# Menstruation and Secondary Amenorrhea

5

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**Learning Objectives**

1. Differentiate the clinical presentations of physiologic, hypothalamic/pituitary, ovarian, and structural causes of amenorrhea.
2. Describe an approach to diagnostic testing in a patient with secondary amenorrhea based upon suspected etiology.
3. Formulate a treatment plan to manage secondary amenorrhea and associated health risks based upon diagnosis.
4. Identify when a patient with amenorrhea should be referred to a subspecialist for advanced diagnostic testing or treatment.

*Rosalia is a 35-year-old woman who presents to primary care clinic with no menses for the past 6 months. She underwent menarche at age 14 with regular menses until a year ago when her cycles started to occur less frequently.*

Secondary amenorrhea is defined as the absence of menses for three cycles or 3 to 6 months in previously menstruating women [1]. Primary amenorrhea is the absence of onset of menses at age 15 for women with secondary sexual characteristics (breast enlargement, body hair, hip widening) or at age 13 in women without secondary sexual characteristics [1]. Important causes of primary amenorrhea are congenital, leading to hormonal dysregulation and anatomical dysgenesis at the level of the hypothalamus (Kallmann syndrome), gonads (Turner syndrome), uterus (Mayer-Rokitansky-Kuster-Hauser syndrome, androgen insensitivity syndrome), outflow tract (transverse vaginal septum, imperforate hymen), or entire reproductive tract (5-alpha reductase deficiency). As it is unusual for women to present to adult primary care with a new diagnosis of primary amenorrhea, the remainder of this chapter will focus on secondary amenorrhea.

## Epidemiology

The prevalence of secondary amenorrhea is approximately 3–5% of women worldwide [2–4]. After excluding pregnancy, the most common causes of secondary amenorrhea are hypothalamic suppression (34%), polycystic ovary syndrome (PCOS) (28–73%), hyperprolactinemia (13–15%), primary ovarian insufficiency (POI) (12%), thyroid dysfunction (2–15%), and Asherman syndrome (7%) [3, 5, 6]. About 1% of women are affected by POI before age 40, with incidence rates of about 10 per 10,000 person-years in women ages 15–29 and 76 per 10,000 person-years in women ages 30–39 years [7].

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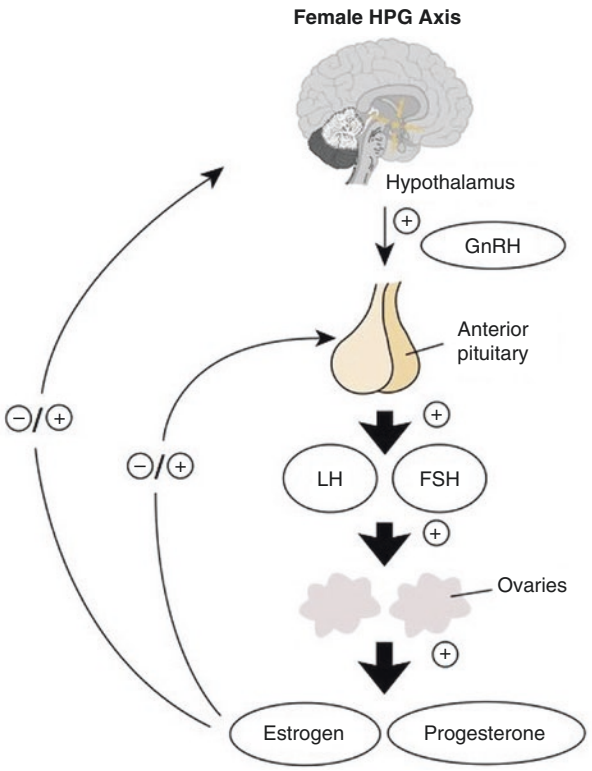


