-induced stress, malnutrition due to eating disorders, excessive exercise or chronic disease. Hypothalamic amenorrhea resulting from stress is usually transient, with the HPO axis returning to normal functioning when the illness or stressor is resolved.

Eating disorders

Eating disorders are one common cause of malnutrition and amenorrhea in adolescent patients. With the release of the 5th edition of the Diagnostic and Statistical Manual (DSM-5) in 2013, amenorrhea was removed as a criterion for the diagnosis of anorexia nervosa, but is a symptom in up to 68% of patients with eating disorders.[8] Predictive factors of amenorrhea in patients with eating disorders include low body weight, excessive exercise, stress and caloric restriction with negative energy balance, which result in the suppression of the HPO axis. Amenorrhea may also occur in patients with atypical AN or bulimia nervosa (BN) who are not considered underweight, as the HPO axis dysfunction can also be related to a state of malnutrition rather than a low body weight per se. Approximately 37−64% of patients with BN have hypothalamic dysfunction with oligomenorrhea, and amenorrhea may occur in up to 40% of cases.[9]

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Weight restoration is the therapeutic goal in patients with eating disorders, although there is no clear consensus for target weight, which should be estimated for each individual based on their prior growth charts, and thus may be higher in patients with higher premorbid weights. As there is a wide range for target body mass index (BMI) percentile for return of menses in patients with eating disorders, it is difficult to predict a target weight precisely. One study showed BMI percentile range for return of menses in patients with AN was 25−50, and 50−75 for those patients with a diagnosis of Eating Disorder Not Otherwise Specified (EDNOS) or BN.[10] Some eating disorder patients remain amenorrheic despite weight restoration, likely due to continued malnutrition in the setting of abnormal eating patterns and avoidance of foods with high fat content.[11] In addition to the correction of the biological sequelae of malnutrition, including the resumption of menstruation, the American Psychiatric Association (APA) recommends that the goals of nutritional rehabilitation in eating disorders should also include correction of the psychological

sequelae of eating disorders, normalization of eating patterns and achievement of normal perceptions of hunger and satiety.[12]

Relative energy deficiency in sport

Amenorrhea may also be seen in athletes as a result of a negative energy balance due to increased energy expenditure and insufficient caloric intake. Relative Energy Deficiency in Sport (RED-S), formerly known as the Female Athletic Triad, is a syndrome characterized classically by the triad of amenorrhea/oligomenorrhea, disordered eating and decreased bone mineral density, now expanded to include male athletes and encompass the many aspects of physiological function, health and athletic performance. The incidence of amenorrhea in athletes ranges from 3% to 66% depending on the sport, level of competition, age and definition of amenorrhea.[13] Menstrual problems are more often seen in sports with a focus on lean body type and with strict weight standards, such as gymnastics, figure skating, ballet and running. In runners, training before menarche is associated with delayed menarche by 5 months for each year of training, thus can present as primary amenorrhea.[14] The incidence of amenorrhea is also related to the intensity of exercise. For example, one study showed an incidence of amenorrhea of 20% in women running 20 miles per week and 43% for those running 60 to 80 miles per week.[15] Many adolescent athletes also have a poor diet that is low in calories and fat. Athletes additionally have a higher incidence of disordered eating behaviors than the general population, ranging from 6% to 45% in female athletes.[16] Amenorrhea in athletes primarily results from a disruption of the HPO axis at the level of the hypothalamus leading to abnormal GnRH levels, but is also associated with additional neuroendocrine abnormalities which play a role in the development of amenorrhea, including activation of the hypothalamic-pituitary-adrenal axis and suppression of the hypothalamic-pituitary-thyroidal axis, as well as low leptin levels.[17]

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Other hypothalamic etiologies

