Amenorrhea

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Contents

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Key Points

- Primary amenorrhea is defined as no menses by age 14 without secondary sexual characteristics or by age 16 with secondary sexual characteristics present.
- The evaluation of amenorrhea requires a thorough physical exam and can answer two fundamental questions: (1) if the patient has a uterus and an intact outflow tract and (2) if breast development is present indicating the presence of estrogen and an intact hypothalamic-pituitary axis.
- Once pregnancy has been excluded, assessment of serum follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and prolactin (PRL) needs to be done as the basis for determining any endocrine cause for amenorrhea.
- A broad differential diagnosis needs to be maintained in approaching primary and secondary amenorrhea with careful consideration of genetic, endocrine, and acquired/congenital structural causes.

6.1 Introduction

Amenorrhea is a condition that can have far-ranging and profound implications for a woman's health. Whether it is primary or secondary in nature, familiarity with the most common causes and a systematic approach to the evaluation of the amenorrheic patient are necessary for rapid diagnosis and treatment, thereby enabling restoration of menses and management of hormonal aberrations to improve quality of life.

Primary amenorrhea is defined as no menses by age 14 without secondary sexual characteristics or no menses by age 16 with secondary sexual characteristics. Secondary amenorrhea is defined as no menses for 3 months with a history of regular menses or no menses for 6 months if the prior menstrual pattern was irregular [1].

Amenorrhea affects approximately 4% of women in the United States. The vast majority of those affected will experience secondary amenorrhea with approximately 0.1% experiencing primary amenorrhea [2, 3]. While the underlying causes are varied, ranging from pre-existing genetic issues to insults to the hypothalamic-pituitary axis, Mullerian anomalies, and iatrogenic causes, this chapter seeks to present a systemic approach to assessing and treating patients with amenorrhea.

In this chapter we will present an overview of the epidemiology, presentation, and etiology of primary and secondary amenorrhea. Additionally, we will present an overview of treatment options for various forms of this condition.

Case Vignette

A 37-year-old gravida 3 para 3 presents to the clinic for evaluation of secondary amenorrhea lasting nearly 1 year. She underwent menarche at age 16 after development of secondary sex characteristics. She has always had irregular cycles occurring every 3–6 months until they ceased about a year ago. Her obstetrical history is notable for two full-term spontaneous vaginal deliveries followed by a preterm cesarean delivery at 34 weeks due to preeclampsia with severe features. She has been experiencing intermittent hot flashes for the past several months along with vaginal dryness and difficulty sleeping. She is sexually active with a male partner and expressed interest in another child in the future. Her medical history is otherwise notable for hypothyroidism and asthma managed with levothyroxine and Symbicort. Physical examination, including pelvic examination, is unremarkable. Pregnancy test is negative and initial testing reveals an elevated FSH to 47 and AMH of 0.01.

6.2 Diagnosis

6.2.1 History and Physical Exam

Obtaining a thorough history is essential to any evaluation of amenorrhea, as with any key issue in reproductive medicine. Information gathered should include a detailed past medical, surgical, menstrual, and sexual history. In addition, a detailed discussion of recent changes in medications, new stressors, and changes in diet and exercise is essential for effective history taking. A thorough general and endocrine review-of-systems may provide insight into whether any signs of hormonal dysfunction are present. Relevant features to ask the patient include signs of hirsutism (acne, male-pattern hair growth), nipple discharge (suggestive prolactin excess), fatigue/lethargy, and excessive sweating (signs of thyroid hypo- or hyperfunction), among others.

A detailed contraceptive history is also crucial, given the risk of post-contraceptive amenorrhea. Numerous current methods of contraception can lead to amenorrhea such as Depo-Provera which can cause iatrogenic amenorrhea for up to 1 year after the last dose [4].

6.2.2 Physical Examination

Following obtaining a thorough history and review-of-systems, a directed physical exam is the next essential step. In general, the physical exam should focus on an assessment of endocrine function and, especially in cases of primary amenorrhea, an assessment of developmental stage (e.g., Tanner staging). Therefore, the physical exam should encompass an evaluation of pubertal development, height, weight, body mass index (BMI), a skin exam looking for any signs of hyperandrogenism, a neurological exam, and a gynecologic exam. However, the most critical questions that must be addressed by the physical exam are: (1) "Does the patient have a uterus?" (2) "Does the patient have breast development?" By answering these two questions, the examiner addresses whether the patient has the physical and endocrine potential to undergo menses.

Special attention should be paid to the development of the genital tract and Tanner staging of pubic hair development. The depth of the vagina and the presence of a cervix and uterus in particular will determine the presence of a Mullerian anomaly. For example, if a uterus is present and no cervix is seen, one should consider an obstructive cause such as a transverse vaginal septum or hymenal obstruction. Assessing the extent of pubic hair will provide information regarding the patient's androgen production and should be judged in the context of breast development. Absent or attenuated pubic hair development, especially with the presence of vaginal atrophy, would be suggestive of hypoestrogenemia (given the conversion of circulating androstenediol and testosterone into estrone and estradiol, respectively).

The examining clinician must carefully look for signs of endocrine dysfunction. The presence of excess terminal hair on the face and/or acne would be suggestive of hyperandrogenism such as seen in PCOS. Furthermore, in the presence of obesity and acanthosis nigricans, this would be suggestive of insulin resistance. More severe signs of androgen excess and virilization such as clitoromegaly may be seen with nonclassical congenital adrenal hyperplasia or the adrenal/ovarian neoplasms. The presence of central obesity, purple striae on the abdomen, and enlarged "moon" facies would indicate Cushing's syndrome. If galactorrhea is noted, prolactin excess should be suspected, and, if confirmed, prolactin-secreting pituitary mass should be ruled out, particularly if any visual field deficits are present. However, it should be noted that only one-third of women with prolactin excess experience galactorrhea [5].

