Amenorrhea

Melissa F. Wellons, Kaitlyn M. Weeber, and Robert W. Rebar

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6.1 Introduction

This chapter serves as an overview of the presentation, initial workup, and most common etiologies of primary and secondary amenorrhea. In this brief introduction, it cannot be comprehensive, and additional sources may be consulted for more detailed information regarding management.

In the USA, approximately 4% of women will experience secondary amenorrhea, while less than 0.1% of women will experience primary amenorrhea [1]. The differential diagnosis for patients with amenorrhea is broad, and the purpose of this chapter is to give the reader a systematic guide for the evaluation of such patients.

Clinical Case

An 18-year-old gravida 0 college freshman presents to the Student Health Service complaining of amenorrhea since beginning college 3 months ago. She underwent menarche at age 13 after appropriate development of secondary sex characteristics. Her menses occurred regularly at approximately 30-day intervals until 4 months ago.

She relates that she is from a small town in Michigan's Upper Peninsula and had never left her family before. Her boyfriend of 2 years went to an Eastern college. The couple was sexually active and she states that she always used condoms for contraception. She admits to being unhappy and homesick in her new setting and has lost 10 lbs. since leaving home. She is on no medications, has no allergies, and has no significant past medical history.

Physical examination reveals her height as 5′-6″ and her weight as 120 lbs (BMI 19.4). Vital signs are normal. She has Tanner stage 5 breasts and pubic and axillary hair development. Pelvic examination shows a good estrogen effect of the vagina and cervix. Pregnancy test is negative. Other laboratory tests are negative.

6.2 Diagnosing Amenorrhea

6.2.1 History

The initial workup of amenorrhea should include a detailed history with particular attention to last menstrual period and sexual history, if applicable, recent changes in physical and emotional stressors that could lead to hypothalamic dysfunction, a detailed review of current and recent medications that may be gonadotoxic, and specific evidence of hormonal dysfunction, including symptoms of *hyperandrogenism*, *hyperprolactinemia*, as well as *hyper-* and *hypothyroidism*. A contraceptive history should be gathered, as several modern means of contraception are prone to iatrogenic amenorrhea, such as methoxyprogesterone acetate (Depo-Provera®). Associated symptoms of systemic diseases, such as the weight gain associated with both hypothyroidism and Cushing syndrome, may also come to light in a detailed history.

6.2.2 Physical Examination

A detailed physical examination should focus on evidence of biologically active reproductive hormones. This includes a gynecologic examination and *Tanner staging* to measure pubertal development, as well as measurement of height, arm span, body mass index, signs of hyperandrogenism, and skin manifestations of endocrine disorders. Arguably the most important single feature in the evaluation of primary amenorrhea is the presence or absence of any evidence of pubertal development. Breast development indicates the presence of biologically active estrogen, and the evidence of any terminal pubic and axillary hair indicates the presence of biologically active androgen. Gynecologic examination will usually reveal the presence of genital abnormalities, including obstructive processes such as a transverse hymen or external cervical stenosis, or vaginal atrophy

associated with hypoestrogenemia. The bilaterally enlarged ovaries sometimes present in women with PCOS often can be detected during bimanual examination.

The clinician should be alert to subtle physical signs, such as those in patients with PCOS. Patients with PCOS will often, but not always, be overweight with increased hair on the upper lip, chin, chest, and inner thighs. In particularly severe cases, acanthosis nigricans may be present. Ovarian and adrenal tumors can also produce sudden and dramatic hirsutism. Short stature and the stigmata of Turner syndrome can suggest primary ovarian insufficiency with a genetic basis. Galactorrhea suggests hyperprolactinemia, although only one-third of women with elevated prolactin will have this finding. When galactorrhea is present, the examiner should note whether it is unilateral or bilateral, constant or intermittent. Cushing syndrome is often associated with central obesity, "moon facies," a ruddy complexion, abdominal striae, and a "buffalo hump," as well as hypertension and insulin resistance.