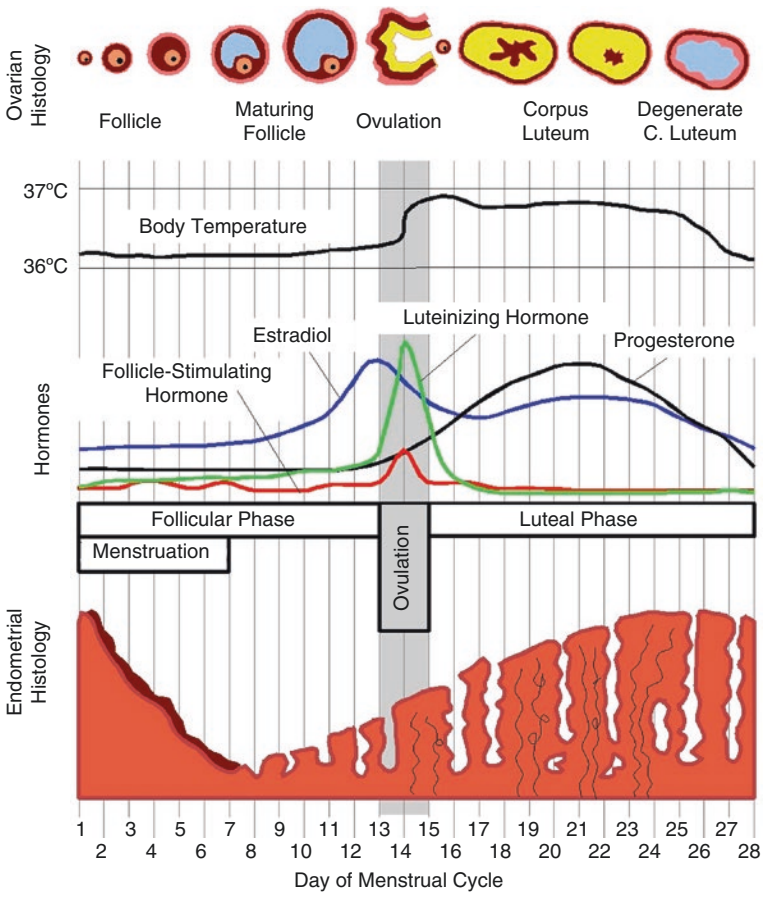

**Fig. 5.1** Hypothalamic-pituitary-gonadal (HPG) axis in women (Reprinted from Hiller-Sturmhofel and Bartke [8])

## Physiology

The majority of secondary amenorrhea is caused by hormonal dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis (Fig. 5.1). Normally, gonadotropic-releasing hormone (GNRH) released by the hypothalamus stimulates release of FSH and luteinizing hormone (LH) from the anterior pituitary, which then stimulate estrogen and progesterone release from the ovaries. Estrogen and progesterone provide regulatory feedback to the HPG axis at the levels of the hypothalamus and pituitary.

Hormones of the HPG axis regulate menstruation (Fig. 5.2). In the early follicular phase, a rise in FSH stimulates recruitment of ovarian follicles and increased estrogen production. Estrogen at first stimulates follicle growth and endometrial proliferation and suppresses LH release in the follicular phase. Once estrogen rises to higher levels, it triggers an LH surge and release of an oocyte from the follicle (ovulation). In the luteal phase, the follicle transforms into a corpus luteum which produces estrogen and progesterone, preparing the endometrial lining for potential implantation. The corpus luteum atrophies if not fertilized, and the subsequent decrease in progesterone stimulates menstruation.

Hormonal dysfunction leading to disruption of the menstrual cycle can occur at any level of the HPG pathway.




*(Average values. Durations and values may differ between different females or different cycles.)*

**Fig. 5.2** The normal menstrual cycle [9] (Source: This Wikipedia and Wikimedia Commons image is from the user Chris 73 and is freely available at //commons.wikimedia.org/wiki/File:MenstrualCycle.png under the creative commons cc-by-sa 3.0 license)

## Pathophysiology

This chapter is organized into sections that discuss the physiologic, structural, pharmacologic, hypothalamic/pituitary (low FSH), ovarian (high FSH), and other endocrine causes of amenorrhea. Notably, many of the above conditions (including POI, breastfeeding, and other chronic diseases) are not reliable inducers of anovulation and amenorrhea; patients who do not desire pregnancy should be offered contraceptive counseling (please see Chap. 4, Patient-Centered Contraceptive Counseling).

### Physiologic

Pregnancy and menopause are important causes of amenorrhea and are described further in Chap. 39, Obstetric Medicine, and Chap. 8, Menopause, respectively. Regular breastfeeding causes amenorrhea through secretion of prolactin by the pituitary, which inhibits GNRH and subsequently suppresses the menstrual cycle.

### Structural

Uterine procedures and operations including dilation and curettage, or infections like endometritis, can cause cervical stenosis and/or intrauterine scarring known as Asherman syndrome. Both of these conditions can lead to outflow obstruction of menses.

### Pharmacologic

Contraceptives, including continuous or extended combined oral contraceptives (COC), hormonal intrauterine devices (IUDs), and intramuscular medroxyprogesterone acetate, commonly induce amenorrhea. There is no physiologic requirement for regular menses in women using these forms of contraception [10]. With each of these methods, amenorrhea is due to constant progestin levels in the uterus that thin the endometrium. COCs and medroxyprogesterone acetate additionally prevent cyclical thickening of the endometrium through hormonal suppression of the HPG axis [10].

Other medications affect prolactin release through inhibition by dopamine or stimulation by serotonin (antipsychotics, antidepressants, prokinetics, antihypertensives) and GNRH suppression (opioids and glucocorticoids) [11–13]. Elevated prolactin leads to feedback inhibition of GNRH with resulting HPG axis suppression (Table 5.1).