6.2.3 Laboratory Testing

First and foremost, a pregnancy test must be performed, regardless of the patient's age, since pregnancy can occur well beyond the conventional limits of a woman's reproductive life. The youngest and oldest known women to spontaneously conceive and give birth were 5 and 59 years old, respectively [1].

Once pregnancy has been excluded, assessment of serum follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and prolactin (PRL) should be done (see Fig. 6.1 for an algorithm to evaluate amenorrhea). FSH and LH typically vary in tandem with each other; hence, obtaining an LH is not necessary. If the FSH is elevated, especially in the setting of signs of hypoestrogenism, then hypergonadotrophic hypogonadism (i.e., premature ovarian insufficiency) should be considered, and a karyotype should be obtained, especially if the patient is less than 30 years of age [3]. An elevated TSH or PRL should prompt a further evaluation for hypothyroidism or pituitary mass, respectively.

Signs of hyperandrogenism should prompt an assessment of the level of 17α-hydroxyprogesterone and total testosterone. Free testosterone levels are less useful as they are prone to substantial laboratory variation [6]. Obtaining a DHEA-S level is most useful if an adrenal tumor is suspected. Of note, excess DHEA-S is often converted to testosterone [7]. Hence, total testosterone is especially high yield in cases of amenorrhea with hirsutism/virilization. If the total testosterone is above 200 ng/dL or the DHEA-S is above 700 μg/dL, then an ovarian or adrenal tumor, respectively, should be suspected.

6.2.4 Imaging

One of the first questions to answer for any patient with primary amenorrhea is if a uterus is present. Transvaginal or transabdominal ultrasonography is an effective first imaging modality. If a uterus cannot be seen on ultrasound or if there appears to be a congenital anomaly of the uterine/Mullerian structures, then subsequent magnetic resonance imaging (MRI) should be performed [8]. Furthermore, MRI can also be used to assess the kidneys and

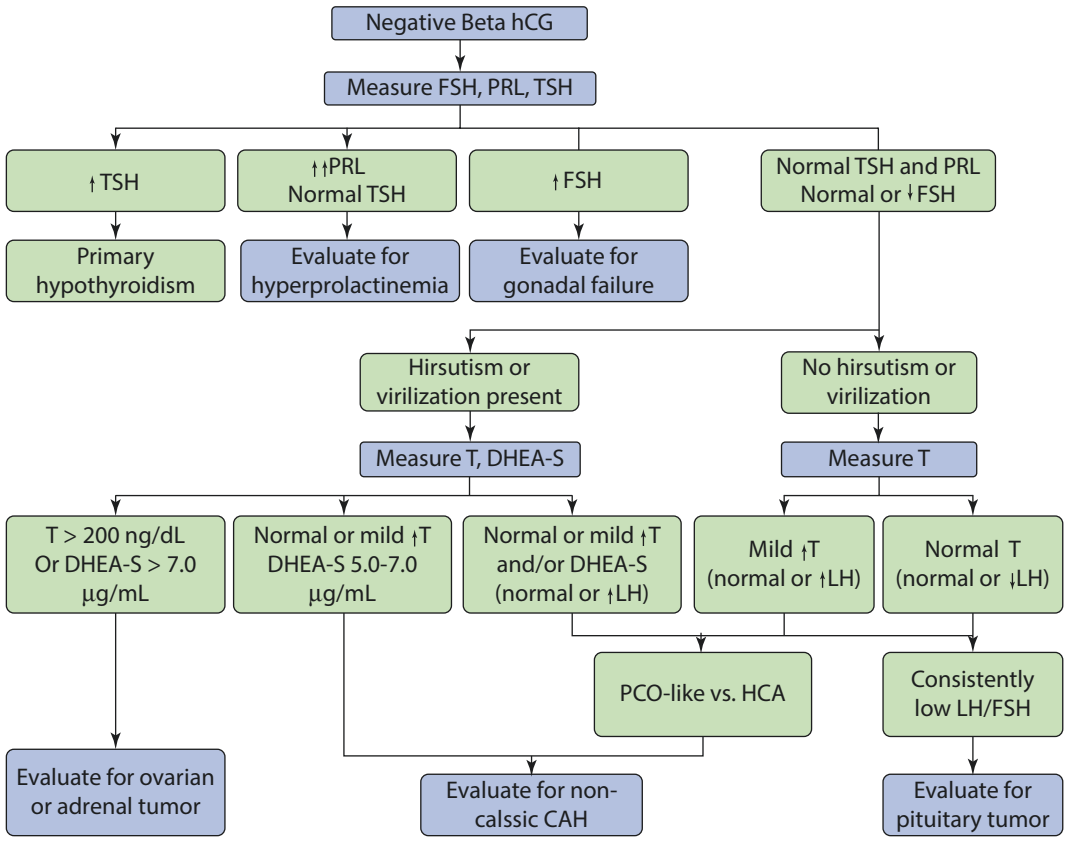

Fig. 6.1 Evaluation of amenorrhea

ureters since approximately 29% of patients with a Mullerian anomaly exhibit renal malformations [1, 9].

Imaging can also be helpful in further narrowing down the cause of the amenorrhea. If a patient has a persistently elevated prolactin, an MRI of the pituitary gland should be done to determine the presence of a lactotroph adenoma or a pituitary stalk-disrupting mass. If a patient presents without any secondary sexual development, presumably due to hypoestrogenism, obtaining a bone age X-ray scan would help confirm this.

6.3 Etiologies of Primary Amenorrhea

Primary amenorrhea can be caused by a plethora of congenital and acquired conditions (Table 6.1). It must be noted that primary amenorrhea can have the same causes as secondary amenorrhea. However, certain disorders are peculiar to primary amenorrhea.

The most common causes of primary amenorrhea include gonadal dysgenesis, Mullerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome), hypothalamic disorders, and constitutional delay of puberty [10]. Rarer causes of primary amenorrhea include androgen insensitivity, hypothalamic-pituitary hypofunction such as Kallmann syndrome, and an obstructed outflow tract as seen with cervical agenesis, transverse vaginal septum, or imperforate hymen. Just based upon this limited differential, one can already discern how the combination of a thorough history and the aforementioned laboratory and imaging can quickly aid in distinguishing between these etiologies.

