

## Evaluation and management of secondary amenorrhea

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**INTRODUCTION** — Amenorrhea (absence of menses) can be a transient, intermittent, or permanent condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina ([table 1](#) and [table 2](#)). It is often classified as either primary (absence of menarche by age 15 years) or secondary (absence of menses for more than three months in girls or women who previously had regular menstrual cycles or six months in girls or women who had irregular menses [1]). Missing a single menstrual period may not be important to assess, but amenorrhea lasting three months or more and oligomenorrhea (fewer than nine menstrual cycles per year or cycle length greater than 35 days) require investigation. The etiologic and diagnostic considerations for oligomenorrhea are the same as for secondary amenorrhea.

The evaluation of secondary amenorrhea and a brief summary of treatment options are reviewed here. The epidemiology and causes of secondary amenorrhea, and overviews of primary amenorrhea and abnormal uterine bleeding in adolescents, are discussed separately. (See "[Epidemiology and causes of secondary amenorrhea](#)" and "[Evaluation and management of primary amenorrhea](#)" and "[Abnormal uterine bleeding in adolescents: Definition and evaluation](#)".)

**APPROACH TO EVALUATION** — Once pregnancy has been ruled out, a logical approach to women with either primary or secondary amenorrhea is to consider disorders based upon the levels of control of the menstrual cycle: hypothalamus, pituitary, ovary, and uterus. Determining the site of the defect is important because it determines the appropriate therapeutic regimen. While the most common causes of secondary amenorrhea are likely to be functional hypothalamic amenorrhea or polycystic ovary syndrome (PCOS), disorders with an anatomic or pathologic cause must be ruled out [2,3].

**Rule out pregnancy** — A pregnancy test is recommended as a first step in evaluating any woman with secondary amenorrhea. Measurement of serum beta subunit of human chorionic gonadotropin (hCG) is the most sensitive test. Commercially available home kits for measurement of hCG in urine are improving, but the clinician who suspects pregnancy should order a serum hCG measurement, even if the woman had a negative home test.

**History** — The woman should be asked about any past medical history, risk factors, or symptoms that might suggest any of the major causes of secondary amenorrhea or oligomenorrhea ([table 1](#)). The history should include the following questions:

- Has there been stress, change in weight, diet, or exercise habits or is there an eating disorder or illness (that might result in functional hypothalamic amenorrhea)?

(See "[Epidemiology and causes of secondary amenorrhea](#)", section on '[Functional hypothalamic amenorrhea](#)'.)

- Is the woman taking any drugs that might cause or be associated with amenorrhea? The drug may be taken for a systemic illness that itself can cause hypothalamic amenorrhea. Newly initiated or discontinued oral contraceptives can be associated with several months of amenorrhea, as can androgenic drugs like [danazol](#) or a high-dose progestin. Other drugs cause amenorrhea by increasing serum PRL concentrations, including [metoclopramide](#) and antipsychotic drugs. (See "[Causes of hyperprolactinemia](#)".)
- Is there hirsutism, acne, and a history of irregular menses (suggestive of hyperandrogenism)? (See "[Clinical manifestations of polycystic ovary syndrome in adults](#)".)
- Are there symptoms of hypothalamic-pituitary disease, including headaches, visual field defects, fatigue, or polyuria and polydipsia? (See "[Causes, presentation, and evaluation of sellar masses](#)".)
- Are there any symptoms of estrogen deficiency, including hot flashes, vaginal dryness, poor sleep, or decreased libido? These symptoms may be prominent with primary ovarian insufficiency (POI). In contrast, women with hypothalamic amenorrhea do **not** usually have these symptoms, despite the presence of similarly low serum estradiol concentrations. (See "[Clinical features and diagnosis of autoimmune primary ovarian insufficiency \(premature ovarian failure\)](#)" and "[Pathogenesis and causes of spontaneous primary ovarian insufficiency \(premature ovarian failure\)](#)".)
- Has the patient had galactorrhea, which suggests hyperprolactinemia?
- Is there a history of obstetrical catastrophe, severe bleeding, dilatation and curettage, or endometritis or other infection that might have caused scarring of the endometrial lining (Asherman syndrome)? (See "[Intrauterine adhesions](#)".)

**Physical exam** — In addition to the medical history, the physical examination may provide clues about the possible cause of amenorrhea ([table 1](#)). The examination in women with secondary amenorrhea should include measurements of height and weight. A body mass index (BMI) greater than 30 kg/m<sup>2</sup> is observed in 50 percent or more of women with PCOS, depending on the population studied. Women with a BMI less than 18.5 kg/m<sup>2</sup> may have functional hypothalamic amenorrhea due to an eating disorder, strenuous exercise, or a systemic illness associated with weight loss.

The patient should also be examined for hirsutism, acne, striae, acanthosis nigricans, vitiligo, and easy bruisability. Breasts should be examined for evidence of galactorrhea, and a vulvovaginal exam should look for signs of estrogen deficiency. Parotid gland swelling and/or erosion of dental enamel would suggest an eating disorder (bulimia nervosa). (See "[Clinical manifestations of polycystic ovary syndrome in adults](#)" and "[Bulimia nervosa and binge eating disorder in adults: Medical complications and their management](#)", section on '[Physical examination](#)'.)

**Initial laboratory testing** — The initial laboratory evaluation (after ruling out pregnancy) for women with secondary amenorrhea should include follicle-stimulating hormone (FSH), serum prolactin [PRL], and thyroid-stimulating hormone (TSH) to test for POI, hyperprolactinemia, and thyroid disease, respectively. If there has been a recent menstrual cycle, a test on days 2 to 4 would be appropriate, but in prolonged amenorrhea, the testing can be performed on a random day.

The clinical utility of this approach (measuring FSH, PRL, TSH) was examined in a study of 127 women with adult-onset amenorrhea [4]. High serum FSH concentrations, high PRL, and

abnormal TSH were seen in 10, 7.5, and 2.5 percent of patients, respectively, suggesting that this is a reasonable approach to initial testing in women with secondary amenorrhea.