**Table 5.1** Medications associated with hyperprolactinemia [11]

| | |
|---|---|
| Psychiatric medications | Antipsychotics (typical and atypical)<br>Tricyclic antidepressants<br>SSRIs<br>MAO-I<br>Others: trazodone, buspirone, alprazolam |
| Estrogens | Combined oral contraceptives |
| Gastrointestinal medications | Antiemetics: prochlorperazine, metoclopramide<br>H2 antagonists: cimetidine, ranitidine |
| Antihypertensives | Methyldopa, reserpine, verapamil |
| Other | Opiates<br>Cocaine |

### Hypothalamic/Pituitary (Low FSH/LH)

Hypothalamic or functional amenorrhea is due to a decrease in GNRH secretion, which can occur in the setting of weight loss, excessive exercise, disordered eating, poor nutrition, and chronic disease. Hypothalamic amenorrhea is a diagnosis of exclusion [14]. Chronic disease such as advanced kidney and liver disease, malignancy, and malabsorption with associated malnutrition and weight fluctuations can lead to hypothalamic amenorrhea and alterations in hormone metabolism. Women with low body mass index (BMI) and disordered eating can present with thin body habitus, enlarged parotid glands, and lanugo. The female athlete triad (amenorrhea/oligomenorrhea, low energy availability with or without disordered eating, and decreased bone density) is further detailed in Chap. 34, Eating Disorders and the Female Athlete Triad.

Pituitary tumors can cause excess or deficient hormone secretion. Tumor compression through mass effect can lead to panhypopituitarism, including deficiency of LH, FSH, and thyroid-stimulating hormone (TSH), with resulting menstrual dysfunction. Patients with prolactinomas can present with galactorrhea, headaches, and vision changes.

Central hypogonadism can result from infiltration or destruction of the hypothalamus and/or pituitary. Infiltrative causes can include hemochromatosis, amyloidosis, inflammatory disorders (sarcoidosis, lymphocytic hypophysitis, Wegener's granulomatosis), infectious diseases (tuberculosis, syphilis, meningitis), or malignancy (carcinoma, lymphoma, leukemia) [15]. Other causes of damage to these structures include traumatic brain injury, radiation, and ischemia. Pituitary ischemia in the setting of postpartum hemorrhage (Sheehan syndrome) generally presents with difficulty breastfeeding and other symptoms of panhypopituitarism such as fatigue, weight change, cold intolerance, decreased appetite, decreased libido, hair loss, and constipation.

In addition to pituitary tumors, hyperprolactinemia occurs with physiologic conditions (stress, breast stimulation), endocrine disorders (Cushing's disease, acromegaly, hypothyroidism, PCOS), neurologic disorders (seizures), sys-

temic disease (chronic renal or liver disease), and medications (as discussed in the pharmacologic section) [11, 12].

### Ovarian (High FSH)

Primary ovarian insufficiency, POI, also previously called premature menopause and primary ovarian failure, is defined as dysfunction or depletion of ovarian follicles with cessation of menses before age 40 years [16, 17]. Patients may present with hot flashes, sleep disturbance, depression, sexual dysfunction, and night sweats.

Various conditions are associated with POI, including congenital disorders (Turner syndrome, fragile X, and Bloom syndrome), signal defects (FSH/LH receptor or G protein mutation), enzyme deficiency (aromatase or 17/20-lyase), iatrogenic causes (chemotherapy, radiation), endocrine/autoimmune diseases (Hashimoto's thyroiditis, Graves' disease, diabetes mellitus type 1, autoimmune adrenal insufficiency), and infection (mumps) [16, 17]. Other tumors that can disrupt ovarian function include granulosa, theca, teratoma, metastatic, and androgen-producing tumors.

### Other Endocrine Disorders

#### Hyperandrogenism

Hyperandrogenic anovulation occurs through multiple endocrinologic conditions. PCOS is the most common cause of mildly elevated androgens and menstrual dysfunction, with mechanisms detailed further in Chap. 6, Polycystic Ovary Syndrome. Obesity, independent from PCOS, can also lead to menstrual anomalies due to dysregulation of metabolic, endocrine, and inflammatory pathways, including increased peripheral conversion of androgens to estrogen by aromatase in adipose tissue [18]. In Cushing's syndrome, excess adrenocorticotropic hormone (ACTH) production by the pituitary increases secretion of both cortisol and androgens from the adrenals [19]. Direct glucocorticoid suppression of GNRH secretion and feedback inhibition by hyperandrogenemia may also result in hypogonadotropic hypogonadism and menstrual dysfunction [19]. Nonclassical adrenal hyperplasia due to 21-hydroxylase deficiency can present with secondary amenorrhea and symptoms and physical exam findings of hirsutism in adult women [20]. With acromegaly, pituitary compression can occur along with direct growth hormone effects on gonadal function [13]. Exogenous androgens and androgen-secreting ovarian or adrenal tumors are important to exclude.

#### Thyroid Dysfunction

Both hyper- and hypothyroidism influence menses through effects on GNRH secretion, prolactin, steroid metabolism, and sex hormone-binding globulin [19]. In hyperthyroidism, associated weight loss can lead to hypothalamic amenorrhea; autoimmune thyroid disease is also associated with POI [19].