6.3.1 Gonadal Dysgenesis

Gonadal dysgenesis is the cause of nearly 50% of cases of primary amenorrhea. This term comprises a group of disorders in which the gonads did not properly form in utero. Among these conditions, Turner's syndrome is the most common exhibiting the classic 45, X karyotype. However, mosaicism which may include a full or partial Y chromosome is possible. Of note, patients with Turner's syndrome are at substantially increased risk for cardiac and endocrine abnormalities (osteoporosis and hypothyroidism) [11]. Patients with Swyer syndrome (46,XY) and 46,XX gonadal dysgenesis typically present as prepubertal-appearing females [12]. Of note, any form of gonadal dysgenesis in which a full or partial Y chromosome is seen does carry a 20% risk of gonadoblastoma; hence, gonadectomy is recommended.

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

(continued)

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		

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		

6.3.2 Mullerian Agenesis

Women with Mullerian agenesis, also known as Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, exhibit a rudimentary or completely absent uterus and absent cervix with a shortened vagina (keeping in mind that the Mullerian ducts contribute to the upper 2/3 of the vaginal canal) in the presence of a 46,XX karyotype [9]. MRKH syndrome is autosomal dominant with an incidence of 1/4500–5000 births and is seen in approximately 10% of primary amenorrhea [13, 14]. In an anatomic sense, MRKH patients share the absence of Mullerian structures like patients with androgen insensitivity syndrome (AIS). However, MRKH patients typically exhibit secondary sexual characteristics such as pubic and axil-

lary hair, while AIS patients typically do not. Furthermore, serum gonadotropins, TSH, prolactin, and androgen will be within normal female limits. Ultrasonography will show either a complete absence of Mullerian structures or rudimentary uterine horns. MRI can further characterize these abnormalities and also assess for the aforementioned renal anomalies. Patients with MRKH also have an increased prevalence of vertebral abnormalities [15].

6.3.3 Hypothalamic-Pituitary Disorders

Various disorders of the hypothalamus can cause amenorrhea (Table 6.1). Some like Kallmann syndrome preclude any gonadotropin secretion and lead to primary amenorrhea. Many others can lead to secondary amenorrhea such as tumors, stress states, intense physical activity, and chronic disease, especially infiltrative disorders.

On initial presentation, various stages of pubertal development may be present; nonetheless, circulating gonadotropin and sex steroid levels are all low. In cases of gonadotropin-releasing hormone (GnRH) deficiency, patients typically present with delayed puberty. In cases when patients also present with additional symptoms such as color blindness and most commonly anosmia, these should raise suspicion for Kallmann syndrome. Kallmann syndrome most commonly arises from X-linked recessive mutations in the KAL1 gene which produces the protein ANOS1, which is necessary for migration of neurons to the olfactory bulb [16]. Similar phenotypes can also be seen with GnRH receptor (GnRHR) inactivating mutations. Furthermore, a whole range of GnRH deficiencies leading to hypothalamic amenorrhea can be seen [17, 18]. Physical or emotional stress, chronic disease, and poor nutrition (e.g., anorexia nervosa) can also induce a state of hypothalamic amenorrhea.

Interruptions in downstream signaling through the FSH and LH receptors can also render a patient insensitive to these gonadotropins. FSH receptor (FSHR) mutations have been described which can lead to amenorrhea, lack of folliculogenesis, and infertility [19, 20]. Patients with LH receptor abnormalities typically have normal puberty development, but will be unable to ovulate [21].

Distinguishing between all of these etiologies requires careful clinical assessment utilizing a complete history, physical exam, and an evaluation of FSH and estradiol levels. GnRH deficiency or inactivating GnRHR mutations will typically present with delayed puberty. Function amenorrhea will often present with primary or secondary amenorrhea with a history notable for the aforementioned conditions.

6.3.4 Constitutional Delay of Puberty

Delayed puberty is defined by lack or delay of pubertal milestones 2.5 standard deviations later than the average age of onset of puberty. This entails lack of breast development by age 12, lack of menses by age 13 in the absence of breast or pubic hair growth, or lack of menses by age 15 with the presence of breast or pubic hair growth [3]. These patients typically experience delay of other pubertal milestones such as thelarche and adrenarche. A family history can be revealing as up to 50–75% of patients have a sibling or parent that also experienced delayed puberty [22].

6.3.5 Androgen Insensitivity Syndrome (AIS)

Androgen insensitivity is found in approximately 5% of patients with primary amenorrhea [23]. This condition stems from the inability of androgen receptors (ARs) in a 46,XY male to bind to androgens. The exact cause ranges from complete absence of a normally functioning receptor to defects in the transcriptional action of the AR [24].The classic presentation of AIS is a phenotypic female with Tanner 3 breast development

with small nipples and pale areolae, absent pubic and axillary hair, and a bind vagina. Due to the lack of testosterone effect, the gonads may be present either abdominally or within the inguinal canal. One can confirm the diagnosis by performing a karyotype showing 46,XY and testosterone levels in the normal male range. A key point to note about AIS compared to other disorders of sexual development in which a whole or partial Y chromosome is present is that the risk of gonadal tumors (gonadoblastoma and dysgerminoma) is much smaller before puberty compared to other such disorders. Nonetheless, gonadectomy should be performed after puberty is complete as there is an approximately 14% risk of germ cell tumor by adulthood [25].