6.2.3 Laboratory Studies

First-line laboratory tests that are relatively quickly and inexpensively obtained include a pregnancy test, followed by serum follicle-stimulating hormone (FSH), serum prolactin, and serum thyroid-stimulating hormone (TSH). (See Fig. 6.1 for a flow diagram for the evaluation of amenorrhea.) FSH and LH typically trend together and generally need not both be obtained as part of the initial workup. Elevated levels of TSH or prolactin are indications that one should evaluate the patient further for hypothyroidism or pituitary adenoma, respectively. Additionally, a

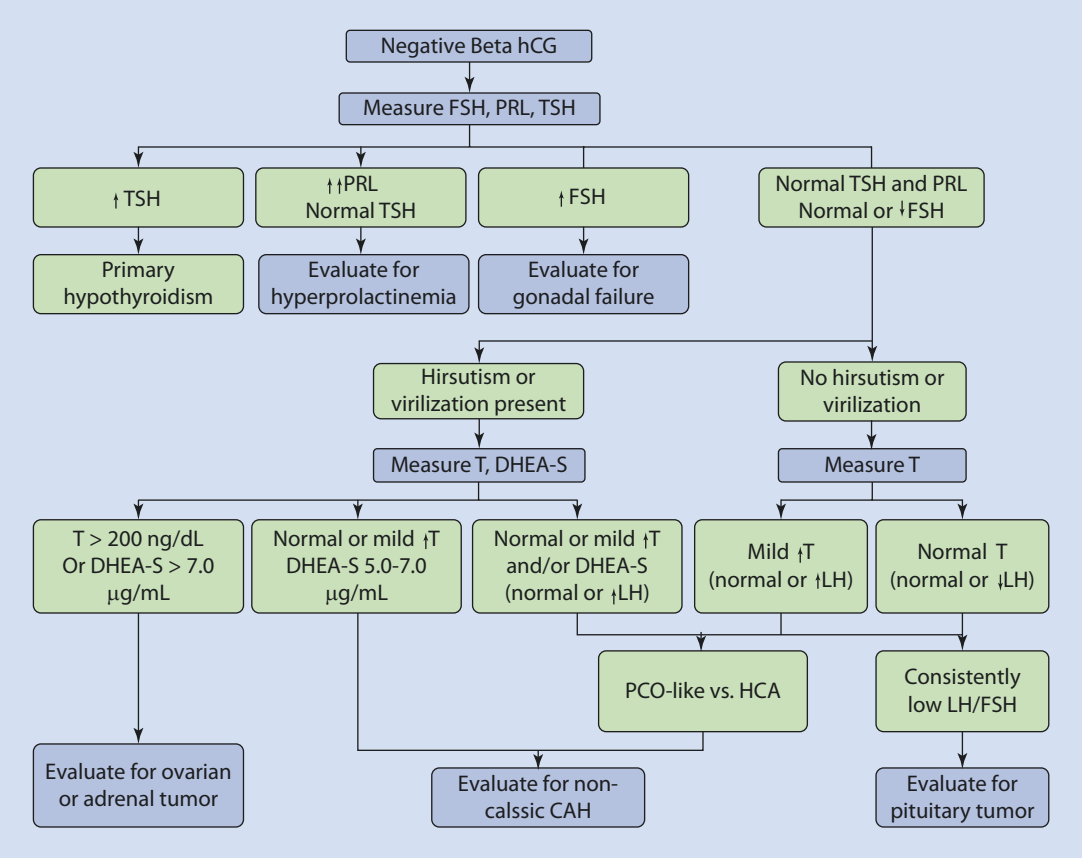

Fig. 6.1 Evaluation of amenorrhea

karyotype is warranted in any young woman with elevated levels of FSH. Serum androgens should be measured if a patient has signs or symptoms of hyperandrogenism, and both a serum 17α-hydroxyprogesterone level and a karyotype should be obtained in the case of sexual ambiguity. Although many reproductive endocrinologists recommend measuring free testosterone levels rather than total testosterone levels, free testosterone levels are calculated and are more inaccurate than are measurements of total testosterone (and commercial laboratories typically measure even total testosterone poorly). A *progestin challenge* test can be conducted to evaluate estrogen production and ovarian function, but both false positives and false negatives are common; it is rarely, if ever, necessary in the contemporary evaluation of the patient with amenorrhea. More dangerous etiologies, for example intracranial masses or tumors and ovarian or adrenal tumors, should be ruled out by appropriate imaging studies.

6.2.4 Imaging

Abdominal ultrasonography can be used to determine the presence or absence of a uterus. Magnetic resonance imaging (MRI) of the pelvis is probably the most effective imaging method for characterizing congenital anomalies if one is suspected on the basis of examination and vaginal ultrasound. Patients without secondary sexual development should undergo radiographic determination of bone age, generally by evaluating the bones of the non-dominant hand. In patients with persistently elevated prolactin levels and no evidence of primary hypothyroidism, an MRI of the pituitary gland is indicated.