## Clinical Manifestations

*Rosalia is sexually active with one male partner and uses condoms intermittently. She has been pregnant twice, with one cesarean section and one spontaneous miscarriage. She takes ibuprofen as needed for menstrual cramps and otherwise denies medication and substance use. There are no known gynecologic or endocrine issues in her family.*

The evaluation of amenorrhea should include a detailed medical, surgical, and social history. A complete review of systems should be documented particularly targeting menstruation, sex, pregnancy, intrauterine procedures, and medications (Table 5.2) [21, 22]. History questions should focus on a potential neurologic, endocrine, or gynecologic etiology for amenorrhea. Family history should include menstrual history of first-degree family members, puberty delay (delayed or incomplete sexual maturation, primary amenorrhea), genetic disorders (Turner syndrome, Bloom syndrome, fragile X), chronic illness (especially autoimmune and endocrine), and infertility. Physical exam should include BMI, cranial nerves (especially II, VI, VI), visual fields, thyroid (enlargement, tenderness, nodules), skin (dryness, lanugo, hirsutism, acne), breast (tenderness, enlargement, nipple discharge), and a pelvic exam (vaginal dryness, cliteromegaly, adnexal mass, uterine enlargement).

*Rosalia has experienced episodes of feeling hot, flushed, and sweaty lasting a few hours. Her review of systems is otherwise negative. On exam, her BMI is 26.6 kg/m$^2$, and she is in no distress with unremarkable visual field, thyroid, breast, abdominal, pelvic, and skin exams.*

## Evaluation

All women with amenorrhea should first have pregnancy testing with a urine or serum hCG test. Pregnancy remains the most common cause of secondary amenorrhea and should always be excluded in the evaluation of menstrual changes.

In nonpregnant women, initial evaluation should focus on the most common endocrinologic causes of amenorrhea with a serum prolactin and TSH [21, 23].

**Table 5.2** Clinical manifestations of secondary amenorrhea [19]

| Etiology | Symptoms and relevant history | Physical exam findings |
|---|---|---|
| Physiologic | | |
| Pregnancy | Breast tenderness, nausea, vomiting, abdominal pain, increased urinary frequency, weight gain | Breast tenderness and/or enlargement, abdominal distension |
| Outflow tract | | |
| Asherman syndrome/cervical stenosis | Cyclical pelvic pain, prior uterine or cervical procedures, recurrent pregnancy loss, prior chemotherapy or radiation | Enlarged, tender uterus (not always present) |
| Hypothalamic/pituitary | | |
| Hypothalamic amenorrhea | Weight loss, excessive exercise, disordered eating, poor nutrition, psychosocial stressors | Thin body habitus, enlarged parotid glands, lanugo |
| Pituitary tumor | Galactorrhea, headaches, vision changes | Visual field deficits, nipple discharge |
| Sheehan syndrome | Significant blood loss during birth, difficulty breastfeeding, fatigue, weight change, cold intolerance | Hypotension |
| Ovarian | | |
| Primary ovarian insufficiency and menopause | Hot flashes, sleep disturbance, depression, sexual dysfunction, night sweats | Vaginal dryness |
| Ovarian tumor (or androgen-producing tumor) | Abdominal pain, rapid-onset hirsutism | Abdominal mass, cliteromegaly, male pattern baldness, acne, facial hair |
| Other endocrine disorders | | |
| PCOS | Weight gain, acne, hirsutism | Male pattern baldness, acne on back/trunk, facial hair, acanthosis nigricans |
| Thyroid dysfunction | Heat or cold intolerance, palpitations, diarrhea, constipation, hair loss, fatigue, depression | Dry skin, brittle nails, thyroid enlargement/ tenderness |
| Hypercortisolism | Weight gain, acne, hirsutism, weakness, headache, fatigue, depression, easy bruising | Hypertension, buffalo hump, rounded face, purple striae, central obesity, muscle atrophy, thin skin |

Prolactin elevated to >100 ng/mL is usually due to a pituitary adenoma and should prompt a brain MRI [12, 21]. Prolactin levels >200 ng/mL are diagnostic of pituitary adenoma, while medications rarely cause prolactinemia >100 ng/mL [12]. If the serum prolactin is elevated but <100 ng/mL, evaluate for contributing medications (Table 5.1) or medical conditions such as primary hypothyroidism. Next steps would include discontinuing these medications if feasible, in collaboration with prescribing specialists as appropriate. The prolactin level should be repeated in the early morning, or consider a pituitary MRI if potentially contributing medication cannot be discontinued [13].

Obtaining an initial FSH level can also be considered [13, 22, 24]. While elevated FSH can suggest ovarian failure and low/normal FSH can suggest hypothalamic/pituitary disease, this hormone level fluctuates with the menstrual cycle (Fig. 5.2). The FSH level should ideally be checked within the first 5 days following onset of menses, which can be challenging in the setting of amenorrhea.

If these initial tests are unrevealing, further evaluation of hypothalamic/pituitary or ovarian causes should occur as discussed below.

## Additional Testing

### Progesterone Withdrawal

In women with amenorrhea, progesterone (medroxyprogesterone acetate 10 mg or norethindrone acetate 5 mg orally daily for 7–10 days) will induce a withdrawal bleed in women who have sufficient endogenous estrogen to build an endometrial lining and who do not have outflow obstruction. Low estrogen can occur in patients due to POI or gonadotropin deficiency (hypothalamic amenorrhea, Sheehan syndrome, hyperprolactinemia, hypothyroidism, pituitary tumors, Cushing's syndrome). The utility of progesterone withdrawal testing, or "challenge" as it is known clinically, has been questioned in women with amenorrhea. For example, about 50% of women with POI may have withdrawal bleeding due to varied ovarian function [22, 25].