Some clinicians, including one of the editors, suggest adding serum estradiol (E2) as one of the initial tests to use with the serum FSH to evaluate the pituitary-ovarian axis. Low or normal E2 that is associated with an elevated FSH indicates POI, while low or normal E2 associated with FSH that is normal or low suggests the possibility of secondary (pituitary or hypothalamic) hypogonadism, either structural or functional. Interpretation of the serum E2 should also take into account that it may be variable in women with either early POI or functional hypothalamic amenorrhea (during recovery). In addition, a single sample may not reflect exposure to E2 over weeks. For this reason, E2 status should also be assessed with a progestin withdrawal test or measurement of endometrial thickness on pelvic ultrasound. (See '[Assessment of estrogen status](#)' below.)

If there is clinical evidence of hyperandrogenism (hirsutism, acne, scalp hair loss [alopecia]), serum total testosterone should be measured in addition to the initial laboratory tests listed for women without hyperandrogenism. Many clinicians also measure serum dehydroepiandrosterone sulfate (DHEAS) concentration. In addition, many measure 17-hydroxyprogesterone at the initial visit to rule out nonclassic 21-hydroxylase deficiency. (See '[High serum androgen concentrations](#)' below and "[Evaluation of premenopausal women with hirsutism](#)", section on '[Biochemical testing](#)'.)

**Follow-up testing based upon initial results** — Further evaluation depends upon the results of the initial evaluation.

**Assessment of estrogen status** — An assessment of estrogen status should be done in some cases to help with interpreting the FSH values and in others to help guide therapy (eg, hypoestrogenic patients need estrogen therapy for prevention of bone loss, while those making estrogen need endometrial protection with [progesterone](#)). Estrogen status over time can be assessed with a progestin withdrawal test (medroxyprogesterone 10 mg for 10 days). Withdrawal bleeding confirms that there has been endogenous estrogen exposure. Absence of bleeding can be due to either hypoestrogenism or an outflow tract disorder. (See '[Normal laboratory results and history of uterine instrumentation](#)' below.)

Some clinicians use endometrial thickness on pelvic ultrasound (<4 mm is consistent with hypoestrogenism), but this is not performed routinely [\[5,6\]](#). We typically perform the progestin withdrawal test instead.

Serum E2 measurements can also be used to assess estrogen status, as described above. (See '[Initial laboratory testing](#)' above.)

**Normal or low serum FSH concentrations** — Women with normal serum PRL and TSH, a low or normal serum FSH concentration, and no history of uterine instrumentation are likely to have a hypothalamic-pituitary disorder or PCOS. A serum FSH concentration that is low or “normal” is inappropriately low in the presence of a low serum estradiol concentration and indicates secondary (hypogonadotropic) hypogonadism. This constellation is one of the most common outcomes of laboratory testing in women with amenorrhea.

Although we do not recommend measuring serum luteinizing hormone (LH) level as one of our initial laboratory tests, it can be helpful in the occasional patient who has features of both functional hypothalamic amenorrhea and PCOS (eg, amenorrhea with mild hirsutism and/or acne, but normal/low BMI and a history of exercise) [\[7,8\]](#). Serum FSH concentrations are low or normal in both functional hypothalamic amenorrhea and PCOS.

Serum FSH is typically higher than LH in women with functional hypothalamic amenorrhea; in women with PCOS, serum FSH is typically lower than LH. In addition, women with functional hypothalamic amenorrhea are hypoestrogenic, while women with PCOS are typically well-estrogenized. (See ['Assessment of estrogen status'](#) above.)

Hypothalamic amenorrhea can also be seen with systemic illness such as celiac disease and type 1 diabetes mellitus. We therefore suggest measurement of fasting blood glucose or glycated hemoglobin (A1C) to rule out diabetes mellitus if the patient has polyuria and polydipsia and serologic screening for celiac disease with immunoglobulin A antibodies against tissue transglutaminase (tTG-IgA) (see ["Diagnosis of celiac disease in children"](#)). Other specific tests may be done, depending upon the clinical history. As an example, iron studies to test for hemochromatosis should be performed if there is an appropriate family history or if the patient has manifestations of iron overload (bronzed skin, diabetes mellitus, or unexplained heart or liver disease). (See ["Approach to the patient with suspected iron overload"](#).)

Magnetic resonance imaging (MRI) of the sella region is indicated in all women without a clear explanation for hypogonadotropic hypogonadism such as weight loss, exercise, or stress, and in all women who have normal laboratory findings and symptoms such as visual field defects, headaches, or other signs of hypothalamic-pituitary dysfunction (see ["Epidemiology and causes of secondary amenorrhea"](#)). In contrast, no further testing is required if the onset of amenorrhea occurred recently or is easily explained and there are no symptoms suggestive of other disease.

**High serum prolactin concentration** — PRL secretion can be transiently increased by stress. As a result, if serum PRL is high, we recommend that it be repeated before pituitary MRI is ordered, particularly in women with mild elevations (<50 ng/mL [ $<50$  mcg/L]). All of these women should be screened for thyroid disease because hypothyroidism can sometimes cause hyperprolactinemia. (See ['Abnormal TSH'](#) below.)

If a mildly elevated serum PRL is confirmed to be high on a second sample, or if the initial sample is >50 ng/mL (>50 mcg/L), a pituitary MRI should be performed unless a very clear explanation is found for the elevation (eg, untreated hypothyroidism or antipsychotic drug use). The goal of imaging is to evaluate the possibility of a hypothalamic or pituitary lesion. In the case of a lactotroph adenoma, the image will allow determination of whether it is a microadenoma or a macroadenoma ( $\leq 1$  or  $> 1$  cm, respectively). (See ["Clinical manifestations and evaluation of hyperprolactinemia"](#), section on ['Laboratory/imaging tests'](#).)

**High serum FSH concentration** — A high serum FSH concentration indicates POI, formerly referred to as premature ovarian failure. It should be kept in mind, however, that intermittent follicular development does occur in women with POI, resulting in transient normalization of serum FSH concentrations. During times of ovarian inactivity and amenorrhea, FSH is high and serum estradiol is low, similar to what is seen in normal menopause. The presence of hot flashes and/or vaginal dryness is suggestive of POI, as these symptoms are uncommon in women with menstrual disturbances due to other causes. (See ["Clinical manifestations and evaluation of spontaneous primary ovarian insufficiency \(premature ovarian failure\)"](#).)