6.3.6 Outflow Obstructions of the Genital Tract

Obstructive genital tract abnormalities result from malformations of the Mullerian ducts and/or external genitalia. Such genital tract malformations can be found in 15% of young women who are seen for primary amenorrhea. In addition to Mullerian agenesis (MRKH), adolescents can present with a transverse vaginal septum or imperforate hymen. The most common obstructive anomaly is an imperforate hymen which is found in 0.1% cases of primary amenorrhea. Transverse vaginal septum is much less frequent, seen in roughly 1 in 80,000 cases of primary amenorrhea [3]. These patients typically present with cyclic pelvic pain due to the retained menstrual products. Of note, these patients are at higher risk of having endometriosis likely attributed to increased retrograde menstruation [26]. On exam, patients with an imperforate hymen can present with a bulging, bluish hymenal membrane with a hematocolpos proximal to this. While significant hematocolpos or hematometra could be seen on ultrasound, MRI will provide improved soft tissue definition to detect a transverse vaginal septum while also assessing for other pelvic structural issues [27].

6.4 Etiologies of Secondary Amenorrhea

Etiologies of secondary amenorrhea are much more varied. Patients with this condition often experience menarche at an appropriate age; however, due to some acquired or congenital reason, these menses cease. We define secondary amenorrhea as a lack of menses for 3 consecutive months before 40 years of age with prior regular/monthly menses or 6 months with previously irregular menses. Three to five percent of all reproductive age women will experience secondary amenorrhea [28]. Secondary amenorrhea is commonly seen in women whose weight is below or exceeds the normal range, such as those with polycystic ovary syndrome (PCOS) or hypothalamic amenorrhea [29].

6.4.1 Hypothalamic Amenorrhea

Secondary amenorrhea can be due to a spectrum of hypothalamic disorders. States of high physical stress, emotional distress, and limited nutrition can result in diminished hypothalamic function and decreased GnRH signaling to the pituitary. A classic case is a competitive athlete presenting for evaluation of amenorrhea. In fact, menstrual cycle abnormalities are seen in up to 43% of ballet dancers and in up to 26% of long-distance runners. In similar fashion, patients with calorie-limiting eating disorders such as anorexia nervosa and bulimia can also experience amenorrhea. Emotional stress such as in aftermath of sexual assault, physical violence, and situations of grief can also lead to hypothalamic amenorrhea. Of growing relevance is opioid use-related amenorrhea, as its use can substantially inhibit GnRH release and may be linked with stressors that a patient may be experiencing [30]. Given all of these contributors to hypothalamic amenorrhea, it is essential for clinicians to assess the patient's lifestyle, diet, and level of exercise [31]. As with all forms of amenorrhea, a thorough menstrual history needs to be obtained in addition to a physical exam focusing on the

thyroid, skin (for signs of hyperandrogenemia), presence of galactorrhea, and any signs of bulimia such as poor dentition.

Treatment first and foremost requires removing the underlying insult that is contributing to the patient's hypothalamic dysfunction. Incorporating nonpharmacologic treatments aimed at improving mental health, such as counseling, in addition to hormone replacement will be essential. Estrogen supplementation is often needed to prevent continued decline in bone mineral density, and oral contraceptives are an excellent first-line treatment option [32]. As with all forms of amenorrhea, occult ovulation cannot be excluded; hence, a pregnancy test should be performed prior to the start of any hormonal therapies.

6.4.2 Post-contraception Amenorrhea

Acquired amenorrhea can occur immediately following the use of hormonal contraceptives. The most likely cause is a pre-existing menstrual disorder as documented by numerous studies in the 1970s when higher-dose oral formulations were more common [33, 34]. Depo medroxyprogesterone (Depo-Provera) has been consistently linked with amenorrhea following discontinuation. Patients should be counseled that menses will typically resume 7–10 months after their last injection [35, 36].

6.4.3 Hyperandrogenic States

6.4.3.1 Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the cause of 70–80% of all cases of anovulation (see ► Chap. 7). While many patients experience oligomenorrhea, 24% of these patients will exhibit amenorrhea [3]. PCOS comprises a wide spectrum of features in addition to menstrual dysfunction, including hirsutism/hyperandrogenemia, obesity, and insulin resistance. The Rotterdam criteria are commonly used to make the diagnosis, requiring two of the three following criteria: (1) oligo-ovulation or anovulation/menstrual irregularity, (2) hyperandrogenism (either biochemical or clinical), and (3) polycystic ovaries seen on ultrasound [37]. Laboratory evaluation often shows elevated LH (possibly secondary to hyperinsulinemia), elevated total testosterone, decreased sex hormone-binding globulin, and signs of glucose intolerance/insulin resistance [38, 39]. PCOS patients are at higher risk of metabolic and cardiovascular disease owing to increased predisposition to insulin resistance (and overt type 2 diabetes mellitus) and increased low-density lipoprotein levels [40].

The treatment of PCOS is multifactorial, aimed at menstrual regulation/endometrial protection, improving features of hyperandrogenism, improving fertility efforts, and mitigating associated metabolic abnormalities. Menstrual function can be restored using oral contraceptive pills (OCPs) which can both lead to regular menses via direct endometrial effects and also suppresses excess LH production and ameliorates excess androgen production. Androgen production is decreased not only via suppression of LH release but also through the increase of SHBG level due to the estrogen component. OCPs are the first-line treatment and should be attempted for at least 6 months to see any meaningful effect. If androgenic symptoms persist, then an antiandrogen such as spironolactone should be used [41]. In patients with infertility, ovulation induction with letrozole with or without intrauterine insemination is the best approach to achieve pregnancy [42]. Any concomitant obesity/metabolic disease should also be simultaneously addressed using lifestyle/exercise and diet counseling to encourage weight loss. Metformin should be initiated if glucose intolerance is present. However, metformin should not be seen as a method to induce ovulation [43]. Expeditious treatment is especially crucial in the setting of fertility since various adverse pregnancy outcomes are increased in patients with PCOS including preeclampsia, gestational diabetes, and overall increased perinatal morbidity and mortality [44].

6.4.3.2 Elevated Androgen States

Other conditions such as Cushing's syndrome and congenital adrenal hyperplasia (CAH) can lead to a hyperandrogenic state like PCOS,

but the onset of hirsutism is typically much more rapid. Cushing's syndrome can lead to amenorrhea due to excess adrenal DHEA and DHEA-S production, which affects follicular development and also suppresses GnRH secretion [45]. A spectrum of enzyme deficiencies which comprise CAH can also lead to amenorrhea via similar mechanisms with excess androgen affecting both follicular and hypothalamic functions [46].

