

**SECONDARY AMENORRHEA**

**Objectives**

1. **Learn the definition of this gynecological problems**
2. **Explain the etiology and pathophysiology**
3. **Gain the ability to diagnose and treat according to different clinical presentation**

**SECONDARY AMENORRHEA**

**Definition:** Secondary amenorrhea is the absence of menstruation for 3 consecutive months after menarche or in a woman who has had a normal menstrual cycle. if previously regular menses, or six months if previously irregular menses.. In women of childbearing age, the most common causes of absent menstrual periods are pregnancy and lactation.

**Causes :**

**Hypothalamus**

**functional hypothalamic amenorrhea (FHA)** is a common condition that results from disruption in this process, which accounts for approximately 35% of all pathologic secondary amenorrhea. FHA is caused by stress from events such as severe restrictive dieting, poor nutritional status, extreme psychological stress, or excessive exercise. Recently, genetic mutations have been associated with FHA, which may explain the variation in susceptibility to this condition in some women. Amenorrhea is typically prolonged, lasting at least 6 months.

Because women with FHA are in a hypo-estrogenic state, there are concerns about bone health. This is referred to as the “female athlete triad,” which includes menstrual dysfunction (amenorrhea most commonly seen), energy availability (ranging from optimal to low energy, with or without disordered eating or inadequate calories), and decreased bone density. Return to normal weight and energy balance is required to restore menstrual cycles back to normal, with referral to a mental health and/or nutrition specialist to assist with this process.

Less commonly, **infiltrative diseases of the hypothalamus**, such as lymphoma, sarcoidosis, can interfere with hypothalamic function. Here, too, the altered GnRH secretion results in amenorrhea. These women usually present with additional symptoms of headache or neurologic changes.

**Pituitary gland**

There are several conditions that affect the pituitary gland and interfere with appropriate gonadotropin production. A common condition is hyperprolactinemia, and modest elevations in prolactin levels can be caused by medications.

A detailed medication history is important to identify the connection between medication changes and onset of change in the menstrual pattern. Nipple stimulation or chest wall injury can also mildly elevate prolactin levels (typically no more than 10 ng/dL above normal), but even a small change in prolactin may be sufficient to change the menstrual pattern. Elevated prolactin levels should also prompt a check of thyroid function because hypothyroidism can cause hyperprolactinemia.

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Modest elevations in prolactin can also be caused by a lesion in or near the pituitary gland that compresses the pituitary stalk. An intact stalk is necessary for transmitting inhibitory signals to the prolactin-secreting cells to prevent secretion. When normal inhibition is lifted by stalk compression, the pituitary gland produces more prolactin. A common cause of stalk compression is **a pituitary adenoma**. Any structural lesion in or near the pituitary gland can cause a modest elevation in prolactin. When prolactin levels are elevated (2 to 10 times normal), this usually indicates a prolactin-lactotroph-secreting pituitary adenoma.

**Pituitary infarction** can cause amenorrhea, and Sheehan syndrome is a result of pituitary infarction following post- partum haemorrhage or severe hypotension. Gland infarction results in partial or total loss of hormone secretion, which can cause various endocrine deficiencies, such as hypogonadotropic hypogonadism (loss of LH and FSH secretion); secondary hypothyroidism (loss of thyroid-stimulating hormone [TSH] secretion); and secondary adrenal insufficiency (loss of adrenocorticotropic hormone secretion). It is thought that vasospasm of the pituitary arteries occurs during severe hypotension, leading to hypoperfusion of the gland. The initial presentation can be indicated by the inability to lactate in postpartum women, with subsequent development of amenorrhea immediately postpartum or in the year following traumatic delivery.

As with the hypothalamus, infiltrative processes can occur in the pituitary gland. Amenorrhea occurs when the process disrupts pituitary function and results in decreased gonadotropin secretion. Hemochromatosis and lymphocytic hypophysitis are examples of infiltrative processes that affect the pituitary gland.

**Ovaries**

**spontaneous primary ovarian insufficiency (POI)** When menopause or spontaneous loss of ovarian function occurs prior to age 40, also referred to as premature ovarian failure. Spontaneous POI is characterized by permanent cessation of ovulation and menstruation. It can be idiopathic, a result of prior surgery or chemotherapy, or a result of an autoimmune process. FSH will be elevated (greater than 30 to 40 IU/L) with low estradiol levels (usually below 30 pg/mL). There may also be symptoms of declining estrogen levels, including hot flushes, night sweats, and vaginal dryness. There can be a history of erratic or progressively less frequent menstrual cycles for years prior to permanent cessation of menstruation. Other causes of spontaneous POI include Turner syndrome (lack of a second X chromosome), fragile X syndrome, radiation to the pelvis, and a history of mumps or cytomegalovirus. The diagnosis of spontaneous POI can be particularly devastating for young women who have not had children, and further reproductive and mental health counseling for these women is warranted.