If possible, obtain lab tests (FSH, LH, estradiol) 1–5 days after withdrawal bleeding starts [23]. Low or inappropriately normal FSH and LH with low estradiol suggests hypothalamic/pituitary disease, and high FSH (with or without elevated LH) and low estradiol suggest POI (Table 5.3). In POI, FSH levels are in the menopausal range (30–40 mIU/mL) with estradiol less than 50 pg/mL [16]. As ovarian function can fluctuate in POI, FSH and estradiol should be checked on at least two occasions at least 1 month apart [17, 24]. An increased LH: FSH ratio can be observed in PCOS but is often not present with this condition and is not part of the diagnostic criteria for PCOS (please see Chap. 6, Polycystic Ovary Syndrome, for further discussion).

**Table 5.3** Expected hormone responses in conditions causing secondary amenorrhea

| Disorder | GNRH | FSH/LH | Estrogen | Androgens |
|---|---|---|---|---|
| Hypothalamic amenorrhea | ↓ | ↓ | ↓ | → |
| Hyperprolactinemia | ↓ | ↓ | ↓ | → |
| Sheehan syndrome | ↑ | ↓ | ↓ | → |
| Primary ovarian insufficiency | ↑ | ↑ | ↓ | → |
| Polycystic ovary syndrome | →[a] | LH: ↑→ FSH:→ | ↑→ | ↑ |

[a]GNRH levels may be normal, but with increased pulse frequency [26]

## Testing for Androgen Excess

In patients with symptoms or physical exam findings of androgen excess, total testosterone and dehydroepiandrosterone-sulfate (DHEA-S) should be checked. DHEA-S is preferred to DHEA due to its longer half-life and lower variability [23]. Marked elevations in total testosterone (>200 ng/dL) or DHEA-S (>700 ng/dL) suggest an androgen-producing tumor from the ovaries or adrenals, respectively. More mildly elevated androgen values should prompt an evaluation for other causes of hyperandrogenic anovulation, for example, nonclassical adrenal hyperplasia (morning serum 17-OH hydroxyprogesterone), hypercortisolism (24-hour urine cortisol or dexamethasone suppression test), and acromegaly (serum IGF-1).

## Imaging and Procedures

Obtain a transvaginal ultrasound in the setting of an abnormal pelvic exam, suspicion for anatomical anomaly, history of prior intrauterine procedures or infection, or highly elevated testosterone. Consider an MRI brain if symptoms, exam, or laboratory workup suggests an intracranial process. Adrenal CT should be completed in the setting of highly elevated DHEA-S. Women with Asherman syndrome should be referred for hysteroscopy, which is considered the most accurate method for diagnosis of this condition in comparison to transvaginal ultrasound, hysterosalpingography, and transcervical sounding [27–29].

*Rosalia has a negative urine hCG, normal TSH and prolactin, and elevated FSH. A progesterone withdrawal test does not result in vaginal bleeding, a repeat FSH and LH is elevated, and estradiol is low. A transvaginal ultrasound shows normal uterine and ovarian size and position.*

## Additional Testing for Primary Ovarian Insufficiency

In a patient diagnosed with POI not associated with a known syndrome, consider screening for fragile X (FMR1 premutation), autoimmune thyroid disease (TPO), diabetes (fasting glucose or hemoglobin A1c), and autoimmune adrenal disease (indirect immunofluorescence or 21-hydroxylase [CYP21] immunoprecipitation) [17]. In one study of women with secondary amenorrhea due to POI, 32% were found to have autoantibodies, with 10% having clinically evident autoimmune disease (hypothyroidism, Graves' disease, diabetes mellitus, Addison's disease) [30]. Additional studies in women with POI showed that 24–25% had anti-TPO antibodies, 6% had FMR1 permutations, and 3% had adrenal autoimmunity [30–33].

Additional workup for systemic and autoimmune disease can be based upon symptoms and signs of these conditions, including free T4, erythrocyte sedimentation rate, serum protein, BMP, CBC, antinuclear antibody, rheumatoid factor, and corticotropin stimulation tests [17, 21]. Consider karyotyping to identify chromosomal abnormalities, especially in women less than 30 years, as 13% of these younger women may have an abnormal karyotype [24, 34]. Evaluate for enlarged, polycystic ovaries which can be seen with autoimmune oophoritis and 17,20 desmolase insufficiency with a pelvic ultrasound [35]. Testing for ovarian antibodies and ovarian biopsy are not currently recommended [36].

*You diagnose Rosalia with primary ovarian insufficiency. Rosalia asks you about the health implications of this condition and if she can become pregnant again.*

## Treatment

Treatment of secondary amenorrhea can be challenging and depends on the etiology and concomitant medical conditions. Most often, primary care providers work closely with specialists and subspecialists to diagnose and manage these patients. All conditions with amenorrhea may lead to infertility and other health risks based upon underlying hormone status (Table 5.4). Women with a diagnosis known to cause infertility who desire pregnancy should be referred to a reproductive endocrinologist without delay. Timing of referral to specialists depends upon the diagnosed condition and expertise of the primary care provider (Table 5.4).