A careful history and physical exam will help discriminate between these conditions. Central obesity and moon facies would be more consistent with Cushing's syndrome, while hirsutism and possibly hypotension (rarely hypertension) would be seen with CAH. If Cushing's is suspected, the best screening test would be a dexamethasone suppression test. A 17-hydroprogesterone level should be obtained to assess for CAH. In addition, all patients with signs of hyperandrogenism should have a total testosterone and dehydroepiandrosterone sulfate (DHEA-S). Ovarian imaging will often show a polycystic appearance.

6.4.4 Pituitary Disorders

6.4.4.1 Disorders of the Anterior Pituitary Gland

Pituitary tumors can lead to menstrual irregularities and even overt amenorrhea due to impairment of proper GnRH release and function of the anterior pituitary gland. Among the most common of these tumors are prolactin-secreting tumors. Patients may present with galactorrhea, and, in cases when tumors exceed 10 mm in size, patients can present with mass effect symptoms such as headaches and bitemporal hemianopsia due to compression of the optic chiasm.

6.4.4.2 Prolactin-Secreting Adenomas and Hyperprolactinemia

Lactotroph tumors or prolactin-secreting adenomas comprise 40% of pituitary tumors. Hyperprolactinemia is the most common etiology of amenorrhea due to pituitary dysfunction [3]. Furthermore up to one-third of secondary amenorrhea patients will have a prolactinoma [47, 48]. Common symptoms include oligomenorrhea/amenorrhea, galactorrhea, infertility, headaches, and visual disturbances. It must be noted, however, that the relationship between galactorrhea, hyperprolactinemia, and menstrual pattern is not always consistent. One-third of women with galactorrhea and hyperprolactinemia will have regular menses, and one-third of women with hyperprolactinemia will not have galactorrhea [49]. One elevated prolactin level should be repeated with a fasting sample. If hyperprolactinemia persists, a pituitary MRI should be performed [47]. A key point is that given the persistent dopaminergic inhibition of pituitary secretion, any pituitary mass could potentially disrupt this signaling and lead to hyperprolactinemia [50]. For example, a nonfunctioning pituitary tumor will often secrete the alpha subunits shared by FSH, LH, and TSH, and, if it compresses the pituitary stalk, would lead to an elevation in prolactin. Other etiologies of hyperprolactinemia include chest wall injury, renal failure, and primary hypothyroidism (due to elevated thyrotropin-releasing hormone).

Treatment of prolactin-secreting tumors, especially if they are smaller than 10 mm and do not lead to symptoms of increased intracranial pressure, includes dopamine agonists like bromocriptine and cabergoline. If a patient is otherwise asymptomatic and desires contraception, she could be treated with oral contraceptives. Both treatments will provide the necessary estrogenic exposure to prevent osteoporosis [51].

6.4.4.3 Postpartum Pituitary Necrosis (Sheehan Syndrome)

Severe obstetrical hemorrhage can lead to postpartum necrosis of the pituitary secondary to prolonged and/or severe hypotension or shock [52]. The low-pressure vascular system in pituitary combined with pituitary hypertrophy during pregnancy increases vascular demand without a commensurate increase in blood flow [1]. Therefore, prolonged disruption in blood flow can easily lead to pituitary ischemia and subsequent necrosis. Symptoms

indicative of pituitary hypofunction include fatigue, slow mentation, hypotension, nausea/vomiting, and lack of lactation [53]. Imaging consisting of a brain MRI will likely show a severely attenuated pituitary gland or an empty sella turcica filled with cerebrospinal fluid [53].

6.4.4.4 Pituitary Apoplexy

This is a serious condition seen in 2–12% of patients with pituitary adenomas [54]. It involves abrupt hemorrhage into often non-functioning pituitary tumors. Patients typically present with abrupt, severe headaches and visual disturbances. Substantial fatigue and even loss of consciousness (LOC) may also occur. Precipitating factors include an acute increase in intracranial pressure, arterial hypertension, hemorrhage due to anticoagulation, and even dynamic testing. If this condition is suspected, head CT or brain MRI will often show a hemorrhagic or even necrotic pituitary tumor. Treatment is almost exclusively dependent on neurosurgical intervention; however, in cases without visual disturbance and lack of LOC, conservative management is increasingly being used. Additionally assessment of other potentially life-threatening conditions, such as cortisol deficiency and other pituitary deficits, should be performed [55].

6.4.4.5 Cushing's Disease and Syndrome

*E*xcess adrenal function due to a pituitary or ectopic source of ACTH can also lead to amenorrhea. Once a patient presents with signs and symptoms suggestive of cortisol excess, screening tests such as the low-dose dexamethasone suppression test, late-night salivary cortisol, and the 24-hr urine free cortisol collection should be performed to confirm cortisol excess. ACTH level then can be drawn to determine if the excess is an ACTH-dependent or ACTH-independent process. If found to be ACTH-dependent, and subsequent provocative testing using a corticotropin-releasing hormone (CRH) stimulation and high-dose dexamethasone suppression test (HD-DST) is positive, then the ACTH excess is from a pituitary tumor and termed Cushing's disease. If the CRH stimulation test and HD-DST are negative, then one is likely dealing with Cushing's syndrome due to an ectopic source of ACTH, often a bronchial carcinoid lung tumor [45].

6.4.4.6 Postirradiation Hypopituitarism

Therapeutic radiation when used to treat midline nasopharyngeal/brain/pituitary tumors can lead to local tissue destruction and later result in hypopituitarism and amenorrhea. In one retrospective review of patients getting up to 60–70Gy of fractionated radiation to the pituitary, 17–55% developed some degree of hypopituitarism [56]. Common hormone deficiencies (from most likely to least) are growth hormone (GH), gonadotropin (FSH/LH), ACTH, and TSH. Symptoms can develop decades after irradiation, which can include fatigue, hypotension, signs of hypoestrogenism (vaginal dryness, vasomotor symptoms), and amenorrhea [56]. Such patients require close follow-up to address any hormone deficiencies.