**Polycystic ovary syndrome (PCOS)** is characterized by chronic, irregular, and infrequent menstrual cycles (defined as occurring fewer than eight times a year or with a cycle length less than 21 or more than 35 days); it also includes signs of hyperandrogenism (hirsutism, acne, and/or male pattern hair loss) and is a common cause of amenorrhea. PCOS has a wide array of clinical presentations and menstrual histories, varying from primary amenorrhea to a history of regular menstrual periods that progress to oligomenorrhea and/or amenorrhea. PCOS is the most common endocrine disorder in women of reproductive age, occurring in 7% to 10% of all young women.

Along with menstrual abnormalities, women with PCOS who are overweight or obese are often insulin resistant. They have an increased risk for prediabetes, type 2 diabetes mel- litus (T2DM), metabolic syndrome, fatty liver disease, and obstructive sleep apnea.

**Uterus**

**Asherman syndrome** is a less common cause of amenorrhea, which is fibrosis of the endometrium and resulting lack of regeneration that leads to amenorrhea. This can occur after instrumentation of the uterine cavity, such as uterine curettage, myomectomy, cervical biopsy, or polypectomy or insertion of an intrauterine device (IUD). More recently, therapeutic endometrial ablation has been used to induce fibrosis of the endometrium, resulting in desired long-term amenorrhea and contraception. Women with endometrial tuberculosis can develop Asherman syndrome. Women who have uterine instrumentation at the time of delivery are at higher risk of developing Asherman syndrome. Relatively low estrogen levels at the time of delivery make the endometrium more susceptible to trauma, with a decreased ability to regenerate. It is treated by hysteroscopic adhesion lysis followed by estrogen stimulation of the endometrium. An inflatable stent is then placed into the uterine cavity to prevent re-adhesion of the uterine walls.

■ **Other causes of amenorrhea  
*Cushing syndrome.***Cushing syndrome is a result of either endogenous cortisol oversecretion or exogenous exposure to high doses of glucocorticoids (iatrogenic). Non-iatrogenic cortisol excess is rare, with an incidence of 3/1,000,000 annually. Cortisol excess can cause the menstrual period to become irregular or absent, and this is thought to be related to low GnRH secretion that occurs in response to high cortisol levels. Other symptoms of Cushing syndrome include unexplained weight gain, purple striae, diabetes mellitus, hypertension, facial plethora, development of a (“buffalo hump”), proximal myopathy, kidney stones, hypokalemia, depression, hirsutism, acne, and unexplained osteoporosis

***Thyroid disorders.***Hypothyroidism and hyperthyroidism can cause changes in the menstrual cycle, including amenorrhea, oligomenorrhea, heavy menstrual bleeding, and frequent menstrual bleeding. Severity of hypo- or hyperthyroidism appears to be important, as more severe abnormalities in thyroid function are associated with a higher incidence of menstrual irregularity.

***congenital adrenal hyperplasia (CAH)*.** A hereditary defect in cortisol synthesis, CAH (an enzyme deficiency) causes a blockage in the pathway leading to cortisol synthesis and results in an accumulation of precursors to cortisol. Some of these precursors are androgens, and elevated levels of adrenal androgens cause symptoms of hyper- androgenism and amenorrhea. Although uncommon, it is important to consider this diagnosis in women with secondary amenorrhea and screen women at high risk for this enzyme deficiency.

■ **Getting a proper history**There are several elements that should be included in the history.



Notes about the history

Use of oral contraceptives, medroxyprogester- one injections, hormonal contraception such as an etonogestrel implant, or progesterone-containing IUDs will result in either amenorrhea or a bleeding pattern induced by estrogen withdrawal and progesterone.

Medications used to treat infertility can also alter the menstrual cycle.

Women who have undergone chemotherapy and/or radiation for cancer treatment can develop amenorrhea.

Chronic opioid use is increasingly recognized as a cause of disrupted cycling. Opioids interfere with the normal pulsatile secretion of GnRH from the hypothalamus.some evidence indicates that opioid use in women leads to reduced LH and FSH and ovarian estrogen production.

Important components of the reproductive history include: pregnancies, lactation intervals, pregnancy losses or pregnancy terminations, history or treatment of infertility and history of uterine instrumentation, such as dilatation and curettage.

■ **Physical exam**The physical exam should include

1. height, weight, and body mass index.
2. The Tanner scale helps confirm normal sexual development and the presence of the physiologic effects of estrogen.
3. Examination of Female genitalia should be inspected carefully for an enlarged clitoris (sign of virilisation).
4. The thyroid gland should be inspected and palpated for enlargement. An eye exam should include inspection for any exophthalmos or lid lag that could signal thyroid disorders.
5. Visual fields should be assessed, as changes in peripheral vision could indicate the presence of a pituitary tumor, creating pressure on the optic chiasm.
6. Careful skin inspection should be performed to assess for facial plethora, purple striae, and bruising (all signs of cortisol excess).
7. Hirsutism, acne lesions or scarring from previous acne lesions (on the face but also on the upper back and chest), and hair thinning in the temporal and/or vertex scalp are all signs of hyperandrogenism.