Other hypothalamic etiologies of amenorrhea include isolated GnRH deficiency, inflammatory or infiltrative diseases, brain tumors, cranial irradiation, traumatic brain injury and certain specific syndromes and chronic diseases. Isolated GnRH deficiency is a genetic disorder resulting in low GnRH levels and, when presenting in combination with anosmia, is known as Kallmann syndrome. Severe cases can present in males in infancy with microphallus and cryptorchidism, and in both sexes may have other congenital abnormalities including midline facial defects or skeletal abnormalities. However, isolated GnRH deficiency will typically present in adolescence with failure to initiate sexual maturation and primary amenorrhea.[18] Stress has also been shown to inhibit reproductive function due to activation of the hypothalamic-pituitary-adrenal axis, leading to elevated cortisol levels, which inhibit GnRH secretion.[19]

Rarely, amenorrhea may be caused by hypothalamic tumors, including craniopharyngiomas and lymphomas, and infiltrative diseases, including Langerhans cell histiocytosis and sarcoidosis, leading to low levels of GnRH and abnormal gonadotropin levels. Usually, these cases will also be associated with other neurologic symptoms including headaches, and personality and mood changes. Injury to the hypothalamus through cranial irradiation and traumatic brain injury may also result in amenorrhea through abnormal GnRH levels.[20]

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Syndromes that are associated with hypothalamic amenorrhea include Prader-Willi, Laurence-Moon-Biedl, and leptin mutations. Chronic diseases, including type 1 diabetes mellitus (DM1) and celiac disease, are also associated with menstrual irregularities due to hypothalamic dysfunction and abnormal GnRH levels.[19] One study showed that 70% of adolescents with DM1 have amenorrhea or oligomenorrhea compared

with 22% of controls,[21] and 40% of patients with untreated celiac disease have menstrual cycle disorders including amenorrhea and oligomenorrhea.[22]

Pituitary causes of amenorrhea

Hyperprolactinemia

Hyperprolactinemia is the most common pituitary cause of amenorrhea, accounting for 13% of total cases of secondary amenorrhea and 90% of cases with a pituitary etiology.[3] Normal serum prolactin levels in women range from 1 to 25 ng/mL. Prolactin is secreted episodically, with the highest levels being at night, but in patients with prolactinomas, prolactin levels will be elevated throughout the day and night. Elevated prolactin levels suppress the HPO axis, resulting in amenorrhea through inhibition of the pulsatile secretion of GnRH. Prolactin is primarily regulated by the hypothalamus with secretion of dopamine, which inhibits prolactin secretion.[23] Thus, dopaminergic drugs may decrease serum prolactin levels, and other drugs, such as antipsychotics, may increase serum prolactin levels through their action on dopamine. Estrogen and breast stimulation also trigger prolactin release, as seen in the postpartum period, which results in galactorrhea.

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In adolescent patients, hyperprolactinemia can present as galactorrhea, delayed pubertal development, or amenorrhea. One half to two thirds of adolescents with hyperprolactinemia and amenorrhea also have galactorrhea.[24] A prolactin level >100 ng/ML is most suggestive of a prolactin-secreting pituitary tumor, also known as a prolactinoma, and diagnosis should be confirmed with a brain MRI. First line treatment for a prolactinoma is typically with a dopamine agonist such as bromocriptine or cabergoline, which results in reduction of tumor size and restoration of menses. Larger or treatment-resistant adenomas may require surgical resection.

Other etiologies of hyperprolactinemia include hypothyroidism, hypothalamic disease/tumors, chronic renal failure, tumors including bronchogenic or renal carcinoma, stress, hypoglycemia, sleep induced, or local factors resulting in nipple stimulation or chest wall injury. Prolactin levels may also appear falsely elevated as the serum assay for prolactin does not distinguish between the biologically inactive macroprolactin and the biologically active monomeric form, which is seen in patients with prolactinoma. Thus, it has been recommended that prolactin levels should only be drawn in symptomatic patients to avoid false positives.[23]