6.4.5 Acquired Disorders of the Genital Tract

Acquired anatomical causes of amenorrhea stem primarily from the development of intrauterine adhesions, commonly known as Asherman's syndrome (AS). AS comprises 7% of all cases of secondary amenorrhea. Any procedure that can potentially denude the endometrium past the stratum basalis and thereby prevent normal regeneration of the endometrial lining can result in AS. The degree of AS can lead to cyclic pain due to obstructed menses, and, similar to women with imperforate hymen or a transverse vaginal septum, these patients are at higher risk of developing endometriosis [57]. Treatment for AS typically involves gentle cervical dilation with hysteroscopic excision of scar tissue. Placement of an intrauterine balloon for at least 7 days postoperatively is often done with concomitant hormone replacement to ensure

that lining regrows properly [58]. Another acquired cause of outflow obstruction is cervical stenosis, which can stem from excisional procedures for the treatment of cervical dysplasia such as electrocautery and cold-knife cone biopsies.

6.4.6 Primary Ovarian Insufficiency

Approximately 10% of women experience menopause by the age of 45, well before the average age of menopause of 51.2 [1]. Such patients experience early ovarian aging that is most likely due to early follicle depletion. Patients who experience signs of menopause before the age of 40 and have elevated FSH levels (>30–40 IU/L) on two occasions more than a month apart meet the criteria for primary ovarian insufficiency (POI). POI, which arises from follicular dysfunction and depletion, comprises 4–18% of cases of secondary amenorrhea.

The vast majority (90%) of POI cases are idiopathic. However, it can be associated with a myriad of underlying pathologies, as outlined in Table 6.2. For example, many instances of POI have genetic causes/chromosomal abnormalities such as fragile X syndrome [59]. In the case of fragile X syndrome, a family history of early menopause and especially of male developmental delay is typically found. For patients experiencing POI before the age of 30, a karyotype is warranted to rule out Turner's syndrome and to determine if a Y chromosome is present, which would necessitate gonadectomy to reduce the risk of gonadal malignancy [60]. It must be noted that POI patients have a 6% chance of achieving a spontaneous pregnancy. Hence, contraceptive counseling should be performed [61].

Autoimmune disease accounts for approximately 5% of cases of POI [62]. In particular, POI is associated with autoimmune adrenal and thyroid conditions. While antithyroid antibodies (anti-thyroglobulin and anti-TPO)

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		

(continued)

Table 6.2 (continued)

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)	
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			

are the most common autoimmune antibodies seen in POI patients, those that have anti-adrenal/anti-steroidogenic enzyme antibodies (e.g., 21-hydroxylase) are at greater risk of developing autoimmune oophoritis [62, 63]. Therefore, any patients with such positive antibodies should have their adrenal function assessed. Addison's disease patients can also experience POI 8–14 years prior to the development of adrenal insufficiency [64]. Any patient positive for anti-adrenal antibodies should have an AM serum cortisol checked and, if less than 18 mg/dL, should undergo an ACTH stimulation test [65].

A key point to note is that POI and early menopause are associated with higher all-cause mortality in numerous studies. In particular, there is a higher risk of cardiovascular disease and osteoporosis [66, 67]. Hence, judicious use of hormone replacement therapy is essential for these patients at least up until the age of natural menopause [68].

6.4.6.1 Other Causes of Primary Ovarian Insufficiency

Patients with FSH abnormalities and defects in steroidogenesis, such as 17-hydroxylase deficiency, can also lead to POI [69]. Patients with these conditions typically exhibit an elevated FSH level. In addition, metabolic disorders, such as galactosemia resulting from a deficiency of galactose-1-phosphate uridyl transferase, can lead to POI. Fortunately, galactosemia is typically diagnosed shortly after birth due to intolerance of milk and signs of galactose excess [70].

6.5 Review Questions

1. A 15-year-old G0 is seen for primary amenorrhea. Her exam is notable for Tanner stage 5 breast development, an absence of pubic hair, and truncal obesity. She has been sexually active for the past year, but intercourse remains painful. She also complains of persistent headaches over the past 6 months. What is your next step in management?
   A. Obtain an ultrasound to assess for a uterus.
   B. Obtain a karyotype.
   C. Recommend that she proceed to gonadectomy.
   D. Perform a brain MRI.
   E. All of the above.

2. A 28-year-old G2P1 presents to your clinic with 3 weeks of nipple discharge, and menses have been absent for the past 4 months (previously monthly). Her primary care physician obtained a random prolactin level which was 96 ng/mL; beta-HCG was negative. Her mother had breast cancer and her sister is BRCA1 positive. What is the next best step in management?
   A. Proceed with a breast exam.
   B. Obtain a morning, fasting prolactin.
   C. Perform a brain MRI.
   D. Perform a mammogram.

3. Your new patient is a 19-year-old G2P0 who present with missed menses for the past 3 months. This patient is also experiencing increasing vaginal dryness. She also has a maternal male cousin with developmental delay. Her history is notable for two surgical pregnancy terminations. All pregnancy tests have been negative. The remainder of her history is unremarkable. Which test is the most helpful in determining the diagnosis?
   A. Saline-infusion sonography
   B. TSH
   C. FSH
   D. Karyotype
   E. All of the above

4. In the course of evaluating an 18-year-old for primary amenorrhea, you note that her karyotype is 45 XO consistent with Turner's syndrome. Her cardiac evaluation is unremarkable, and you counsel her on her reproductive outlook. Her AMH is 0.04 ng/mL. What is the best characterization of her ability to conceive?

A. While unlikely, she still has a 6% chance of conceiving.
B. It will be impossible for her to conceive.
C. She will need in vitro fertilization to achieve conception.