■ **Lab evaluation**Initial lab evaluation for amenorrhea should include

* a **pregnancy test**
* **TSH**
* **FSH** to rule out the more common causes of amenorrhea.
* **prolactin**

If the FSH is elevated (as in menopause or spontaneous POI) or abnormally low (as in hypothalamic amenorrhea),

* obtaining an **estradiol** level can be helpful to further confirm a hypoestrogenic state.
* If clinical signs of hyperandrogenism are present, **testosterone** (both free and total) and **dehydroepiandrosterone sulfate** can be measured to determine the degree of hyperandrogenism. Androgen values that are greater than two times the upper limit of normal may indicate an androgen-secreting tumor and should prompt referral to an endocrinologist.
* If the prolactin level is elevated, another measurement to confirm elevation is prudent; if the prolactin level remains elevated with no clear cause for this (lactation, nipple stimulation, or medications), magnetic resonance imaging (**MRI**) of the pituitary gland should be done to assess for a pituitary adenoma.
* Lab screening for late-onset CAH consists of a morning **17 hydroxyprogesterone** level.
* **Pelvic ultrasound** can be performed to assess for changes in the endometrial lining, including thickening of the lining (indicating lack of adequate endometrial shedding) or absence of lining, as seen in FHA or Asherman syndrome. Ultrasound can be used to support the diagnosis of PCOS.
* In recent years, anti-Müllerian hormone **(AMH**) has been identified as a way to measure ovarian ovulatory capacity and has become an additional diagnostic tool in the evaluation of amenorrhea. AMH is produced in the ovarian granulosa cells by the antral and preantral follicles and is involved in the regulation of follicular growth, along with suppression of follicular sensitivity to FSH. AMH levels do not fluctuate substantially during phases of the menstrual cycle. Studies have shown that AMH is two to four times higher in women with PCOS compared with healthy ovulatory controls. Women with POI have very low AMH levels, whereas women with FHA have AMH levels similar to controls. Therefore, an elevated AMH is supportive of a PCOS diagnosis and can help to distinguish it from POI (low AMH) and hypothalamic amenorrhea (normal AMH).
* To identify metabolic problems associated with PCOS, lab evaluation should include a screen for T2DM (such as an **oral glucose tolerance test, fasting glucose, or hemoglobin A1C).**

**Approach to diagnosis and Treatment**

**progesterone challenge test** A useful diagnostic maneuver is the administration of a progesterone challenge test (PCT). This can be done with a 7- to 10-day course of medroxyprogesterone or micronized progesterone. If a woman is secreting adequate levels of estradiol (such as in PCOS) and exposing the uterine lining to estrogen effects, a course of progesterone will initiate a withdrawal of menstruation. Typically, a woman will respond to progesterone within 2 to 7 days of the last dose of progesterone, indicating functional endometrium and estrogen production.

Patients who respond to the progestin challenge require occasional progestin administration to prevent the development of endometrial hyperplasia and carcinoma. Oral contraceptive pills may be used to regulate the menstrual cycle. Oral contraceptives also help with management of hirsutism. Alternatively, progestational medication for 10–13 days every month or every other month is sufficient to induce withdrawal bleeding and to prevent the development of endometrial hyperplasia. Patients with hyper-prolactinemia need periodic prolactin measurements and radiographic cone views of the sella turcica to rule out the development of macroadenoma.

If estradiol levels are low (such as in spontaneous POI, menopause, Sheehan syndrome, or hypothalamic amenorrhea), a woman will not respond to progesterone with vaginal bleeding. Likewise, a woman with Asherman syndrome will not respond to a PCT because the uterine lining cannot regenerate.

Patients who are hypoestrogenic must be treated with a combination of estrogen and progesterone to maintain bone density and prevent genital atrophy. The dose of estrogen varies with the age of the patient. Oral contraceptives are good replacement therapy for most women. Combinations of 0.625– 1.25 mg of conjugated estrogens orally daily on days 1 through 25 of the cycle with 5–10 mg of medroxyprogesterone acetate on days 16 through 25 are a suitable alternative. Calcium intake should be adjusted to 1–1.5 g of elemental calcium daily.

treatment should be directed to the cause and depends on the patient's current desire for fertility. Specific pathologies that require intervention include:

* Hysteroscopic resection of intrauterine adhesions in cases with Asherman syndrome. In one series, the conception rate after treatment ranged from 33 to 58 per cent, depending on the severity of adhesions.
* Removal of space-occupying pituitary or brain tumours. The majority of pituitary microadenomas, however, can be managed conservatively with a dopamine agonist. For women with hyperprolactinaemia, not due to a pituitary adenoma, dopamine agonists can lead to resumption of ovulation and menstruation.
* Treatment of feeding disorders and normalization of body weight.
* Correction of thyroid disorders.