Physiological causes of hyperprolactinemia resulting in amenorrhea include pregnancy and lactation. Pregnancy is the most common cause of hyperprolactinemia and should be considered in adolescents who are sexually active. During pregnancy, prolactin levels increase, and peak at delivery, reaching up to 600 ng/mL. In women who do not breast feed, levels return to normal by 3 weeks.[20] For women who breastfeed, sucking increases prolactin levels. By approximately 12 weeks postpartum, the drop in estradiol levels leads to decreased lactotroph hyperplasia and prolactin levels decrease. The duration of amenorrhea in lactating women is associated with multiple factors, including prolactin levels, in response to suckling, and prolactin bioactivity. Reduced LH-pulse amplitude and frequency and reduced response to estrogen are also seen with lactational amenorrhea, and is likely related to GnRH suppression.[20]

Other pituitary etiologies

Other etiologies for amenorrhea originating from the pituitary include empty sella syndrome (1.5%), Sheehan's syndrome (1.5%), and Cushing's syndrome (1%).[3] In empty sella syndrome, the pituitary shrinks or flattens and the sella turcica, which is the bony structure surrounding the pituitary, fills with cerebrospinal fluid, appearing empty. In primary empty sella syndrome, a small anatomical defect above the pituitary gland causes increased pressure in the sella turcica, leading to flattening of the pituitary gland. Patients are often asymptomatic, with fewer than 1% of people developing symptoms,[25] but may present with amenorrhea due to deficiency of the pituitary hormones LH and FSH. Secondary empty sella syndrome occurs as a result of external trauma such as injury, surgery or radiation causing the pituitary gland to decrease in size. Sheehan's

syndrome occurs with blood loss and hypovolemic shock during and after childbirth, resulting in necrosis of the pituitary gland.

Another pituitary cause of amenorrhea is Cushing's syndrome, which results from prolonged exposure to glucocorticoids like cortisol and is characterized by a myriad of signs and symptoms including high blood pressure, abdominal obesity, striae, moon facies, buffalo hump, acne, hirsutism and irregular menstruation, including oligomenorrhea and amenorrhea. Cushing's syndrome may result from a variety of causes, but most commonly occurs in patients taking steroid medications such as prednisone, and in patients with pituitary adenoma with increased adrenocorticotropic hormone (ACTH), resulting in excess cortisol production from the adrenal glands (also known as Cushing's disease). Other types of brain tumors or inherited disorders like multiple endocrine neoplasia and Carney complex may also lead to Cushing's syndrome.[20] Elevated cortisol levels can lead to suppression of the HPO axis and resultant amenorrhea.

Ovarian etiologies of amenorrhea include polycystic ovary syndrome (PCOS), primary ovarian insufficiency (POI), gonadal dysgenesis, tumor, bilateral oophorectomy, irradiation and chemotherapy.

Ovarian causes of amenorrhea

Polycystic ovary syndrome

Ovarian etiologies of amenorrhea include polycystic ovary syndrome (PCOS), primary ovarian insufficiency (POI), gonadal dysgenesis, tumor, bilateral oophorectomy, irradiation and chemotherapy. PCOS is one of the most common etiologies of menstrual abnormalities, affecting 6 to 12% of females of reproductive age in the United States.[26] For adults, there are several proposed diagnostic criteria for PCOS. The Rotterdam criteria is the most widely used diagnostic criteria and requires two out of the following three signs for diagnosis of PCOS: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, or polycystic ovaries by ultrasound.[27] However, using diagnostic criteria established for adults is problematic when applied to adolescents for several reasons. First, anovulatory cycles, and thus irregularities in the menstrual cycle, are normal in adolescents, particularly in the first few years following menarche. Additionally, clinical signs of hyperandrogenism such as acne and hirsutism can also be seen in adolescents and can be a normal part of puberty and development. Biochemical evidence of hyperandrogenism such as elevated testosterone levels are also unreliable in adolescents since testosterone levels rise during anovulatory cycles, and may not predict adult androgen levels. Finally, the ultrasound findings of polycystic ovaries can be normal in adolescence.[28] International consensus diagnostic criteria for PCOS in adolescents, therefore, is the otherwise unexplained combination of an abnormal menstrual pattern as evidence of ovulatory dysfunction, which is abnormal for age or gynecologic age and persistent for 1 to 2 years, and clinical and/or biochemical evidence of hyperandrogenism marked by hirsutism clinically or elevation in serum total or free testosterone biochemically.[29] If a patient meets these diagnostic criteria, but is within one to two years after menarche, she should be given the diagnosis of "at risk for PCOS," since irregularity of the menstrual cycle is normal at this stage due to the frequency of anovulatory cycles, and should be monitored closely.