6.6 Answers

1. A
2. A
3. C
4. A

References

1. Fritz M, Speroff L. In: Taylor HS, Seli E, Pal L, editors. Clinical gynecologic endocrinology and infertility. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2020.
2. Marsh CA, Grimstad FW. Primary amenorrhea: diagnosis and management. Obstet Gynecol Surv. 2014;69(10):603–12.
3. Practice Committee of American Society for Reproductive Medicine. Current evaluation of amenorrhea. Fertil Steril. 2008;90(5 Suppl): S219–25.
4. Sims J, Lutz E, Wallace K, Kassahun-Yimer W, Ngwudike C, Shwayder J. Depomedroxyprogesterone acetate, weight gain and amenorrhea among obese adolescent and adult women. Eur J Contracept Reprod Health Care. 2020;25(1):54–9.
5. Luciano AA. Clinical presentation of hyperprolactinemia. J Reprod Med. 1999;44(12 Suppl): 1085–90.
6. Miller KK, Rosner W, Lee H, Hier J, Sesmilo G, Schoenfeld D, et al. Measurement of free testosterone in normal women and women with androgen deficiency: comparison of methods. J Clin Endocrinol Metab. 2004;89(2):525–33.
7. Kamilaris TC, DeBold CR, Manolas KJ, Hoursanidis A, Panageas S, Yiannatos J. Testosterone-secreting adrenal adenoma in a peripubertal girl. JAMA. 1987;258(18):2558–61.
8. Robbins JB, Broadwell C, Chow LC, Parry JP, Sadowski EA. Müllerian duct anomalies: embryological development, classification, and MRI assessment. J Magn Reson Imaging. 2015;41(1): 1–12.
9. Chandler TM, Machan LS, Cooperberg PL, Harris AC, Chang SD. Mullerian duct anomalies: from diagnosis to intervention. Br J Radiol. 2009;82(984):1034–42.
10. Timmreck LS, Reindollar RH. Contemporary issues in primary amenorrhea. Obstet Gynecol Clin N Am. 2003;30(2):287–302.
11. Allybocus ZA, Wang C, Shi H, Wu Q. Endocrinopathies and cardiopathies in patients with Turner syndrome. Climacteric. 2018;21(6): 536–41.
12. McDonough PG, Byrd JR. Gonadal dysgenesis. Clin Obstet Gynecol. 1977;20(3):565–79.
13. Committee on Adolescent Health Care. ACOG Committee Opinion No. 728: Müllerian agenesis: diagnosis, management, and treatment. Obstet Gynecol. 2018;131(1):e35–42.
14. Simpson JL. Genetics of the female reproductive ducts. Am J Med Genet. 1999;89(4):224–39.
15. Bjørsum-Meyer T, Herlin M, Qvist N, Petersen MB. Vertebral defect, anal atresia, cardiac defect, tracheoesophageal fistula/esophageal atresia, renal defect, and limb defect association with Mayer-Rokitansky-Küster-Hauser syndrome in co-occurrence: two case reports and a review of the literature. J Med Case Rep. 2016;10(1):374.
16. Stamou MI, Georgopoulos NA. Kallmann syndrome: phenotype and genotype of hypogonadotropic hypogonadism. Metabolism. 2018;86:124–34.
17. Beneduzzi D, Trarbach EB, Min L, Jorge AA, Garmes HM, Renk AC, et al. Role of gonadotropin-releasing hormone receptor mutations in patients with a wide spectrum of pubertal delay. Fertil Steril. 2014;102(3):838–46.e2.
18. Fourman LT, Fazeli PK. Neuroendocrine causes of amenorrhea--an update. J Clin Endocrinol Metab. 2015;100(3):812–24.
19. Desai SS, Roy BS, Mahale SD. Mutations and polymorphisms in FSH receptor: functional implications in human reproduction. Reproduction. 2013;146(6):R235–48.
20. Gromoll J, Simoni M, Nordhoff V, Behre HM, De Geyter C, Nieschlag E. Functional and clinical consequences of mutations in the FSH receptor. Mol Cell Endocrinol. 1996;125(1–2):177–82.
21. Toledo SP, Brunner HG, Kraaij R, Post M, Dahia PL, Hayashida CY, et al. An inactivating mutation of the luteinizing hormone receptor causes amenorrhea in a 46,XX female. J Clin Endocrinol Metab. 1996;81(11):3850–4.
22. Harrington J, Palmert MR. Clinical review: distinguishing constitutional delay of growth and puberty from isolated hypogonadotropic hypogonadism: critical appraisal of available diagnostic tests. J Clin Endocrinol Metab. 2012; 97(9):3056–67.
23. Jagiello J. Prevalence of testicular feminization. Lancet. 1962;1:329.

