

Amenorrhea

The menstrual cycle is an important indicator of a female's health. Disruptions of this cycle are common complaints seen by both women's health and primary care providers. Amenorrhea is the absence of menses and can occur for a variety of reasons; some are normal during the course of a female's life, while others may be a side effect of medication or a sign of a medical problem.

Amenorrhea can be intermittent or transient; however, it can also be a permanent condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina. The most common cause of amenorrhea in females of childbearing age is pregnancy and lactation.

It is important to distinguish between primary and secondary amenorrhea. A detailed reproductive and health history and an appropriate diagnostic workup with a physical exam are essential for making a correct diagnosis.

Health History

When working a patient up for amenorrhea, be sure to ask about the following:

- Age at menarche (if applicable)
- Menstrual cycle – interval between menses, length, and flow
- Details regarding puberty and secondary sex characteristics
- Symptoms of hyperandrogenism (hirsutism, acne, male pattern hair loss)
- Number of pregnancies (terminations, miscarriages, and/or live births)
- Use of medications, including hormones (contraceptive or hormone replacement therapy)
- Medical and surgical history
- Weight and exercise history
- Nutritional lifestyle
- Stress (psychological, severe illness or injury)
- Family history of delayed puberty

Primary Amenorrhea

Primary amenorrhea is the absence of menses by 15 years old in the presence of normal growth and secondary sex characteristics. It is usually the result of a genetic or anatomical abnormality; however, all causes of secondary amenorrhea can also present as primary amenorrhea. Evaluation for primary amenorrhea should begin in any patient 13 years of age with no menses and with complete absence of secondary sex characteristics.

Etiology

The most common etiologies of primary amenorrhea are:

- Chromosomal abnormalities causing gonadal dysgenesis (including Turner syndrome)
- Mullerian agenesis, absence of the uterus, cervix and/or vagina
- Physiologic delay of puberty
- Polycystic ovarian syndrome (PCOS)
- Gonadotropin-releasing hormone (GnRH) deficiency

- Transverse vaginal septum
- Weight loss/anorexia nervosa
- Hypopituitarism

Less common etiologies include imperforate hymen, complete androgen insensitivity syndrome, hyperprolactinemia/prolactinoma or other pituitary tumors, congenital adrenal hyperplasia, hypothyroidism, central nervous system defects, craniopharyngioma, and Cushing's disease.

Physical exam

Physical exam should include:

- Pelvic exam
 - Evaluation for intact hymen, clitoral size, and pubic hair development
 - Vaginal length, presence of cervix, uterus, and ovaries
 - Pelvic ultrasound, as necessary
- Tanner staging for breast development
- Growth assessment (height, weight, arm span, and growth chart, BMI)
- Skin assessment (hirsutism, acne, striae, increased pigmentation and vitiligo)
- Physical features of Turner syndrome: low hairline, webbed neck, shield chest, widely spaced nipples

Diagnosis

Primary amenorrhea is evaluated most efficiently by determining if a uterus is present, as well as focusing on the presence or absence of breast development and initial lab values. Initial laboratory testing should include the following:

- Human chorionic gonadotropin (hCG)
- Follicle-stimulating hormone (FSH) (estradiol [E2] can be helpful if FSH is abnormal)
- Thyroid-stimulating hormone (TSH)
- Prolactin (PRL)
- Free and total testosterone and dehydroepiandrosterone sulfate (DHEAS), if clinical signs of hyperandrogenism are present

Most females with primary amenorrhea have a uterus; of these, most have chromosomal abnormalities causing gonadal dysgenesis. Further evaluation is determined by initial lab results (most importantly FSH), the presence or absence of breast development (as a marker of ovarian function), and the presence or absence of any anatomic abnormalities on physical exam that suggest an outflow tract disorder.

The absence of the uterus during the pelvic exam should be confirmed by pelvic ultrasound. Further evaluation should include karyotype and measurement of serum total testosterone. Distinguishing between abnormal Mullerian development and complete androgen insensitivity syndrome can be aided by history, physical exam, and results of laboratory testing.