6.3 Etiologies of Primary Amenorrhea

While it is true that virtually any disorder that leads to secondary amenorrhea may also cause primary amenorrhea, certain disorders more commonly present as primary amenorrhea (Table 6.1). The four most common etiologies of primary amenorrhea are reported to be gonadal dysgenesis, Müllerian agenesis, hypothalamic disorders, and constitutional delay of puberty [4]. Less common causes include androgen insensitivity syndrome, inborn defects in gonadotropin secretion or response, and outflow obstructions of the genital tract, such as imperforate hymen and transverse vaginal septum.

Table 6.1 Classification of amenorrhea, both primary and secondary, and primary ovarian insufficiency [2]

Anatomic defects (outflow tract)	Müllerian agenesis (Mayer–Rokitansky–Kuster–Hauser syndrome)
	Complete androgen resistance (testicular feminization)
	Intrauterine synechiae (Asherman syndrome)
	Imperforate hymen
	Transverse vaginal septum
	Cervical agenesis—isolated
	Cervical stenosis—iatrogenic
	Vaginal agenesis—isolated
	Endometrial hypoplasia or aplasia—congenital

Table 6.1 (continued)

Primary hypogonadism	Gonadal dysgenesis	Abnormal karyotype	Turner syndrome 45,X	
			Mosaicism	
		Normal karyotype	Pure gonadal dysgenesis	46,XX
				46,XY (Swyer syndrome)
	Gonadal agenesis			
	Enzymatic deficiency	17α-Hydroxylase deficiency		
		17,20-Lyase deficiency		
		Aromatase deficiency		
	Primary ovarian insufficiency (see also Table 6.2)	X Chromosomal causes		
		Mutations associated with a 46,XY karyotype		
		Autosomal causes		
		Environmental insults		
		Immune disturbances		
		Idiopathic causes		
Hypothalamic causes	Dysfunctional	Stress, Exercise, or Nutrition-related		
		Pseudocyesis		
	Other disorders	Isolated gonadotropin deficiency	Kallmann syndrome	
			Idiopathic hypogonadotropic hypogonadism (IHH)	
	Infection			
	Tuberculosis			
	Syphilis			
	Encephalitis/meningitis			
	Sarcoidosis			
	Chronic debilitating disease			
	Tumors	Craniopharyngioma		
		Germinoma		
		Hamartoma		
		Teratoma		
		Endodermal sinus tumor		
		Metastatic carcinoma		
	Proliferative	Langerhans cell histiocytosis		

(continued)

Table 6.1 (continued)

Pituitary causes	Tumors	Prolactinomas	
		Other hormone-secreting pituitary tumor (corticotropin, thyrotropin-stimulating hormone, growth hormone, gonadotrophin)	Mutations of FSH or LH receptor
			Fragile X syndrome
		Autoimmune disease	
		Galactosemia	
Other endocrine gland disorders	Adrenal disease	Adult-onset adrenal hyperplasia	
		Cushing syndrome	
	Thyroid disease	Hypothyroidism	
		Hyperthyroidism	
	Ovarian tumors	Granulosa-theca cell tumors	
		Brenner tumors	
		Cystic teratomas	
		Mucinous/serous cystadenomas	
		Krukenberg tumors	
		Nonfunctional tumors (craniopharyngioma)	
		Metastatic carcinoma	
	Space-occupying lesions	Empty sella	
		Arterial aneurysm	
	Necrosis	Sheehan syndrome	
		Panhypopituitarism	
	Inflammatory/infiltrative	Sarcoidosis	
		Hemochromatosis	
		Lymphocytic hypophysitis	
	Gonadotropin mutations (FSH)		
Multifactorial causes	Polycystic ovary syndrome		

6.3.1 Gonadal Dysgenesis

The term "gonadal dysgenesis" refers to a number of disorders in which the gonads have not formed normally. This condition can occur in individuals with normal karyotypes as well as in a variety of abnormal or mosaic states. Gonadal dysgenesis accounts for almost half of all cases of primary amenorrhea. Gonadal dysgenesis with the stigmata of Turner syndrome is the most common variation, which has a wide spectrum of genotypes (most commonly 45,X but including individuals who may have a portion of a Y chromosome as well) and phenotypes. Individuals with gonadal dysgenesis may develop hypothyroidism and also commonly develop hypertension and glucose intolerance. Swyer syndrome (46,XY) is also associated with gonadal dysgenesis, and 46,XX

gonadal dysgenesis may occur as well; in both cases, the individual presents as a normal appearing but sexually immature female.