For patients without an obvious precipitating factor for POI (gonadotoxic chemotherapy or radiotherapy), additional testing to rule out the most common etiologies of POI should be performed, including a karyotype to look for Turner syndrome (including mosaicism). In women with 46,XX spontaneous POI, we also suggest testing for anti-adrenal antibodies and the fragile X premutation. (See ["Clinical manifestations and diagnosis of Turner syndrome"](#), section on ['Diagnosis'](#) and ["Pathogenesis and causes of spontaneous primary ovarian insufficiency"](#).)

[\(premature ovarian failure\)](#)" and ["Clinical manifestations and evaluation of spontaneous primary ovarian insufficiency \(premature ovarian failure\)"](#).)

**Normal laboratory results and history of uterine instrumentation** — Women with normal laboratory results and a history of uterine instrumentation should be evaluated for intrauterine adhesions (Asherman syndrome). Many clinicians start with a progestin challenge ([medroxyprogesterone acetate](#) 10 mg for 10 days). If withdrawal bleeding occurs, an outflow tract disorder has been ruled out.

If bleeding does not occur, estrogen and progestin may be administered. The endometrium may be primed with oral conjugated estrogens 0.625 mg/day or their equivalent (oral estradiol 1 mg/day, transdermal estradiol 0.05 mg) for 35 days. A progestin is then added from days 26 to 35 (typically medroxyprogesterone 10 mg/day). Failure to bleed upon cessation of this therapy strongly suggests endometrial scarring. In this situation, a hysterosalpingogram or direct visualization of the endometrial cavity with a hysteroscope can confirm the diagnosis of intrauterine adhesions. (See ["Intrauterine adhesions"](#).)

**High serum androgen concentrations** — Depending upon the clinical picture, a high serum androgen value may be consistent with the diagnosis of PCOS, or if it is extremely high, it may raise the question of an androgen-secreting tumor of the ovary or adrenal gland. Of note, many women with PCOS present with hyperandrogenism (acne, hirsutism) without hyperandrogenemia. (See ["Clinical manifestations of polycystic ovary syndrome in adults"](#) and ["Diagnosis of polycystic ovary syndrome in adults", section on 'Diagnosis'](#).)

Androgen-secreting tumors are typically associated with the rapid onset of virilizing symptoms and, in some adrenal cases, with glucocorticoid excess. Most clinicians initiate evaluation for a tumor if the serum concentration of testosterone is greater than 150 to 200 ng/dL (5.2 to 6.9 nmol/L) or that of DHEAS is greater than 700 mcg/dL (18.9 μmol/L). This topic is discussed in detail separately. (See ["Evaluation of premenopausal women with hirsutism", section on 'Biochemical testing'](#) and ["Evaluation of premenopausal women with hirsutism", section on 'Additional evaluation for severe hyperandrogenemia'](#).)

**Abnormal TSH** — Both hypo- and hyperthyroidism can be associated with oligo- or amenorrhea. A third-generation TSH assay is usually all that is needed to diagnose hypo- or hyperthyroidism. The only exception would be in central hypothyroidism, where free T4 and TSH will both be low. In severe eating disorders, a suppressed TSH and free T4 may also be seen.

In some cases of profound hypothyroidism, there may be a slight increase in serum PRL (due to a presumed increase in hypothalamic thyrotropin-releasing hormone [TRH], which stimulates both TSH and PRL secretion) [9] (see ["High serum prolactin concentration"](#) above). Treatment of the hypothyroidism restores serum PRL to normal. Therefore, a pituitary MRI should not be performed unless hyperprolactinemia persists after the patient is euthyroid.

## MANAGEMENT

**Goals** — The overall goals of management in women with secondary amenorrhea include:

- Correcting the underlying pathology, if possible
- Helping the woman to achieve fertility, if desired
- Preventing complications of the disease process (eg, estrogen replacement to prevent osteoporosis)

A brief summary of treatment options is presented here. More detailed discussions are found separately.

### **Hypothalamic amenorrhea**

- **Lifestyle changes** – For many athletic women, explaining the need for adequate caloric intake to match energy expenditure sometimes results in increased caloric intake or reduced exercise, followed by resumption of menses. However, many women are reluctant to modify their behaviors. (See "[Amenorrhea and infertility associated with exercise](#)", section on 'Relative caloric deficiency'.)

Nonathletic women who are underweight or who appear to have nutritional deficiencies should have nutritional counseling, and they can be referred to a multidisciplinary team specializing in the assessment and treatment of individuals with eating disorders. (See "[Eating disorders: Overview of treatment](#)".)

- **Cognitive behavioral therapy** – Cognitive behavioral therapy (CBT) may be effective for restoring ovulatory cycles in some women. In one 20-week study, 16 women with functional hypothalamic amenorrhea were randomly assigned to receive CBT (16 individual sessions with a clinician over the 20 weeks, focusing on healthy eating patterns and modifying maladaptive attitudes towards eating and weight) or observation [10]. Six of eight women in the CBT arm resumed ovulatory cycles, compared with two of eight in the observation group. Although this study was small, it suggests that CBT may be a reasonable intervention for women with functional hypothalamic amenorrhea.

- **Experimental (leptin administration)** – Women with functional hypothalamic amenorrhea have relative leptin deficiency (see "[Physiology of leptin](#)"). Two studies of recombinant leptin therapy have reported restoration of ovulatory cycles in some women with functional hypothalamic amenorrhea [11,12]. Leptin therapy is experimental; additional data are required to better determine its effects on weight, the reproductive axis, bone, and other endocrine systems, as well as to establish its safety. [Metreleptin](#), an analog of human leptin, is approved in some countries, including the United States, for treatment of leptin deficiency in patients with congenital generalized or acquired generalized lipodystrophy. (See "[Lipodystrophic syndromes](#)", section on 'Leptin replacement'.)

- **Management of low bone density** – The effect of estrogen therapy on bone and the approach to women with exercise-associated amenorrhea are discussed separately. An overview of low bone density is also reviewed separately. (See "[Amenorrhea and infertility associated with exercise](#)", section on 'Bone density' and "[Evaluation and treatment of premenopausal osteoporosis](#)".)