The following references provide more detailed clinical guidelines for management of the conditions in Table 5.4:

**Table 5.4** Treatment of causes of secondary amenorrhea

| Etiology | Health implications | Treatment | Where/when to refer |
|---|---|---|---|
| Hypothalamic/pituitary | | | |
| Hypothalamic amenorrhea | Bone density loss | Nutrition<br>Exercise modification<br>Stress reduction<br>Cognitive behavioral therapy<br>Calcium and vitamin D supplementation<br>Combined oral contraceptives | Nutritionist<br>Psychologist/psychiatrist as needed |
| Pituitary tumor | Dependent on size and functionality of tumor | Surgery<br>Radiation<br>Medication suppression (e.g., dopamine agonists for hyperprolactinemia) | Endocrinology and neurosurgery upon diagnosis |
| Sheehan syndrome | Panhypopituitarism | Corticosteroid, thyroid, sex hormones, and growth hormone supplementation | Endocrinology upon diagnosis |
| Ovarian | | | |
| Primary ovarian insufficiency | Urogenital atrophy<br>Vasomotor symptoms<br>Osteoporosis<br>Cardiovascular disease<br>Increased all-cause mortality | Combined oral contraceptive<br>Combined cyclical hormone therapy<br>Calcium and vitamin D supplementation<br>Reproductive technology | Consider endocrinology, rheumatology, and genetics during initial evaluation of etiology.<br>Gynecology if persistent sexual dysfunction beyond expertise<br>Endocrinology if osteoporosis with first-line treatments |
| Ovarian tumor | Virilization | Surgery | Gynecology or gynecology-oncology upon diagnosis |
| Outflow tract | | | |
| Asherman syndrome/ cervical stenosis | Chronic pelvic pain | Hysteroscopic lysis of adhesions | Gynecology for diagnosis and management |
| Multifactorial | | | |
| PCOS | Endometrial hyperplasia<br>Metabolic syndrome | Combined oral contraceptives<br>Metformin<br>Antiandrogens<br>Fertility treatment | Nutritionist<br>Endocrinology as needed |
| Thyroid dysfunction | Cardiovascular risk<br>Hypothyroidism: Myxedema<br>Hyperthyroidism: thyrotoxicosis | Hypothyroidism: thyroid hormone replacement<br>Hyperthyroidism: surgery, iodine ablation, medication suppression | Endocrinology as needed |
| Cushing's syndrome | Metabolic syndrome<br>Hypertension | Surgery and/or radiation (if tumor present)<br>Medication suppression of corticosteroid production (e.g., metyrapone) or receptors (e.g., mifepristone) | Endocrinology at diagnosis<br>Neurosurgery if intracranial tumor present |

hypothalamic amenorrhea [37, 38], hyperprolactinemia/pituitary tumor [39, 40], hypopituitarism [41], POI [42], ovarian tumor [43], Asherman syndrome [29], PCOS [44, 45], thyroid dysfunction [46, 47], and Cushing's syndrome [48].

## Hypothalamic Amenorrhea

The mainstay of treatment for hypothalamic amenorrhea includes treatment of the underlying chronic condition if present. Multidisciplinary teams involving primary care, nutrition, and psychiatry may be most effective in the setting of an underlying eating disorder. Pharmacologic treatments can include calcium and vitamin D supplementation for prevention of bone loss and combined oral contraceptives (COCs) for regulation of menses, endometrial protection, and pregnancy prevention. Generally, use of low-dose (0.02 mg) ethinyl estradiol and a second-generation progestin (e.g., levonorgestrel 0.01 mg/day) is considered first-line treatment. Additional information for this condition can be found in the cited clinical practice guidelines and in Chap. 34, Eating Disorders and the Female Athlete Triad, in the section on the female athlete triad [37, 38].

## Polycystic Ovary Syndrome

In women with PCOS that do not desire pregnancy, COCs are typically used to regulate menses and provide contraception. Symptoms of excess androgen, particularly acne, are most often managed with COCs, specifically those containing third- or fourth-generation progestins with higher relative antiandrogenic activity compared to early generation progestins. Antiandrogen medications, such as spironolac-

tone, can also help with hair growth and acne but can cause hypotension and electrolyte imbalance. Topical creams and cosmetic routes, like hair plucking and electrolysis, are often used by patients for hirsutism. Women with PCOS who have amenorrhea for over 3 months should have induced menses with a progesterone withdrawal bleed. Providers should have a low threshold to obtain an endometrial biopsy in the setting of prolonged amenorrhea or abnormal uterine bleeding given the increased risk for endometrial hyperplasia and malignancy with this disorder. Metformin can improve weight loss, insulin resistance, and fertility in women with PCOS. Women with PCOS who desire pregnancy should be managed in coordination with an infertility specialist. Additional information for this condition can be found in the cited clinical practice guidelines and in Chap. 6 on Polycystic Ovary Syndrome [44, 45].