6.3.2 Müllerian Agenesis

Müllerian agenesis (Mayer–Rokitansky–Kuster–Hauser syndrome) is a condition in which all or part of the uterus and vagina are absent with blind vaginal pouch in the presence of otherwise normal female sexual characteristics and a normal 46,XX karyotype (which generally need not be assessed because the diagnosis is evident on examination). This condition accounts for approximately 10% of cases associated with primary amenorrhea and occurs in 1 in 4000–5000 births; it is autosomal dominant with incomplete penetrance and variable expressivity [5, 6]. A karyotype can be performed to rule out androgen insensitivity, but individuals with Müllerian agenesis have completely developed secondary sexual characteristics whereas those with androgen insensitivity generally have only Tanner stage 3 breast development and very little, if any, pubic and axillary hair. Serum FSH, LH, estradiol, TSH, prolactin, and testosterone will be within normal limits barring iatrogenic effects of hormonal therapy. Pelvic ultrasound shows variable absence of Müllerian structures, and follow-up MRI of the abdomen and pelvis can reveal associated renal abnormalities, found in 30% of patients [1]. Other associated findings include skeletal abnormalities of the spine, syndactyly, and auditory deafness.

6.3.3 Hypothalamic Disorders

Hypothalamic disorders that may cause amenorrhea include emotional/physical stress, intense exercise, malnutrition or a chronic disease state, as well as primary or secondary gonadotropin deficiency, and a wide variety of rare tumors and diseases (Table 6.1). Patients with hypothalamic amenorrhea may present with the absence of secondary sexual characteristics or following normal puberty. Circulating levels of FSH, LH, and estradiol levels are all low. In a patient with a history concerning for emotional or physical stress, malnutrition, or a chronic disease state, growth charts can be very illustrative when combined with low to normal FSH and low estradiol concentrations. Dual energy X-ray absorptiometry (DEXA) scan will reveal low bone density when compared to age-matched controls.

Gonadotropin-releasing hormone deficiency presents with the delayed development of secondary sexual characteristics, but most commonly with associated anosmia and sometimes color blindness due to an absent olfactory bulb in 50% of cases, in which case it is termed Kallmann syndrome. Kallmann syndrome can be difficult to distinguish from both constitutional delay (discussed subsequently) and other forms of hypothalamic amenorrhea in which there is an environmental stressor. Other forms of isolated hypogonadotropic hypogonadism are associated with GnRHR (GnRH receptor) inactivating mutations [7, 8]. There actually is a whole spectrum of midline abnormalities associated with GnRH deficiency and hypothalamic amenorrhea, with absence of the septum pellucidum representing the most extreme example.

Isolated gonadotropin deficiency is characterized by decreased or absent endogenous gonadotropin-releasing hormone (GnRH) secretion, resulting in very low to undetectable levels of LH and FSH, along with incomplete development of secondary sexual characteristics and primary amenorrhea. These characteristics may be accompanied by eunuchoid features, anosmia, and, more rarely, color blindness (and again is termed Kallmann syndrome). Abnormalities of GnRH receptors have also been found, but are difficult to distinguish from isolated gonadotropic deficiency. Abnormalities of the LH receptor in 46,XX females result in normal female sexual development and primary amenorrhea [9]. Serum LH may be normal or increased, and FSH will be normal, as will follicular phase estradiol levels. Progesterone will be low. The uterus in patients with LH receptor abnormalities is small, and the ovaries are consistent with the absence of ovulation.

6.3.4 Constitutional Delay of Puberty

Constitutional delay is the single most common cause of delayed puberty in both genders and is defined as the onset of otherwise normal puberty 2.5 standard deviations later than the mean age of

pubertal onset (breast development by 13 years in girls and testicular development by 14 years in boys). Patients with constitutional delay frequently experience concomitant delay in adrenarche and pubarche. Fifty to 75% of patients have a family history of delayed puberty followed by normal pubertal development, as well as short stature [10]. This is a diagnosis of exclusion.

6.3.5 Androgen Insensitivity Syndrome

Although an abnormality of sexual differentiation, androgen insensitivity syndrome is identified in as many as 5% of all patients presenting with primary amenorrhea [11]. The disorder is due to the inability of biologically active testosterone to act normally in cells, generally because of the absence of the androgen receptor but sometimes because of a defect in the post-receptor action of androgens. Patients with androgen insensitivity commonly present with distinctive physical characteristics, including a blind vagina, eunuchoid habitus, breasts that have matured only to Tanner stage 3, and small nipples with pale areolae. Pubic and axillary hair is generally scant or absent. There may be fullness in the inguinal area if the normal testicles are located there rather than intra-abdominally. The diagnosis can be confirmed by determining that serum testosterone levels are within or above the range normally found in males and by the presence of a 46,XY karyotype. The gonads, which are histologically normal testes, should be removed after the age of sexual maturity to eliminate the 30% risk of gonadal tumors later in life [1]; estrogen should be provided exogenously. Such individuals first may be identified after straddle injuries in childhood associated with intense pain due to trauma to the sometimes present inguinal testes.