Primary Amenorrhea: Interpreting the FSH Level	
Serum FSH level	Diagnosis/evaluation
Elevated FSH, with uterus present	<ul style="list-style-type: none"> • Primary ovarian insufficiency (POI) • Gonadal dysgenesis is probable diagnosis (karyotype should be obtained) • CYP17 deficiency
Normal FSH, with blood in uterus/vagina and breast development present	<ul style="list-style-type: none"> • Obstructed outflow tract
Low/normal FSH, with presence of uterus	<ul style="list-style-type: none"> • Central hypothalamic-pituitary disorder • Congenital GnRH deficiency • Constitutional delay of puberty • Outflow tract disorder (anatomic abnormality) • Systemic illness/endocrine disorder (secondary amenorrhea) <p><i>*Note: Evaluation is guided by the degree of pubertal development</i></p>
Normal FSH, with absent uterus	<ul style="list-style-type: none"> • Mullerian agenesis (testosterone level will be in normal range) • Androgen insensitivity syndrome (testosterone level will be in male range)

Management

Treatment of primary amenorrhea is directed at correcting the underlying pathology (if possible) and prevention of complications of the disease process. Special consideration is directed to the individual patient's treatment goal (i.e., fertility plan, relief of pain, reduction of symptoms, or resumption of menses).

Secondary Amenorrhea

Secondary amenorrhea is the absence of menses for more than three cycle intervals in patients who previously had regular menses, or more than six months in those with a history of irregular menses.

Etiology

A variety of factors can contribute to secondary amenorrhea, including medication use, lifestyle factors, hormone imbalances, and structural issues. A review of nutrition, exercise, and stress is essential when evaluating a patient for secondary amenorrhea. Most cases of secondary amenorrhea can be attributed to PCOS, hypothalamic amenorrhea, hyperprolactinemia, or primary ovarian insufficiency. Pregnancy should be excluded in all cases.

The most common etiologies for secondary amenorrhea are:

- Pregnancy
- Hypothalamic dysfunction
- Hyperprolactinemia

- PCOS
- Primary ovarian insufficiency

Physical exam

A stepwise approach to history, physical examination, and laboratory testing will aid in appropriate specific diagnosis. Physical exam should include:

- Measurements of height and weight with BMI
- Examination for hirsutism, acne, striae, and acanthosis nigricans
- Breast exam for galactorrhea
- Vulvovaginal exam for signs of estrogen deficiency
- Parotid gland swelling and/or erosion of dental enamel for signs of eating disorder

Diagnosis

A serum hCG test is recommended as a first step in evaluating any female with secondary amenorrhea, even those who have had a negative urine hCG test at home. Once pregnancy has been ruled out, evaluation of disorders leading to amenorrhea should be based upon the levels of control of the menstrual cycle: hypothalamus, pituitary, ovary, and uterus.

Initial laboratory testing should include the following:

- Serum HCG
- FSH
- Serum PRL
- TSH
- Serum total testosterone, if there is clinical evidence of hyperandrogenism

Secondary Amenorrhea: Interpreting Lab Values	
Laboratory value	Diagnosis/evaluation
Serum hCG	<p>Positive hCG = Pregnant</p> <p>Negative hCG = Not pregnant; look at other initial lab tests</p>
PRL/TSH	<p>Elevated PRL</p> <ul style="list-style-type: none"> • Repeat PRL elevated <ul style="list-style-type: none"> ○ Hyperprolactinemia ○ Pituitary MRI <p>Normal PRL</p> <ul style="list-style-type: none"> • TSH level abnormal <ul style="list-style-type: none"> ○ Further evaluation and treatment for thyroid disease • TSH level normal <ul style="list-style-type: none"> ○ Other initial lab tests
FSH	<p>Elevated FSH</p> <ul style="list-style-type: none"> • Primary ovarian insufficiency • Typically, low E2 levels

	<ul style="list-style-type: none"> • Hot flashes/vaginal dryness common <p>Low or normal FSH</p> <ul style="list-style-type: none"> • E2 low <ul style="list-style-type: none"> ○ Hypogonadotropic hypogonadism <ul style="list-style-type: none"> ▪ Functional hypothalamic amenorrhea ▪ Systemic illness (celiac disease or type 1 diabetes mellitus) ▪ Other hypothalamic or pituitary disorders • E2 normal <ul style="list-style-type: none"> ○ Evidence of hyperandrogenism by history, exam or high serum testosterone <ul style="list-style-type: none"> ▪ PCOS likely diagnosis ○ No evidence of hyperandrogenism <ul style="list-style-type: none"> ▪ Perform progesterone withdrawal test
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Management

The overall goals of the management of secondary amenorrhea are the same as for primary amenorrhea: correct the underlying pathology (if possible) and prevent complications of the disease process (if applicable). The ultimate treatment goal depends on the patient's specific personal goals (i.e., desired fertility or symptom control).

References:

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