## Primary Ovarian Insufficiency

Treatment of POI should focus on minimizing associated cardiovascular disease, bone density loss, mortality, sexual dysfunction, and psychosocial stress [16, 49–56]. Women with POI may benefit from a multidisciplinary team to address their complex medical and psychosocial care, especially if a primary cause of POI is identified [55–57].

If the cause of POI is idiopathic and not treatable or amenorrhea continues with treatment, cyclical combined hormone therapy (HT) or COCs are recommended to prevent bone density loss and increase quality of life [42, 58, 59]. Women should be evaluated for contraindications to hormones (please see Chap. 4 on Patient-Centered Contraceptive Counseling and Chap. 8 on Menopause for more details), although the findings of the Women's Health Initiative may not apply to younger women with POI [42]. Examples of cyclical combined HT include estrogen (estradiol 100 μg/day transdermal, conjugated equine estrogen 0.625–1.25 mg oral/day, or micronized estradiol 1–2 mg oral/day) and progesterone, which can be dosed daily (100 mg micronized progesterone oral/day or medroxyprogesterone acetate 2.5–5.0 mg/day) or at higher dosing for 12 days per month (200 mg micronized progesterone oral/day or medroxyprogesterone acetate 10 mg oral/day) [42]. Current recommendations are to continue hormonal treatment until the age of natural menopause (50–51 years) [42].

Women with POI have a 5–10% chance of spontaneous pregnancy due to varied ovarian function [60]. For this reason, women with POI not desiring pregnancy should use contraception. COCs provide more hormone than needed for physiologic replacement but have the added benefit of contraception. However, the effectiveness of COCs for contraception in this population is uncertain due to potentially inadequate suppression of FSH [17, 61]. HT provides lower hormone doses and can be used in conjunction with other contraceptive methods such as IUDs and barrier methods. If pregnancy is desired, options include awaiting spontaneous conception, oocyte donation, and embryo donation [57, 62].

To optimize bone health, women with POI should also strive for regular weight-bearing exercise; 1200 mg of calcium per day, preferably through diet than supplements; and 1000 IU of vitamin D per day [63]. Bisphosphonates are not currently recommended for reproductive age women due to the long half-life of this medication, teratogenicity, and uncertain safety profile in this population [16, 64].

Monitoring of women with POI should focus on cardiovascular risk factors, with regular blood pressure and weight measures, screening for dyslipidemia and diabetes, and counseling on lifestyle modification if appropriate. Dual energy X-ray absorptiometry (DEXA) is recommended to evaluate for bone density loss in women with POI, but there is a lack of consensus about timing of testing, testing intervals, and appropriate treatment [16, 17, 52–54].

## Tumors and Endocrinopathies

While some endocrinopathies such as thyroid disorders or PCOS are managed in primary care, many other causes of secondary amenorrhea discussed in this chapter are co-managed with specialists. Primary care providers should initiate an evaluation of patients with secondary amenorrhea and facilitate referral as needed to endocrinologists, gynecologists, rheumatologists, geneticists, or neurosurgeons who may play a role in managing patients with these conditions.

*Following a discussion about the health risks associated with POI, Rosalia would like to attempt another pregnancy. You start a prenatal vitamin and refer her to reproductive endocrinology.*

## Summary Points

1. The history and physical exam in women with amenorrhea should focus on signs of intracranial, uterine, ovarian, and endocrine anomalies to guide the differential and diagnostic workup.
2. Pregnancy is the first diagnosis of exclusion in all presentations of amenorrhea, with TSH, FSH, and prolactin as the next initial testing in nonpregnant women.
3. Amenorrhea can be associated with health risks including infertility, osteoporosis, and endometrial hyperplasia

depending upon the etiology, with treatment individualized to minimize these risks.
4. Patients should be referred to subspecialists if the workup reveals neurologic, endocrinologic, or gynecologic abnormalities beyond the scope of your practice.

## Review Questions

1. A 35-year-old woman with a history of dysmenorrhea presents to clinic with pelvic pain and amenorrhea. She has not had a period in 4 months and has experienced a few days of bilateral cramping pelvic pain each month. Her history is notable for three prior pregnancies, one elective dilation and curettage, and two cesarean sections. She had a copper intrauterine device placed for contraception 2 years ago. On pelvic exam, the patient has a non-tender uterus of normal size. Which of the following tests is most likely to diagnose this patient's underlying condition?
   A. Hysteroscopy
   B. Transvaginal ultrasound
   C. CT abdomen and pelvis
   D. MRI brain

   The correct answer is A. This patient's history of cyclical pelvic pain with multiple intrauterine procedures is suggestive of amenorrhea due to uterine adhesions (Asherman syndrome). Uterine anomalies in women with uterine adhesions are not always detected on physical exam. Transvaginal ultrasound has been found to have a sensitivity of 0 to 52% in the diagnosis of uterine adhesions compared to hysteroscopy (gold standard) [27, 28]. In the primary care setting, transvaginal ultrasound may be a reasonable first diagnostic imaging study, especially in a patient with a palpable uterine or adnexal anomaly on pelvic exam. In patients with suspected uterine adhesions, however, a normal transvaginal ultrasound should not preclude a referral for hysteroscopy, which has a higher sensitivity for diagnosing this disorder. Hysteroscopy also has the added benefit of providing an opportunity for treatment (lysis of adhesion) upon diagnosis.