While the etiology of PCOS is unclear, it is likely related to a complex interaction between multiple systems, including ovarian function, steroid hormone production, metabolism, the neuroendocrine system, genetics and the environment.[30] The pathophysiology of PCOS involves an exaggerated LH response resulting in increased androgen levels, and inadequate FSH production that leads to decreased conversion of androgens to estradiol and follicular arrest. Patients with PCOS may also develop insulin resistance, and this is exacerbated in patients who are overweight and obese. Studies estimate that 40% to 80% of women with PCOS meet the criteria for overweight or obesity.[31]

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Insulin resistance may be related to increases in androgen levels in PCOS which reduce insulin sensitivity, and corresponding increases in insulin lead to further androgen secretion in fat tissue. Insulin also augments the ovarian response to LH, potentiates adrenal androgen production, and inhibits the hepatic synthesis of sex hormone binding globulin, resulting in increased circulating androgen levels.[32]

PCOS can present with a spectrum of menstrual disorders including amenorrhea, oligomenorrhea, and abnormal uterine bleeding resulting from anovulation. Patients may also present with a range of clinical findings of androgen excess including hirsutism, acne, male pattern baldness, and alopecia. Hirsutism can be graded using the Ferriman-Gallway scoring system, which divides the body into nine areas each of which is assigned a score from 0 (no hair) to 4 (frankly virile), and these are summed to provide a hirsutism score.[33] The clinical examination may be complicated due to hair removal practices including shaving, waxing, tweezing, depilatories, electrolysis and laser treatments. Male pattern baldness and alopecia can be seen with significantly elevated androgen levels, and can be assessed with tools like the Ludwig visual score.[32] As previously discussed, acne is common in adolescence, but if severe and associated with menstrual abnormalities, can be considered as a possible sign of androgen excess.

Laboratory evaluation for PCOS includes assessment of androgen levels, LH and FSH, as well as evaluating for associated clinical issues like diabetes and hyperlipidemia when indicated. Biochemical evidence of hyperandrogenism includes elevations in total testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEAS) and androstendione. DHEAS, a steroid hormone produced by the adrenal glands, may be elevated in PCOS, but severely elevated DHEAS levels (>700 ug/dl) are concerning for adrenal tumors and warrant further workup and imaging. FSH can be measured to assess ovarian function, and LH is often ordered to assess the LH:FSH ratio, which can be elevated in patients with PCOS, but is not diagnostic of the syndrome, as the ratio may be impacted by when it is drawn in an individual's menstrual cycle, with normal LH elevations seen prior to ovulation. In patients with obesity or clinical evidence of insulin resistance, such as acanthosis nigricans, a hemoglobin A1C (HbA1C) level can be checked to assess for diabetes mellitus and lipid levels checked to evaluate for hyperlipidemia. A routine pelvic ultrasound to evaluate for the classic ovarian morphology of multiple small follicles in a "string of pearls" appearance, as seen in adults, is not recommended in adolescents.[32]

Goals of treatment for PCOS include decreasing the risk of endometrial cancer (due to unopposed estrogen leading to endometrial hyperplasia), managing menstrual irregularities, reducing hirsutism and acne, and minimizing risks for development of type 2 diabetes mellitus and cardiovascular disease. The first line intervention for adolescents with PCOS is lifestyle modification, including diet changes, exercise and weight loss. Weight loss has been shown to decrease androgen production, improve insulin sensitivity, and lower lipid levels.[34] The first line pharmacologic therapy for treatment of PCOS is combined oral contraceptives (COCs), containing the hormones estrogen and progesterone. COCs can improve both hirsutism and acne, as well as regulate menses, although they do not change insulin sensitivity. Antiandrogens such as spironolactone can be used either alone or as an adjunct to COCs for acne and hirsutism if there is no improvement within 6 months of treatment, and can be helpful in patients with significant hirsutism and/or male pattern hair loss. Insulin sensitizing agents such as metformin can be used in patients with insulin resistance and those who are at high risk for development of type 2 diabetes mellitus.[32]