24. Hughes IA, Werner R, Bunch T, Hiort O. Androgen insensitivity syndrome. Semin Reprod Med. 2012;30(5):432–42.
25. Deans R, Creighton SM, Liao LM, Conway GS. Timing of gonadectomy in adult women with complete androgen insensitivity syndrome (CAIS): patient preferences and clinical evidence. Clin Endocrinol. 2012;76(6):894–8.
26. Amitai E, Lior Y, Sheiner E, Saphier O, Leron E, Silberstein T. The impact of hymenectomy on future gynecological and obstetrical outcomes. J Matern Fetal Neonatal Med. 2020;33(8):1400–4.
27. Williams CE, Nakhal RS, Hall-Craggs MA, Wood D, Cutner A, Pattison SH, et al. Transverse vaginal septae: management and long-term outcomes. BJOG. 2014;121(13):1653–8.
28. Meczekalski B, Katulski K, Czyzyk A, Podfigurna-Stopa A, Maciejewska-Jeske M. Functional hypothalamic amenorrhea and its influence on women's health. J Endocrinol Investig. 2014;37(11): 1049–56.
29. Golden NH, Carlson JL. The pathophysiology of amenorrhea in the adolescent. Ann N Y Acad Sci. 2008;1135:163–78.
30. Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, et al. Functional hypothalamic amenorrhea: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2017;102(5):1413–39.
31. Berga SL. Behaviorally induced reproductive compromise in women and men. Semin Reprod Endocrinol. 1997;15(1):47–53.
32. Hergenroeder AC, Smith EO, Shypailo R, Jones LA, Klish WJ, Ellis K. Bone mineral changes in young women with hypothalamic amenorrhea treated with oral contraceptives, medroxyprogesterone, or placebo over 12 months. Am J Obstet Gynecol. 1997;176(5):1017–25.
33. Jacobs HS, Knuth UA, Hull MG, Franks S. Post-"pill" amenorrhoea--cause or coincidence? Br Med J. 1977;2(6092):940–2.
34. Steele SJ, Mason B, Brett A. Amenorrhoea after discontinuing combined oestrogen-progestogen oral contraceptives. Br Med J. 1973;4(5888):343–5.
35. Schwallie PC, Assenzo JR. The effect of depomedroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: a review. Contraception. 1974;10(2):181–202.
36. Fotherby K, Howard G. Return of fertility in women discontinuing injectable contraceptives. J Obstet Gynaecol (Lahore). 1986;6 Suppl 2:S110–5.
37. Lauritsen MP, Bentzen JG, Pinborg A, Loft A, Forman JL, Thuesen LL, et al. The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Mullerian hormone. Hum Reprod. 2014;29(4):791–801.
38. Rebar R, Judd HL, Yen SS, Rakoff J, Vandenberg G, Naftolin F. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. J Clin Invest. 1976;57(5):1320–9.
39. Lobo RA, Carmina E. The importance of diagnosing the polycystic ovary syndrome. Ann Intern Med. 2000;132(12):989–93.
40. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012;97(1):28–38.e25.
41. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(12):4565–92.
42. Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2018;5(5):Cd010287.
43. Practice Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org; Practice Committee of the American Society for Reproductive Medicine. Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline. Fertil Steril. 2017;108(3):426–41.
44. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update. 2006;12(6):673–83.
45. Barnett R. Cushing's syndrome. Lancet. 2016; 388(10045):649.
46. El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. Lancet. 2017;390(10108): 2194–210.
47. Schlechte J, Dolan K, Sherman B, Chapler F, Luciano A. The natural history of untreated hyperprolactinemia: a prospective analysis. J Clin Endocrinol Metab. 1989;68(2):412–8.
48. Kleinberg DL, Noel GL, Frantz AG. Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. N Engl J Med. 1977;296(11):589–600.
49. Schlechte J, Sherman B, Halmi N, VanGilder J, Chapler F, Dolan K, et al. Prolactin-secreting pituitary tumors in amenorrheic women: a comprehensive study. Endocr Rev. 1980;1(3):295–308.
50. Chen L, White WL, Spetzler RF, Xu B. A prospective study of nonfunctioning pituitary adenomas: presentation, management, and clinical outcome. J Neuro-Oncol. 2011;102(1):129–38.
51. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273–88.
52. Sheehan HL, Murdoch R. Postparum necrosis of the interior pituitary: pathological and clinical aspects. J Obstet Gynaecol Br Emp. 1938;45:456.

53. Kilicli F, Dokmetas HS, Acibucu F. Sheehan's syndrome. Gynecol Endocrinol. 2013;29(4):292–5.
54. Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary apoplexy. Endocr Rev. 2015;36(6):622–45.
55. Barkhoudarian G, Kelly DF. Pituitary apoplexy. Neurosurg Clin N Am. 2019;30(4):457–63.
56. VanKoevering KK, Sabetsarvestani K, Sullivan SE, Barkan A, Mierzwa M, McKean EL. Pituitary dysfunction after radiation for anterior skull base malignancies: incidence and screening. J Neurol Surg B Skull Base. 2020;81(1):75–81.
57. March CM. Management of Asherman's syndrome. Reprod Biomed Online. 2011;23(1):63–76.
58. Yang X, Liu Y, Li TC, Xia E, Xiao Y, Zhou F, et al. Durations of intrauterine balloon therapy and adhesion reformation after hysteroscopic adhesiolysis: a randomized controlled trial. Reprod Biomed Online. 2020;40(4):539–46.
59. Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med. 2009;360(6):606–14.
60. De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet. 2010;376(9744):911–21.
61. Committee opinion no. 605: primary ovarian insufficiency in adolescents and young women. Obstet Gynecol. 2014;124(1):193–7.
62. Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. Endocr Rev. 1997;18(1):107–34.
63. Bakalov VK, Vanderhoof VH, Bondy CA, Nelson LM. Adrenal antibodies detect asymptomatic auto-immune adrenal insufficiency in young women with spontaneous premature ovarian failure. Hum Reprod. 2002;17(8):2096–100.
64. Turkington RW, Lebovitz HE. Extra-adrenal endocrine deficiencies in Addison's disease. Am J Med. 1967;43(4):499–507.
65. Kim TJ, Anasti JN, Flack MR, Kimzey LM, Defensor RA, Nelson LM. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. Obstet Gynecol. 1997;89(5 Pt 1):777–9.
66. Gong D, Sun J, Zhou Y, Zou C, Fan Y. Early age at natural menopause and risk of cardiovascular and all-cause mortality: a meta-analysis of prospective observational studies. Int J Cardiol. 2016;203:115–9.
67. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. Climacteric. 2015;18(4):483–91.
68. Committee opinion no. 698 summary: hormone therapy in primary ovarian insufficiency. Obstet Gynecol. 2017;129(5):963–4.
69. Kovanci E, Schutt AK. Premature ovarian failure: clinical presentation and treatment. Obstet Gynecol Clin N Am. 2015;42(1):153–61.
70. Spencer JB, Badik JR, Ryan EL, Gleason TJ, Broadaway KA, Epstein MP, et al. Modifiers of ovarian function in girls and women with classic galactosemia. J Clin Endocrinol Metab. 2013;98(7):E1257–65.