6.3.6 Outflow Obstructions of the Genital Tract

Disorders of the genital tract encompass abnormalities of the Müllerian system as well as abnormalities of the external genitalia. Genital tract disorders will be found in 15% of adolescents who present with normal adolescent development and primary amenorrhea. Common disorders of the genital tract include Müllerian agenesis (see above), imperforate hymen, and transverse vaginal septum. Imperforate hymen is the most frequent obstructive female genital tract anomaly, with an estimated frequency of approximately 0.1%. Transverse vaginal septum is less common, occurring in fewer than one in 20,000 females. Patients with these abnormalities often present with adult secondary sexual characteristics, cyclic pelvic pain, and lack of menses. A bulging hymen with hematocolpos, evidence of an imperforate hymen, may be detected on pelvic exam. MRI of the pelvis may be used to detect transverse vaginal septum and is also more sensitive than ultrasound when excluding other structural abnormalities [1, 12]. If a normal uterus and fallopian tubes are present, these individuals will develop endometriosis as well because of the obstructed outflow tract.

6.4 Etiologies of Secondary Amenorrhea

In secondary amenorrhea, menstruation begins at the appropriate age, but later stops for reasons other than pregnancy, lactation, or menopause. To arrive at this diagnosis, the length of amenorrhea should be equal to at least three of the previous cycle intervals, or 6 months, although patients with *oligomenorrhea* often have similar underlying pathology. Three to 5% of women of reproductive age are affected by secondary amenorrhea [13]. Secondary amenorrhea is more common in those whose weight is below or above the normal range, with hypothalamic amenorrhea and the polycystic ovary syndrome being the most common causes of secondary amenorrhea, excluding pregnancy [14]. Two more common causes of secondary amenorrhea include pituitary disorders and primary ovarian insufficiency.

6.4.1 Hypothalamic

Hypothalamic forms of amenorrhea result from diminished GnRH input to the pituitary gland and commonly occur in women stressed mentally, emotionally, or physically as well as in those who are nutritionally deficient. Often a combination of these stressors is present, resulting in

anovulation. Menstrual cycle disturbances are common among competitive athletes, especially in those sports that encourage a low body weight. Menstrual irregularities appear to be greatest in ballet dancers (6–43%) and middle- and long-distance runners (24–26%). Hypothalamic amenorrhea is also common in women who have experienced a profound stress, such as rape, incest, or loss of someone particularly close. Severe eating disorders such as bulimia and anorexia nervosa can disrupt menstrual function in a similar manner. Clinicians should screen for stressors by reviewing the patient's lifestyle, including diet, exercise, and drug use [8, 15].

Patients with hypothalamic amenorrhea typically have a history of normal menarche and regular menstruation, but several cases of primary amenorrhea have been reported. The physical examination should focus on identifying thyroid dysfunction, galactorrhea (suggestive of central lesion), and evidence of hyperandrogenemia such as acne and hirsutism (suggestive of an androgen-secreting tumor or PCOS). Oral examination may reveal the distinctive eroded "moth-eaten" dentition and enlarged salivary glands of a bulimic patient. The results of the pelvic examination should be normal except for a thinned vaginal mucosa or absent cervical mucus, which are characteristics of hypoestrogenism.

The simplest treatment often includes counseling as well as estrogen replacement. Oral contraceptives can be used, but affected women should be told that they may be amenorrheic when the estrogen is discontinued, and infertility may be an issue. Estrogen is warranted in these women due to their increased risk of accelerated bone loss, although simultaneous relative hypercortisolism may limit the efficacy of estrogen therapy in preventing this bone loss. [16] Because ovulation may precede the first menses, these women sometimes become pregnant unexpectedly if contraception is not utilized.

Post-Contraception Amenorrhea

Modern low-dose oral contraceptives do not affect fertility long term. However, as noted, women with amenorrhea prior to the administration of oral contraceptives may still be amenorrheic when contraceptives are discontinued. Amenorrhea following contraceptive use is generally due to a preexisting cause, except when there is a history of depot medroxyprogesterone acetate (e.g., Depo-Provera®). Return to ovulation or baseline fertility upon discontinuation of medroxyprogesterone is reported to range from 7 to 10 months after last injection and may rarely be even longer [17, 18].