**Hyperprolactinemia** — The management of women with amenorrhea due to hyperprolactinemia depends upon the cause of the hyperprolactinemia and the patient's goals (eg, pursuing fertility or not). This topic is reviewed in detail separately. (See "[Management of hyperprolactinemia](#)".)

**Primary ovarian insufficiency (premature ovarian failure)** — Women with primary ovarian insufficiency (POI) should receive estrogen therapy for prevention of bone loss. This can be either an oral contraceptive (if the patient is having intermittent ovarian function and does not wish to become pregnant), or replacement doses of estrogen and progestin. Regimens for the latter are reviewed separately. (See "[Management of spontaneous primary ovarian insufficiency \(premature ovarian failure\)](#)".)

**Intrauterine adhesions** — Therapy of Asherman syndrome (intrauterine adhesions) consists of hysteroscopic lysis of adhesions followed by long-term estrogen administration to stimulate regrowth of endometrial tissue [13]. (See ["Intrauterine adhesions"](#).)

**Polycystic ovary syndrome** — Treatment of hyperandrogenism is directed toward achieving the woman's goal (eg, relief of hirsutism, resumption of menses, fertility) and preventing the long-term consequences of polycystic ovary syndrome (PCOS), such as endometrial hyperplasia, obesity, and metabolic disorders. For women with PCOS, the type of therapy depends upon whether fertility is desired. (See ["Treatment of polycystic ovary syndrome in adults"](#).)

**Thyroid disease** — The management of thyroid disorders is reviewed separately. (See ["Treatment of hypothyroidism"](#) and ["Graves' hyperthyroidism in nonpregnant adults: Overview of treatment"](#).)

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5<sup>th</sup> to 6<sup>th</sup> grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10<sup>th</sup> to 12<sup>th</sup> grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see ["Patient information: Absent or irregular periods \(The Basics\)"](#))
- Beyond the Basics topics (see ["Patient information: Absent or irregular periods \(Beyond the Basics\)"](#))

**SUMMARY AND RECOMMENDATIONS** — Secondary amenorrhea is defined as the absence of menses for more than three months in girls or women who previously had regular menstrual cycles or six months in girls or women who previously had irregular menses. A step-wise approach to the history, physical examination, and laboratory testing usually results in a specific diagnosis. (See ["Approach to evaluation"](#) above.)

- Pregnancy is a common cause of secondary amenorrhea and should be excluded based on a sensitive pregnancy test (human chorionic gonadotropin [hCG]). (See ["Rule out pregnancy"](#) above.)
- The history and physical exam may provide clues about the possible cause of amenorrhea ([table 1](#)). (See ["History"](#) above.)
- The initial laboratory evaluation (after ruling out pregnancy) for women with secondary amenorrhea is slightly different for those with and without hyperandrogenism. (See ["Initial laboratory testing"](#) above.)
  - Initial laboratory testing for women with amenorrhea without hyperandrogenism should include serum prolactin (PRL), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH) to test for hyperprolactinemia, ovarian failure, and thyroid disease, respectively. (See ["Initial laboratory testing"](#) above.)
  - Assessment of estrogen status is done in some cases to help with interpreting the FSH values, and in others to help guide therapy (eg, hypoestrogenic patients need

estrogen therapy for prevention of bone loss, while those making estrogen need endometrial protection with [progesterone](#)). (See ['Assessment of estrogen status'](#) above.)

•If there is clinical evidence of hyperandrogenism (hirsutism, acne, scalp hair loss [alopecia]), serum total testosterone should be measured in addition to the initial laboratory tests. (See ['High serum androgen concentrations'](#) above.)

•Further evaluation depends upon the results of the initial evaluation. Important categories include normal or low serum FSH, high FSH, high serum PRL, normal lab results with a history of uterine instrumentation, high serum androgen concentrations, and abnormal TSH. (See ['Follow-up testing based upon initial results'](#) above.)

•Detailed discussions of treatment options for each disorder are found elsewhere. Treatment depends upon the cause of the secondary amenorrhea and the patient's goals. The overall goals of management include (see ['Management'](#) above):

- Correcting the underlying pathology, if possible
- Helping the woman to achieve fertility, when desired
- Preventing complications of the disease process (eg, estrogen replacement to prevent osteoporosis)

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**INTRODUCTION** — Amenorrhea (absence of menses) can be a transient, intermittent, or permanent condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina ([table 1](#) and [table 2](#)). It is often classified as either primary (absence of menarche by age 15 years) or secondary (absence of menses for more than three months in girls or women who previously had regular menstrual cycles or six months in girls or women who had irregular menses).

The causes and diagnosis of primary amenorrhea, as well as a brief summary of treatment options, are reviewed here. The etiology, diagnosis, and treatment of secondary amenorrhea are discussed separately. (See "[Causes of primary amenorrhea](#)" and "[Epidemiology and causes of secondary amenorrhea](#)" and "[Evaluation and management of secondary amenorrhea](#)".)

## EVALUATION

**Background** — Primary amenorrhea is defined as the absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics. However, at age 13 years, if no menses have occurred and there is a complete absence of secondary sexual characteristics such as breast development, evaluation for primary amenorrhea should also begin. In addition, some girls with secondary sexual characteristics may present before age 15 years with amenorrhea and cyclic pelvic pain. These girls should be evaluated for possible outflow tract obstruction. (See "[Causes of primary amenorrhea](#)", section on '[Outflow tract disorders](#)'.)