   This patient does not have symptoms or physical exam findings of an intracranial process to prompt an MRI brain. A CT abdomen could be considered if the patient had physical exam, symptoms, or laboratory findings of hyperandrogenism of a suspected adrenal source.
2. A 28-year-old woman with a history of obesity and prediabetes presents to clinic with amenorrhea for the past 6 months. She is sexually active with a male partner and uses condoms regularly. She feels fatigued at times but denies weight change, heat/cold intolerance, diarrhea, constipation, palpitations, abdominal pain, galactorrhea, and hair or skin changes. Her BMI is 38, and skin, abdominal, thyroid, and pelvic exams are normal. Her medications include metformin. Testing includes a negative urine pregnancy test, normal TSH and prolactin, and a slightly elevated FSH. A progesterone withdrawal test results in vaginal bleeding. What is the next best step in evaluating this patient's amenorrhea?
   A. Androgen testing
   B. Repeat FSH and estrogen
   C. Karyotype
   D. Transvaginal ultrasound

   The correct answer is B. While this patient does have risk factors associated with PCOS (obesity and insulin resistance), her elevated FSH is not consistent with this diagnosis and more suggestive of POI. Progestin withdrawal testing generally results in withdrawal bleeding in women with sufficient endogenous estrogen to build an endometrial lining, including PCOS, and no outflow tract obstruction. While women with POI typically have reduced production of estrogen, ovarian function can vary with as many as 50% of women with POI having a withdrawal bleed [25]. The next best step would be to repeat an FSH and estrogen 1 to 5 days following the onset of menses from the progestin withdrawal. If FSH is again elevated, this would confirm a diagnosis of POI.

   It can be reasonable to check androgens when there is a high clinical suspicion for PCOS, but this patient does not have any symptoms or physical exam findings of androgen excess. A karyotype should be checked in this patient if POI is confirmed with an additional high FSH given her age of less than 30 years. This patient does not have any abnormalities on pelvic exam to prompt transvaginal ultrasound as a next step, but if POI is confirmed, this study can be considered to evaluate for enlarged, multicystic ovaries which can be seen with autoimmune oophoritis and 17,20 desmolase insufficiency.
3. A 38-year-old woman with a history of Graves' disease treated with iodine ablation with resulting hypothyroidism presents to clinic with 5 months of amenorrhea. She otherwise feels well and review of systems is negative. She is sexually active with a male partner and does not desire pregnancy. She takes levothyroxine daily and does not currently use contraception. Her vitals and physical exam are normal and a pregnancy test is negative. Initial workup shows a normal TSH and prolactin with an elevated FSH. A progesterone withdrawal test did not produce a withdrawal bleed, with repeat labs showing an elevated FSH and low estrogen. What is the next best step in management of this patient?
   A. Combined cyclic hormone therapy
   B. Bisphosphonate
   C. Levonorgestrel intrauterine device
   D. Combined oral contraceptive

The correct answer is D. Women with POI are at risk for cardiovascular disease, bone density loss, higher mortality, sexual dysfunction, and psychosocial stress. Either COC or combined HT can be considered for management of vasomotor symptoms and preservation of bone density in women with POI. It is important to counsel patients with POI that they have a 5–10% chance of spontaneous pregnancy due to varied ovarian function [60]. COC have the added benefit of contraception, but their contraceptive effectiveness in women with POI is uncertain due to potentially inadequate suppression of FSH [17, 61]. Combined cyclic hormone therapy would not be recommended in this patient who does not desire pregnancy without an additional contraceptive.

Bisphosphonates are not currently recommended for reproductive age women due to the long half-life of this medication, teratogenicity, and uncertain safety profile in this population [16, 64]. While a levonorgestrel intrauterine device would provide effective contraception, hormone from this method is minimally systemically absorbed and would not be expected to mitigate the systemic side effects of POI.

4. A 33-year-old woman with a history of idiopathic primary ovarian insufficiency presents to clinic because she desires pregnancy. She was regularly taking a combined oral contraceptive pill until 2 months ago, and she has not had a period since stopping this medication. She is sexually active with her husband twice weekly. She currently takes a prenatal vitamin. A pregnancy test is negative. What is the next best step in management of this patient?
   A. Encourage more regular sexual activity
   B. Counsel that pregnancy is not possible
   C. Refer to infertility specialist
   D. Prescribe course of progesterone

   The correct answer is C. Because POI is a known risk factor for infertility, women with POI who desire pregnancy should be referred to an infertility specialist without delay. Women with POI have a 5–10% chance of spontaneous pregnancy due to varied ovarian function and should be counseled that spontaneous pregnancy without fertility treatment is possible but less likely compared to women without POI [60]. Progesterone may induce a withdrawal bleed but would not influence the underlying ovarian insufficiency that is the source of infertility.

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