6.4.2 Hyperandrogenic States

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common causes of ovulatory dysfunction. According to the Rotterdam criteria, the overall prevalence of PCOS is 16.6%, with up to 33.3% prevalence in women under 30 years old [19]. As originally described, large, pale polycystic ovaries with thickened capsules were found in women with amenorrhea (usually secondary), hirsutism, and "sterility" [20]. Over time it was recognized that PCOS was heterogeneous, with a wide clinical spectrum that include gradual onset hirsutism, infertility, amenorrhea, obesity, and irregular menses. Defined early as "LH-dependent ovarian hyperandrogenism" commonly beginning around puberty, the definition was broadened by the Rotterdam Consensus Conference in 2004 to include the presence of two of the three following features after exclusion of other etiologies: (1) hyperandrogenism (clinical and/or biochemical), (2) oligo- and/or anovulation, and (3) polycystic ovaries. This last (and now most frequently used) definition has resulted in inclusion of many more women into the "PCOS spectrum" and may well contribute to confusion about the pathophysiology. Using this definition, PCOS is now regarded as the most common endocrinopathy in women.

Common laboratory features include elevated levels of LH (compared to those found in the normal follicular phase) in many women with the ratio of LH:FSH > 2:1, elevated levels of testosterone and virtually any other ovarian androgen measured, and decreased levels of sex hormone-binding globulin [21]. More recently, it has become recognized that insulin resistance and lipid and lipoprotein abnormalities are common in PCOS as well [22]. These laboratory abnormalities may put women with PCOS at higher risk of cardiovascular disease and metabolic abnormalities that shorten lifespan, but this remains to be established [23]. In fact, it appears that the severity of PCOS decreases toward menopause, as documented by longitudinal studies [24].

Management of PCOS is directed at treating the primary complaint, whether it is hirsutism, irregular menses or amenorrhea, infertility, or glucose intolerance. Commonly utilized therapies include oral contraceptives and spironolactone for the irregular menses and hyperandrogenism. Ovulation induction with clomiphene citrate or an aromatase inhibitor such as letrozole is often needed for women desiring pregnancy. Obese individuals should be encouraged to lose weight because signs and symptoms are not as severe in normal-weight women as they are in those who are overweight [1]. Metformin is commonly provided to women with glucose intolerance. It is known that adverse pregnancy outcomes, including pregnancy-induced hypertension and preeclampsia, gestational diabetes, pre-term birth, and perinatal mortality, are increased in women with PCOS [25].

Other Hyperandrogenic States

Other hypoandrogenic states, such as ovarian and adrenal tumors, mimic the symptoms of PCOS, although the onset of symptoms is generally more rapid, and can also result in amenorrhea. Similarly, Cushing syndrome can cause amenorrhea secondary to increased androgens (or to hypothalamic suppression of GnRH secretion). Another cause is adult-onset congenital adrenal hyperplasia. The ovary apparently can respond to increased androgens in only limited ways, and polycystic ovaries are invariably present in all of these disorders. To rule out these conditions, the patient's serum androgens should be measured, including total testosterone, dehydroepiandosterone sulfate (DHEA-S), and 17-hydroxyprogesterone. Imaging of the ovaries and of the adrenal glands may be indicated in some cases.

6.4.3 Pituitary Disorders

Disorders of the Anterior Pituitary Gland

Small pituitary tumors often present as irregular or absent menses or galactorrhea due to the impairment of prolactin suppression or GnRH regulation. Large pituitary tumors may manifest as headaches and compression of the optic chiasm with bitemporal hemianopsia related to their growth in a confined anatomical space.

Prolactin-Secreting Adenomas and Hyperprolactinemia

Prolactin-secreting adenomas are the most common pituitary tumors, with hyperprolactinemia being the most common cause of pituitary-associated amenorrhea [8]. As many as one-third of patients with secondary amenorrhea will have a prolactinoma [26, 27]. Hyperprolactinemia is associated with decreased estradiol concentrations as well as amenorrhea or oligomenorrhea, galactorrhea, headaches, and infertility. About one-third of women with amenorrhea will have elevated prolactin levels, one-third of women with galactorrhea and elevated prolactin levels will have normal menstrual cycles, and one-third of women will have high prolactin levels without galactorrhea [28]. In patients presenting with hyperprolactinemia, the prevalence of a pituitary tumor is 50–60%. [29, 30]. Whenever serum prolactin levels are consistently elevated, MRI or CT scanning of the pituitary should be performed [26]. The so-called non-functioning pituitary tumors commonly secrete the alpha subunit common to LH, FSH, and TSH, and may present only with amenorrhea. Other causes of hyperprolactinemia include pituitary stalk disruption, primary hypothyroidism, renal failure, and chest wall injury. Prolactin-secreting pituitary tumors less than 10 mm in diameter rarely increase in size or cause "pressure" symptoms; these can be treated medically with dopamine agonists such as cabergoline or merely managed expectantly. There is no evidence that estrogen-containing oral contraceptives cause tumor growth, and these agents may be administered to those women who desire contraception. Either a dopamine agonist or an estrogen is warranted to prevent the osteoporosis and other signs and symptoms of estrogen deficiency that typically accompany the hyperprolactinemia.