Primary amenorrhea is usually the result of a genetic or anatomical abnormality. However, all causes of secondary amenorrhea can also present as primary amenorrhea ([table 1](#) and [table 2](#)). In a large case series of primary amenorrhea, the most common etiologies were [1]:

- Gonadal dysgenesis, including Turner syndrome – 43 percent
- Müllerian agenesis (absence of vagina, sometimes with absence of uterus) – 15 percent
- Physiological delay of puberty (constitutional delay of puberty, chronic systemic disease, acute illness) – 14 percent (of note, constitutional delay of puberty is common in boys but uncommon in girls) (see "[Causes of primary amenorrhea](#)", section on '[Constitutional delay of puberty](#)')
- Polycystic ovary syndrome (PCOS) – 7 percent
- Isolated gonadotropin-releasing hormone (GnRH) deficiency – 5 percent (extremely rare; the frequency seen in this study likely reflects that it was performed in an academic referral center; the incidence in females based upon a national hospital database was only 1 out of 125,000 [2]) (see "[Congenital gonadotropin-releasing hormone deficiency \(idiopathic hypogonadotropic hypogonadism\)](#)")

- Transverse vaginal septum – 3 percent
- Weight loss/anorexia nervosa – 2 percent
- Hypopituitarism – 2 percent

The least common etiologies ( $\leq 1$  percent each) included imperforate hymen, complete androgen insensitivity syndrome, hyperprolactinemia/prolactinoma, other pituitary tumors, congenital adrenal hyperplasia, hypothyroidism, central nervous system defects, craniopharyngioma, and Cushing's disease. (See "[Causes of primary amenorrhea](#)", section on '[Causes](#)'.)

A logical approach to the woman with either primary or secondary amenorrhea is to consider disorders based upon the level of control of the menstrual cycle: hypothalamus and pituitary, ovary, and uterus and vagina. In addition, steroid receptor abnormalities and deficiencies in enzymes of steroidogenesis cause primary amenorrhea at the level of the ovary and the adrenal gland.

**Overview of approach** — Primary amenorrhea is evaluated most efficiently by focusing on the presence or absence of breast development (a marker of estrogen action and therefore function of the ovary), the presence or absence of the uterus (as determined by ultrasound, or in more complex cases by magnetic resonance imaging [MRI]), and the follicle-stimulating hormone (FSH) level ([algorithm 1](#)) [3].

- If the serum FSH concentration is elevated, the probable diagnosis is gonadal dysgenesis (including Turner syndrome) and a karyotype should be obtained. In this scenario, a 46,XY karyotype is associated with a high risk for the development of gonadoblastoma and dysgerminoma, and surgical removal of the gonads is necessary. (See "[Causes of primary amenorrhea](#)", section on '[Gonadal dysgenesis/POI](#)'.)
- If FSH is normal and the ultrasound indicates that the uterus is absent, the probable diagnosis is müllerian agenesis or androgen insensitivity syndrome. In the case of müllerian agenesis, the circulating testosterone is in the normal range for women, and in the case of androgen insensitivity, the circulating testosterone is in the male range. (See "[Causes of primary amenorrhea](#)", section on '[Müllerian agenesis](#)' and "[Causes of primary amenorrhea](#)", section on '[Complete androgen insensitivity syndrome](#)'.)
- If the FSH is normal, breast development is present, and the ultrasound detects blood in the uterus (hematometra) or vagina (hematocolpos), an obstructed outflow tract is present. (See "[Causes of primary amenorrhea](#)", section on '[Outflow tract disorders](#)'.)
- If the FSH is low or normal and the uterus is present, further evaluation is guided by the degree of pubertal development. This could include distinguishing between constitutional delay of puberty and congenital gonadotropin-releasing hormone (GnRH) deficiency, or investigating some of the common causes of secondary amenorrhea that also cause primary amenorrhea. (See "[Diagnosis and treatment of delayed puberty](#)" and "[Congenital gonadotropin-releasing hormone deficiency \(idiopathic hypogonadotropic hypogonadism\)](#)" and "[Epidemiology and causes of secondary amenorrhea](#)".)

**History** — Although there are several unique causes of primary amenorrhea, all causes of secondary amenorrhea can also cause primary disease (see "[Evaluation and management of secondary amenorrhea](#)"). Thus, the following questions should be asked of a woman with primary amenorrhea:

- Has she completed other stages of puberty, including a growth spurt, development of axillary and pubic hair, apocrine sweat glands, and breast development? Lack of pubertal

development suggests deficient estradiol secretion, which could be due to a hypothalamic or pituitary disorder, ovarian failure, and/or a chromosomal abnormality.

- Is there a family history of delayed or absent puberty (suggesting a possible familial disorder)?
- What is the woman's height relative to family members? Short stature may indicate Turner syndrome or growth hormone deficiency due to hypothalamic-pituitary disease.
- Were neonatal and childhood health normal? Neonatal crisis suggests congenital adrenal hyperplasia. Alternatively, poor health may be a manifestation of hypothalamic-pituitary disease.
- Are there any symptoms of hyperandrogenism (acne, hirsutism) or virilization? The presence of acne or hirsutism is consistent with a diagnosis of polycystic ovary syndrome (PCOS), while virilization suggests more severe androgen excess, due to an androgen-secreting ovarian or adrenal tumor, or 5-alpha-reductase deficiency.
- Has there been stress; change in weight, diet, or exercise habits; or illness that might result in hypothalamic amenorrhea?
- Is she taking any drugs that might cause or be associated with amenorrhea? The medication may be taken for a systemic illness that itself can cause hypothalamic amenorrhea (eg, sarcoidosis). Alternatively, drugs such as heroin and [methadone](#) can decrease GnRH, and therefore gonadotropin secretion.
- Does she have galactorrhea, which would suggest excess prolactin? This could be caused by hypothalamic or pituitary disease or by drugs, such as [metoclopramide](#) and antipsychotic drugs. (See "[Causes of hyperprolactinemia](#)".)
- Are there symptoms of other hypothalamic-pituitary disease, including headaches, visual field defects, fatigue, or polyuria and polydipsia?

**Physical examination** — The single most important step in the evaluation is to determine by physical examination (or ultrasonography if needed) if a uterus is present [3]. In addition, the vagina and cervix should be examined for anatomic abnormalities. Anatomic abnormalities that can cause primary amenorrhea include an intact hymen, transverse vaginal septum, or vaginal agenesis, also known as müllerian agenesis or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, which refers to congenital absence of the vagina with variable uterine development. It is usually accompanied by cervical and uterine agenesis. (See "[Causes of primary amenorrhea](#)".)