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Primary ovarian insufficiency

Primary ovarian insufficiency (POI), also called premature ovarian failure, occurs due to the depletion or dysfunction of the ovarian follicles, causing the cessation of menstruation prior to 40 years of age. The incidence of POI in patients with amenorrhea ranges from 2% to 10%,[35] although there is often a delay in diagnosis in adolescence because irregular menstrual cycles are common during early adolescence. Though there is no consensus criteria on diagnosis, POI is typically diagnosed in patients with menstrual irregularity for at

least 3 consecutive months and elevated FSH and low estradiol levels (two random tests at least 1 month apart).[36] Lab results should reveal hypergonadotropic hypogonadism with elevated FSH levels and low estradiol levels. Other diagnoses, including hyperprolactinemia and thyroid disease, should also be ruled out. A common cause of POI in adolescents is gonadal dysgenesis due to a chromosomal abnormality with or without Turner syndrome, thus a karyotype as well as a pelvic ultrasound should be performed once the diagnosis is confirmed. Fifty percent of adolescents presenting with primary amenorrhea who have no associated comorbidities are found to have abnormal karyotypes.[4]

Turner syndrome is a chromosomal disorder that results from the complete or partial absence of one X chromosome, and patients may experience delayed puberty and infertility. Turner syndrome is characterized by distinct physical features including short stature, webbed neck, broad chest, low hairline and short fourth or fifth metacarpals, hyperconvex nails, rotated ears, lymphedema, micrognathia and high arched palate, and may also include cardiac abnormalities and horseshoe kidney. Amenorrhea occurs in patients with Turner Syndrome due to absent or limited ovarian function due to gonadal dysgenesis.[37] Breast development is absent when ovarian failure occurs before puberty, but pubic hair growth is normal. Although patients with the mosaic form of Turner syndrome may experience breast development or menses, most girls with Turner syndrome require hormone therapy for breast development, uterine growth and bone health.[37]

Patients with POI should also be evaluated for the FMR1 premutation for fragile X. Six percent of patients with POI and a normal karyotype will have a premutation in the FMR1 gene.[37] POI is also associated with multiple endocrinopathies including hypoparathyroidism and hypoadrenalism, and should be evaluated for adrenal antibodies (21-hydroxylase by immunoprecipitation or indirect immunofluorescence), the presence of which would be suggestive of an autoimmune mechanism of disease.[36] Chemotherapy and radiation therapy may also cause a loss of ovarian function, which may be transient depending on the degree of damage.

In adolescents with POI, the goal of treatment is to replace the normal ovarian hormones, estrogen and progesterone, to levels that support bone, cardiovascular and sexual health, and complete normal pubertal development. The approach for patients with POI differs from the hormonal therapy in menopause, which focuses on symptom relief. Patients require long term hormonal therapy, usually with transvaginal or transdermal estradiol with addition of cyclic progesterone to protect against unopposed estrogen, which increases the risk of endometrial hyperplasia and cancer. Oral contraceptives are not recommended as first line maintenance hormonal therapy due to the higher doses of estrogen, as well as higher risk for thromboembolism, as compared with transdermal estradiol. Occasionally there is spontaneous resumption of ovarian function and fertility may persist with few follicles, with a resultant 5% to 10% chance of pregnancy, and patients should therefore use contraception when sexually active.[38]

Women with congenital adrenal hyperplasia (CAH) may develop infertility or menstrual abnormalities, including amenorrhea, due to the reduced activity of adrenal enzymes that affect cortisol production.