Postpartum Pituitary Necrosis (Sheehan Syndrome)

Postpartum pituitary necrosis can be a life-threatening condition usually preceded by a history of severe obstetrical hemorrhage with hypotension, circulatory collapse, and shock [31]. It is known that diminished perfusion to the pituitary gland must be present for a considerable number of hours and most of the pituitary gland must undergo necrosis for Sheehan syndrome to

result. Patients often experience nausea, vomiting, slowed mental function, postural hypotension, and adrenal crisis [12]. These women often present for their first postpartum visit complaining of inability to lactate and profound malaise. MRI of the brain may show an empty or CSF-filled sella turcica or a small pituitary gland.

Pituitary Apoplexy

Pituitary apoplexy is a serious condition characterized by an acute infarction of the pituitary gland. Patients experience a sudden onset of a severe retro-orbital headache and visual disturbances that may be accompanied by lethargy or a loss of consciousness.

Cushing Disease and Syndrome

Amenorrhea and galactorrhea are usually encountered with pituitary prolactinomas, but these symptoms may also precede adrenocorticotropic hormone (ACTH) or growth hormone–secreting tumors. If the patient presents with clinical symptoms of excessive glucocorticoid, suggesting Cushing disease, a corticotropin serum level test, a midnight salivary cortisol level, and/or a 24 h urine collection for free cortisol may be indicated. The term Cushing Disease is used for individuals who have a corticotropin-secreting pituitary tumor, whereas Cushing Syndrome refers to hypercortisolism of extrapituitary origin (typically iatrogenic or due to a pulmonary carcinoma).

Post-irradiation Hypopituitarism

Exposure to therapeutic radiation sources for treatment of midline central nervous system tumors can place patients at increased risk for delayed development of hypopituitarism. Common symptoms include vaginal dryness, decreased libido, fatigue, weight gain, and vasomotor symptoms [12]. This disorder usually arises decades after the irradiation.

6.4.4 Disorders of the Genital Tract

Intrauterine adhesions (i.e., Asherman syndrome) account for 7% of cases of secondary amenorrhea, with the incidence rising secondary to the increasing use of hysteroscopy and appropriate diagnosis [32]. Patients with Asherman syndrome have been found to have higher rates of endometriosis. Another infrequent cause is an outflow obstruction secondary to cervical stenosis. This usually results from treatment of cervical dysplasia with modalities such as cryosurgery, electrocautery, or cold knife cone biopsy.

6.4.5 Primary ovarian insufficiency

Among all women, 10% may become menopausal by age 45, and these women may have experienced an accelerated decline of fertility in their young life and before women who experience menopause at a more average age (i.e., ~age 50–51). These patients may be considered to have "early ovarian aging" in spite of having menstrual function. Although the absence of ovarian function before the age of 40 ("primary ovarian insufficiency" sometimes also referred to as premature ovarian failure or "premature menopause") can be the result of a "normal" physiologic process at an unusually young age, it is sometimes due to an identifiable underlying pathology (◘ Table 6.2). Regardless of etiology, the clinical results are hypoestrogenemia and decreased fertility.

Primary ovarian insufficiency (POI) accounts for 4–18% of cases of secondary amenorrhea, with the primary mechanisms being follicular dysfunction or depletion. Ovarian function can be unpredictable, and 5–10% of women conceive and deliver a child after receiving a diagnosis of POI [33]. Although 90% of cases are idiopathic, it is likely that many cases of POI result from genetic mutations [34] and abnormalities in sex chromosomes (such as fragile X syndrome); 10–15% of patients have a first-degree family history of secondary amenorrhea. For patients <30 years of age presenting with amenorrhea, a karyotype should be obtained to rule out chromosome abnormalities, because conditions in which a portion of the Y chromosome is present are associated with an increased risk of ovarian malignancies.