Other findings on physical examination that can provide clues to the etiology of the amenorrhea include:

- Breast development, as assessed by Tanner staging ([table 3](#) and [figure 1](#)). (See "[Normal puberty](#)".)
- Growth, including height, weight, and arm span (normal arm span for adults is within 5 cm of height) and the growth chart.
- Skin findings such as hirsutism, acne, striae, increased pigmentation, and vitiligo.
- Physical features of Turner syndrome such as low hairline, webbed neck, shield chest, and widely spaced nipples. The blood pressure should be measured in both arms if Turner syndrome is suspected, because it is associated with an increased incidence of coarctation of the aorta. (See "[Clinical manifestations and diagnosis of Turner syndrome](#)".)
- A careful genital examination should be performed for clitoral size, pubic hair development, intactness of the hymen, vaginal length, and presence of a cervix, uterus,

and ovaries. If the vagina cannot be penetrated with a small cotton swab (Q-tip) or finger, rectal examination may allow evaluation of the internal organs.

**Pelvic ultrasound** — If a normal vagina or uterus is not obviously present on physical examination, pelvic ultrasonography should be performed to confirm the presence or absence of ovaries, uterus, and cervix. In addition, ultrasonography can be useful to look for vaginal or cervical outlet obstruction in patients with amenorrhea and cyclic pain.

**Initial laboratory testing** — All women with primary amenorrhea should have serum human chorionic gonadotropin (hCG), FSH, thyroid-stimulating hormone (TSH), and prolactin (PRL) measured, similar to the approach for women with secondary amenorrhea ([algorithm 1](#)) (see "[Evaluation and management of secondary amenorrhea](#)"). Some clinicians suggest additional testing, including serum estradiol (E2) to assess estrogen status and thyroxine (T4) to look for central hypothyroidism. However, serum E2 measurements may be variable in women with either early ovarian failure or functional hypothalamic amenorrhea during recovery, and they may not reflect exposure to estradiol over weeks. On the other hand, E2 can be helpful when trying to interpret FSH values. We measure T4 only when central hypothyroidism is suspected.

Additional testing depends upon the results of the physical exam; in particular, whether müllerian structures are present or absent.

#### **Further evaluation based upon initial findings**

**Uterus present** — Most women with primary amenorrhea have a uterus; most of these have chromosomal abnormalities causing gonadal dysgenesis (ovarian insufficiency due to the premature depletion of all oocytes and follicles). For women with a uterus, further evaluation is determined by the initial lab results (most importantly FSH, and sometimes PRL or TSH), the presence or absence of breast development (usually a marker of ovarian function, except in the case of complete androgen insensitivity syndrome), and the presence or absence of any anatomic abnormalities on physical exam that suggest an outflow tract disorder ([algorithm 1](#)).

#### **High FSH**

- A high serum FSH concentration is indicative of primary ovarian insufficiency (POI). A karyotype is then required and may demonstrate complete or partial deletion of the X chromosome (Turner syndrome) and/or the presence of Y chromatin. The presence of a Y chromosome material, (SRY) is associated with a higher risk of gonadal tumors and makes gonadectomy mandatory ([algorithm 1](#)) [4-6]. (See "[Causes of primary amenorrhea](#)", [section on 'Gonadal dysgenesis/POI'](#).)

In addition, evaluation for other diseases associated with the specific type of ovarian insufficiency should be performed. As examples, congenital heart disease, hypertension, and hearing loss are common in women with Turner syndrome. Although 46,XX spontaneous POI typically presents as secondary amenorrhea, it can sometimes present as primary amenorrhea. If the etiology is thought to be autoimmune, additional evaluation for autoimmune thyroid and adrenal disease should be done. (See "[Clinical manifestations and diagnosis of Turner syndrome](#)" and "[Clinical features and diagnosis of autoimmune primary ovarian insufficiency \(premature ovarian failure\)](#)" and "[Pathogenesis and causes of spontaneous primary ovarian insufficiency \(premature ovarian failure\)](#)".)

For girls with high FSH who are also hypertensive (and who may have other features of 17-alpha-hydroxylase [CYP17] deficiency, such as minimal body hair and absent

secondary sexual characteristics), blood tests should be drawn for evaluation for CYP17 deficiency. The characteristic findings are elevations in serum progesterone (>3 ng/mL [9.5 nmol/L]) and deoxycorticosterone and low values for serum 17-alpha-hydroxyprogesterone (<0.2ng/mL [0.6 nmol/L]) ([algorithm 1](#)). (See "[Uncommon congenital adrenal hyperplasias](#)", section on 'CYP17A1 deficiencies'.)

## Low or normal FSH

- A low or normal serum FSH concentration suggests a central hypothalamic-pituitary process, outflow tract disorder due to an anatomic abnormality, or an endocrine disorder (that more typically causes secondary amenorrhea). The presence or absence of breast development (an indicator of ovarian function and estrogen secretion) helps to further categorize these disorders ([algorithm 1](#)).

- Girls with low/normal FSH and breast development have either an anatomic abnormality (which is identified on ultrasound) or an endocrine disorder such as PCOS, hyperprolactinemia, or thyroid disease, disorders that more commonly cause secondary amenorrhea. (See "[Evaluation and management of secondary amenorrhea](#)".)

- About 15 percent of girls with primary amenorrhea will have an anatomic abnormality identified on ultrasound or exam such as imperforate hymen, transverse vaginal septum, or müllerian agenesis (congenital absence of the vagina with variable uterine development). Cyclic pelvic or lower abdominal pain is a common presenting symptom in these girls. (See "[Causes of primary amenorrhea](#)".)

- The evaluation of endocrine disorders that cause secondary amenorrhea are reviewed in detail separately. Although uncommon, all of these disorders can cause primary amenorrhea, including hyperprolactinemia, thyroid disease, and PCOS. A high serum prolactin should be repeated once to confirm hyperprolactinemia prior to performing pituitary MRI. Hypothyroidism as a cause of hyperprolactinemia should be ruled out by measuring a serum TSH. (See "[Clinical manifestations and evaluation of hyperprolactinemia](#)" and "[Laboratory assessment of thyroid function](#)".)