Thyroid

Amenorrhea or oligomenorrhea can be seen in both hyper- and hypothyroidism. Thyroid releasing hormone (TRH) is secreted by the hypothalamus, and in addition to triggering the release of thyroid stimulating hormone (TSH) also stimulates the release of prolactin. Patients with primary hypothyroidism also have a greater prolactin response to TRH, leading to hyperprolactinemia and thus amenorrhea.[21] Thyroid hormone replacement leads to normalization of prolactin levels and return of regular menstruation.[39] In women with hyperthyroidism, amenorrhea may result from anovulation due to the failure of estrogen to stimulate LH release, since these women have higher SHBG, FSH, LH and estradiol levels, but no midcycle LH peak.[40]

Adrenal

Congenital adrenal hyperplasia

Women with congenital adrenal hyperplasia (CAH) may develop infertility or menstrual abnormalities,

including amenorrhea, due to the reduced activity of adrenal enzymes that affect cortisol production. CAH is characterized by a defect in cortisol production, which leads to increased adrenocorticotropic hormone (ACTH) from the negative feedback loop and results in adrenal gland proliferation. Rare forms that can result in infertility include 11B-hydroxylase deficiency, 17a-hydroxylase deficiency and 3b-hydroxysteroid dehydrogenase deficiency, but the most common form is 21-hydroxylase deficiency (21-OHD).[20] 21-OHD exists on a spectrum, with the rare classic form diagnosed at birth with salt wasting and virilization of the external female genitalia and the more common nonclassic form presenting later, often in adolescence, with signs of hyperandrogenism including acne, hirsutism and oligomenorrhea or amenorrhea. Menstrual irregularities are likely secondary to elevated androgen and progesterone levels that are associated with reduced LH-pulse amplitude and frequency.[20,41] Nonclassic 21-OHD is one of the most common autosomal recessive diseases with a frequency of 1 in 100 individuals of mixed ethnic backgrounds and 1 in 27 in the Ashkenazi Jewish population. The prevalence of nonclassic 21-OHD ranges from 1.2 to 13.8% in women with signs of hyperandrogenism and oligomenorrhea.[20] Nonclassic 21-OHD is diagnosed using an ACTH stimulation test, which measures serum concentrations of 17-hydroxyprogesterone, a substrate of 21-OH, after administration of ACTH.

Addison's disease

Addison's disease is characterized by adrenal insufficiency and the production of low levels of adrenal hormones including glucocorticoids, mineralocorticoids and androgens. Ten percent of women with Addison's disease experience primary ovarian insufficiency due to autoimmunity with signs and symptoms of estrogen deficiency including amenorrhea, flushing, fatigue, and poor concentration.[43] Amenorrhea may also occur in these patients due to weight loss, as discussed in greater detail above (see hypothalamic amenorrhea).

Reproductive tract anomalies

Imperforate hymen

Anatomic abnormalities should be ruled out in cases of primary amenorrhea. Imperforate hymen is the most common cause of vaginal outflow obstruction, although overall is rare with a prevalence of 0.014–0.1%.[43] Imperforate hymen is a congenital disorder where the hymen does not have an opening and creates an outflow obstruction in the vagina. It typically presents in adolescence with delayed menstruation. Patients may describe a history of cyclic abdominal pain, but are sometimes asymptomatic. On examination, classic findings include a bulging blue hymen and distention of the vagina with blood, known as hematoculpos, that can be palpated on abdominal or rectal examination. If diagnosis is delayed, complications include peritonitis or endometriosis due to retrograde bleeding, as well as urinary retention, constipation and urinary tract infections. Imperforate hymen is treated with surgical incision of the hymen.[43]

Imperforate hymen is the most common cause of vaginal outflow obstruction, although overall is rare with a prevalence of 0.014–0.1%.[43]

Vaginal abnormalities

Vaginal abnormalities, including transverse vaginal septum and vaginal atresia, may present similarly. A transverse vaginal septum occurs when a wall of tissue runs horizontally across the vagina, and may be found either low or high in the vagina. On examination, the vagina appears short, and a mass may be palpable on vaginal examination and on rectoabdominal palpation. A transverse vaginal septum typically has a small perforation, but can still present with hematoculpos and amenorrhea. This condition is also treated surgically. Vaginal agenesis, which is often associated with cervical and uterine abnormalities, may also be found in adolescent patients with primary amenorrhea.[5] One rare syndrome associated with these abnormalities is Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. Patients with MRKH have a normal chromosomal pattern of 46XX and have normal breast and pubic hair development, as well as normal ovaries and hormone levels, but the cervix, uterus and fallopian tubes are absent or underdeveloped and the upper portion of the vagina is absent due to abnormal Mullerian duct development. Diagnosis is confirmed on

ultrasound. Patients with MRKH may also have anatomic abnormalities of the kidneys and spine and may have hearing deficits.[44]