There is a growing understanding of the relationship between POI and underlying or associated autoimmune diseases. Five percent of cases of POI are caused by underlying autoimmune disease, with 60–80% being adrenal in origin [35]. Additionally, up to 30% of women with primary ovarian insufficiency have an autoimmune abnormality, the most common of which are autoimmune thyroiditis resulting in hypothyroidism, pernicious anemia, type 1 diabetes mellitus, and

Table 6.2 Causes of primary ovarian insufficiency [3]

X Chromosomal causes	Structural alterations or mutations in or absence of an X chromosome	With the stigmata of Turner syndrome (45,X or mosaic)	
		Without the stigmata of Turner syndrome	Mutations in premature ovarian failure 1 (Xq26-q28)
			Mutations in premature ovarian failure1 in association with Fragile X premutation (Xq27.3)
			Mutations in premature ovarian failure 2A (Xq22)
			Mutations in premature ovarian failure 2B (Xq21)
			Mutations in premature ovarian failure 4 in association with mutations in bone morphogenetic protein 15 (Xp11.2
	Trisomy X with or without mosaicism		
Mutations associated with a 46,XY karyotype	Mutations in Xp22.11-p21.2 (Swyer syndrome)		
	Mutations in 5 cen		
Autosomal causes	Mutations involving enzymes important for reproduction	Galactosemia (galactose-1-phosphate uridyltransferase deficiency) (9p13)	
		17α–Hydroxylase deficiency (CPY17A1) (10q24.3)	
	Mutations involving reproductive hormones, their receptors, and action	Mutations of luteinizing hormone or follicle-stimulating hormone or both rendering them biologically inactive (theoretical)	
		Mutations of inhibin (theoretical)	
		Receptor mutations	Follicle-stimulating hormone receptor (2p21-p16)
			Luteinizing hormone/human chorionic gonadotropin receptor (2p21)
		Mutations in the hormone action pathways	
	Other mutations	Blepharophimosis, ptosis, and epicanthus inversus, type 1 (BPES) (premature ovarian failure 3) (3q23)	
		Premature ovarian failure 5 (newborn ovary homeobox) (7q35)	
		Autoimmune polyendocrine syndrome, type 1(APS1) (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, APECED) (autoimmune regulator gene, AIRE) (21q22.3)	
		Vanishing white matter leukodystrophy with ovarian failure (genes encoding the translation initiation factor E1F2B) (14q24, Chr 12, 1p34.1, 3q27, 2p23.3)	
		Congenital disorders of glycosylation, type 1a (CDG1a) (genes encoding phosphomannomutase-2, PMM2) (16p13.3-p13.2)	

(continued)

Table 6.2 (continued)

Environmental insults	Chemotherapeutic (especially alkylating) agents
	Ionizing radiation
	Viral infection (documented for mumps)
	Surgical injury or extirpation
Immune disturbances	In association with other autoimmune diseases
	Isolated
	In association with congenital thymic aplasia
Idiopathic causes	

myasthenia gravis [35–39]. In 10–60% of cases, Addison disease patients also may have autoimmune ovarian insufficiency, with POI often preceding symptoms of adrenal insufficiency by 8–14 years [40]. Patients with POI should be screened for adrenal disease with evaluation for anti-adrenal antibodies, as 50% of women with autoimmune POI will develop adrenal insufficiency. If these are positive, then more sophisticated testing, such as a corticotropin stimulation test, is in order (a fasting morning serum cortisol is not sufficiently sensitive). In order to exclude other autoimmune disorders, patients with unexplained primary ovarian insufficiency should undergo more complete biochemical evaluation, including measurement of serum calcium, phosphorus, fasting glucose, adrenal antibodies to 21-hydroxylase enzyme, free T4, TSH, and thyroid antibodies [41].

Early menopause has been associated with an increase in all-cause mortality in multiple large well-designed studies, although the evidence supporting associations between POI and cancer, cardiovascular disease, and cerebrovascular disease is mixed. [42]

Other Causes of Primary Ovarian Insufficiency

Although elevated serum FSH levels are virtually synonymous with ovarian disorders, there are less common conditions that can raise FSH but that are associated not with a primary ovarian problem but a central problem. These are pituitary adenomas that secrete FSH, abnormalities of the FSH receptor precluding normal FSH action, and defects in specific enzymes such as 17-hydroxylase (P450c17) (a form of congenital adrenal hyperplasia) and galactose-1-phosphate uridyl transferase (galactosemia). In closing, tt should be emphasized again that a variety of autoimmune (AI) disorders are associated with POF, including AI hypothyroidism, adrenal insufficiency, type 1 diabetes mellitus, pernicious anemia, and hypoparathyroidism [43].

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