- If there are signs or symptoms of hyperandrogenism, serum testosterone and dehydroepiandrosterone sulfate (DHEAS) should be measured. While most adolescents presenting with hyperandrogenism and primary amenorrhea likely have PCOS, androgen-secreting tumors must be ruled out in those with virilization and/or severe hyperandrogenemia ([algorithm 1](#)). (See "[Evaluation of premenopausal women with hirsutism](#)".)

- Girls with **low or normal FSH and no evidence of breast development** most likely have a central hypothalamic-pituitary disorder; they should have a second serum sample obtained for both luteinizing hormone (LH) and FSH measurements ([algorithm 1](#)).

- If **LH and FSH are both very low** (undetectable or near the lower limit of the assay), congenital GnRH deficiency, constitutional delay of puberty, or other disorders of the hypothalamic-pituitary axis should be considered. Constitutional delay of puberty is very uncommon in girls and is a diagnosis of exclusion. For girls with primary amenorrhea due to hypogonadotropic hypogonadism who are undergoing evaluation for hypothalamic or pituitary disease, a serum T4 and TSH should be drawn to look for central hypothyroidism. The evaluation of both disorders is reviewed in detail separately. (See "[Diagnosis and treatment of delayed puberty](#)" and "[Congenital gonadotropin-releasing hormone deficiency \(idiopathic hypogonadotropic hypogonadism\)](#)".)

- If **LH is low and FSH is low or normal**, functional hypothalamic amenorrhea is likely if there is also a history of an eating disorder, excessive exercise, or stress. Systemic illness may be associated with menstrual cycle disorders (including delayed puberty/primary amenorrhea) when it is severe enough to result in a decrease in hypothalamic GnRH secretion and/or when it is associated with nutritional deficiencies. Examples include celiac disease, type 1 diabetes mellitus, and inflammatory bowel disease. We therefore suggest measurement of fasting blood glucose or glycated hemoglobin (A1C) to rule out diabetes mellitus and serologic screening for celiac disease with IgA antibodies against tissue transglutaminase (tTG-IgA). (See "[Epidemiology and causes of secondary amenorrhea](#)", section on 'Functional hypothalamic amenorrhea' and "[Epidemiology, presentation, and diagnosis of type 1 diabetes mellitus in children and adolescents](#)" and "[Diagnosis of celiac disease in children](#)".)

- Contrast-enhanced MRI of the sella region is indicated in most cases of primary amenorrhea due to hypogonadotropic hypogonadism to evaluate for hypothalamic or pituitary disease. We recommend pituitary MRI in all women with hypogonadotropic hypogonadism, visual field defects, headaches, and/or any other signs of hypothalamic-pituitary dysfunction. Pituitary MRI may not be required in those with a clear explanation for their hypogonadotropic amenorrhea (eg, celiac disease, type 1 diabetes mellitus, or inflammatory bowel disease).

**Uterus absent** — For those with absence of the uterus, further evaluation should include a karyotype and measurement of serum total testosterone ([algorithm 1](#)). The history, physical exam, and results of these tests should distinguish between abnormal müllerian development (a normal 46,XX karyotype, female phenotype, and normal female serum testosterone concentrations) and complete androgen insensitivity syndrome (46,XY karyotype, normal female phenotype, sparse axillary and pubic hair, and normal male serum testosterone concentrations) ([algorithm 1](#)). (See "[Clinical manifestations and diagnosis of congenital anomalies of the uterus](#)" and "[Pathogenesis and clinical manifestations of disorders of androgen action](#)".)

Patients with 5-alpha-reductase deficiency also have a 46,XY karyotype and normal male serum testosterone concentrations, but in contrast to the androgen insensitivity syndrome (which is associated with a female phenotype), these patients undergo striking virilization at the time of puberty (normal development of secondary sexual hair, muscle mass, and deepening of the voice). This disorder is reviewed in detail separately. (See "[Steroid 5-alpha-reductase 2 deficiency](#)".)

**MANAGEMENT** — Treatment of primary amenorrhea is directed at correcting the underlying pathology (if possible), helping the woman to achieve fertility (if desired), and prevention of complications of the disease process (eg, estrogen replacement to prevent osteoporosis). A brief summary of treatment options is presented here, while the treatment of specific disorders is discussed in detail in the appropriate topic reviews.

- All women with primary amenorrhea should be counseled regarding its cause, potential treatment, and their reproductive potential. Psychological counseling is particularly important in patients with absent müllerian structures and/or a Y chromosome. (See "[Diagnosis and management of congenital anomalies of the vagina](#)" and "[Ovarian germ cell tumors: Pathology, clinical manifestations, and diagnosis](#)", section on '[Dysgerminoma](#)'.)

- Surgery may be required in patients with either congenital anatomic lesions or Y chromosome material. The etiology of the primary amenorrhea will determine the type of surgical procedure required. As an example, surgical correction of a vaginal outlet obstruction is necessary as soon as the diagnosis is made after menarche to allow passage of menstrual blood. Creation of a neovagina for patients with müllerian failure is usually delayed until the women are emotionally mature and ready to participate in the postoperative care required to maintain vaginal patency. (See ["Diagnosis and management of congenital anomalies of the vagina"](#) and ["Surgical management of congenital uterine anomalies"](#).)

In those patients in whom Y chromosomal material is found, gonadectomy should be performed to prevent the development of gonadal neoplasia [4-6]. Gonadectomy is now typically delayed until after puberty in patients with complete androgen insensitivity syndrome, but this was not true in the past. These patients have a normal pubertal growth spurt and feminize at the time of expected puberty; tumors do not usually develop until after this time. (See ["Diagnosis and treatment of disorders of the androgen receptor"](#).)

- Women with primary ovarian insufficiency (POI; premature ovarian failure) should be counseled regarding the benefits and risks of hormone therapy. For young women, the benefits and risks of hormone therapy are markedly different than those for a 50-year-old woman. In general, in women of reproductive age with hypoestrogenism, hormone replacement is important to prevent bone loss and to prevent the potential excess risk of premature coronary heart disease. (See ["Menopausal hormone therapy: Benefits and risks"](#) and ["Management of spontaneous primary ovarian insufficiency \(premature ovarian failure\)"](#).)