Asherman's syndrome

Asherman's syndrome is a rare syndrome that should be considered in patients with amenorrhea after an obstetric or gynecologic procedure. This is an acquired syndrome that leads to amenorrhea after development of adhesions in the uterus or cervix. FSH, LH, and estradiol levels are normal in these patients, but they will not have a withdrawal bleed if challenged with progestin. Diagnosis is with hysteroscopy.[45]

46, XY disorders of sex development

Another group of disorders that can lead to amenorrhea are the 46, XY disorders of sex development. In these conditions, patients have one X chromosome and one Y chromosome in each cell, and may have ambiguous genitalia. Conditions that fall within this spectrum include: 46, XY complete gonadal dysgenesis (Swyer syndrome), 46 XY, partial gonadal dysgenesis (Denys-Drash syndrome), testicular regression syndrome, leydig cell aplasia/hypoplasia, persistent Mullerian duct syndrome, 5 alpha-reductase type2 deficiency, and complete and partial androgen insensitivity syndromes.[46]

Conclusions

The wide and diverse range of causes of amenorrhea in adolescents who are not pregnant may originate from any level of the HPO axis, as well as anatomic and chromosomal etiologies. Treatment should be focused on the underlying cause. Of note, adolescence is a critical period for bone acquisition, with 60% of peak bone mass acquired at this time. Therefore, preservation of bone density and risk of fractures should be discussed with amenorrheic patients, since many causes of amenorrhea including low weight, low fat intake, estrogen deficiency, hypercortisolism, low DHEAS, and IGF-1 deficiency can result in decreased bone density and may be irreversible. A dual-energy X-ray absorptiometry (DEXA) bone density scan can determine the degree of bone density loss. Adequate calcium and vitamin D supplementation as well as weight bearing exercise can help prevent bone loss. In patients with eating disorders, weight restoration has the most significant impact on bone mineral density. Most studies have demonstrated that oral estrogen replacement in the combined estrogen-progesterone pill is not effective in increasing bone density in adolescents with eating disorders.[47] Transdermal estrogen may lead to maintenance of bone mineral density Z-scores in these patients, but does not lead to an increase bone mineral density, and thus would not replace losses that have already occurred.[48] Patients with amenorrhea from other etiologies where the hormonal imbalance cannot be treated with weight restoration, including POI or estrogen deficiency, benefit from hormone replacement therapy with physiologic estrogen. Patients with adequate estrogen levels, such as patients with PCOS, are at risk for endometrial hyperplasia and cancer due to unopposed estrogen, and should receive either long term progestin therapy or combined oral contraceptives.[49] In patients with hypothalamic amenorrhea or PCOS who do not need contraception, hormonal therapy may be discontinued intermittently to assess for the resumption of menses.

Amenorrhea can be stressful for patients and families, particularly in cases where fertility is affected, and the hormonal changes that result in amenorrhea can also negatively affect mood. Low estrogen levels in adolescents with functional hypothalamic amenorrhea are associated with fluctuations in several neuropeptides, neurotransmitters and hormones, including serotonin, dopamine, allopregnanolone and cortisol, which can affect mood in amenorrheic women.[50] These patients may also have higher levels of anxiety, depressive symptoms and mood disorders.[51] Since anxiety and psychological distress are also risk factors for further suppression of the HPO axis,[20] it is important to address these psychiatric issues and facilitate access to therapeutic resources and support groups. Physicians should treat these patients with sensitivity and provide sufficient time to address questions and concerns.

Declaration of Competing Interest

The authors do not have any conflicts to declare.

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