- In women with polycystic ovary syndrome (PCOS), treatment of hyperandrogenism is directed toward achieving the woman's goal (eg, relief of hirsutism, resumption of menses, fertility) and preventing the long-term consequences of PCOS (eg, endometrial hyperplasia/cancer, obesity, and metabolic defects). (See ["Treatment of polycystic ovary syndrome in adults"](#).)

- Functional hypothalamic amenorrhea can usually be reversed by weight gain, reduction in the intensity of exercise, and/or resolution of illness or emotional stress. For women who want to continue to exercise, estrogen-progestin replacement therapy should be given to those not seeking fertility to prevent osteoporosis and heart disease. Women who want to become pregnant can be treated with exogenous gonadotropins or pulsatile gonadotropin-releasing hormone (GnRH), but increased caloric intake is simpler and clearly preferable. Furthermore, if a woman does not eat enough to have regular cycles and normal fertility, her nutrient intake during a hormonally-induced pregnancy is likely to be inadequate for normal fetal growth and development. (See ["Amenorrhea and infertility associated with exercise"](#) and ["Evaluation and management of secondary amenorrhea"](#).)

- The same considerations apply to women with hypothalamic or pituitary dysfunction that is not reversible (eg, congenital GnRH deficiency). For women who want to become pregnant, either exogenous gonadotropins or pulsatile GnRH can be given. In a retrospective comparative study, pulsatile GnRH produced a higher rate of conception (96 versus 72 percent) and a lower rate of higher-order multiple gestations [7-9]. (See ["Congenital gonadotropin-releasing hormone deficiency \(idiopathic hypogonadotropic hypogonadism\)"](#).)

- Advances in assisted reproductive technologies (ART) now make it possible for many women with primary amenorrhea to participate in reproduction. For women with gonadal dysgenesis, the use of donor oocytes and their partners' sperm with in vitro fertilization

(IVF) allows the women to carry a pregnancy in their own uterus (see ["Oocyte donation for assisted reproduction"](#)). For women with an absent uterus, use of their own oocytes in IVF and transfer of their embryos to a gestational carrier can allow these women to have genetically related children.

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5<sup>th</sup> to 6<sup>th</sup> grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10<sup>th</sup> to 12<sup>th</sup> grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see ["Patient information: Absent or irregular periods \(The Basics\)"](#) and ["Patient information: Late puberty \(The Basics\)"](#))
- Beyond the Basics topics (see ["Patient information: Absent or irregular periods \(Beyond the Basics\)"](#))

## SUMMARY AND RECOMMENDATIONS

- Primary amenorrhea is defined as the absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics. However, at age 13 years, if no menses have occurred and there is a complete absence of secondary sexual characteristics such as breast development, evaluation for primary amenorrhea should also begin. (See ['Background'](#) above.)
- All causes of secondary amenorrhea can also present as primary amenorrhea. However, primary amenorrhea is usually the result of genetic or anatomic abnormalities ([table 1](#)). The most common causes of primary amenorrhea include (see ['Background'](#) above):
  - Chromosomal abnormalities causing gonadal dysgenesis (ovarian insufficiency due to the premature depletion of all oocytes and follicles) – 50 percent
  - Hypogonadotropic hypogonadism, including functional hypothalamic amenorrhea – 20 percent
  - Absence of the uterus, cervix, and/or vagina, müllerian agenesis – 15 percent
  - Transverse vaginal septum or imperforate hymen – 5 percent
  - Pituitary disease – 5 percent
  - The etiology in the remaining 5 percent of cases includes a combination of disorders, such as androgen insensitivity due to mutations in the androgen receptor, congenital adrenal hyperplasia, and polycystic ovary syndrome (PCOS)
- Primary amenorrhea is evaluated by determining the presence or absence of a uterus, the presence or absence of breast development (a marker of estrogen action and therefore function of the ovary, except in complete androgen insensitivity syndrome), and the serum follicle-stimulating hormone (FSH) level ([algorithm 1](#)). (See ['Overview of approach'](#) above.)
- Most women with primary amenorrhea have a uterus; most of these have chromosomal abnormalities causing gonadal dysgenesis (ovarian insufficiency due to the premature

depletion of all oocytes and follicles). For women with a uterus, further evaluation is determined by the initial lab results (prolactin [PRL], thyroid-stimulating hormone [TSH], and most importantly, FSH), the presence or absence of breast development (a marker of ovarian function, except in complete androgen insensitivity syndrome), and the presence or absence of any anatomic abnormalities on physical exam that suggest an outflow tract disorder ([algorithm 1](#)). (See '[Uterus present](#)' above.)

- If there is a uterus and the FSH level is elevated, the probable diagnosis is gonadal dysgenesis, and a karyotype should be obtained. In this scenario, a 46,XY karyotype is associated with a high risk for the development of gonadoblastoma and dysgerminoma, and surgical removal of the gonads is necessary. (See '[Overview of approach](#)' above.)

- If the FSH is low or normal and the uterus is present, further evaluation is guided by the degree of pubertal development. This could include distinguishing between constitutional delay of puberty and congenital gonadotropin-releasing hormone (GnRH) deficiency, or investigating some of the common causes of secondary amenorrhea that also cause primary amenorrhea. (See '[Overview of approach](#)' above.)

- If the estradiol is low and the FSH is low or normal and the uterus is present, the probable diagnosis is secondary hypogonadism, which could be caused by constitutional delay of puberty, congenital GnRH deficiency, or some of the common causes of secondary amenorrhea that also cause primary amenorrhea. (See '[Overview of approach](#)' above.)

- For those with absence of the uterus, further evaluation should include a karyotype and measurement of serum total testosterone. These tests should then allow the clinician to distinguish between abnormal müllerian development (a normal 46,XX karyotype with normal female serum testosterone concentrations) and androgen insensitivity syndrome (46,XY karyotype and normal male serum testosterone concentrations) ([algorithm 1](#)). (See '[Uterus absent](#)' above.)

- Treatment of primary amenorrhea is directed at correcting the underlying pathology (if possible), helping the woman to achieve fertility (if desired), and prevention of complications of the disease process (eg, estrogen replacement to prevent osteoporosis). A brief summary of treatment options is presented in this topic, while the treatment of specific disorders is discussed in detail in the appropriate topic reviews. (See '[Management](#)' above.)

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