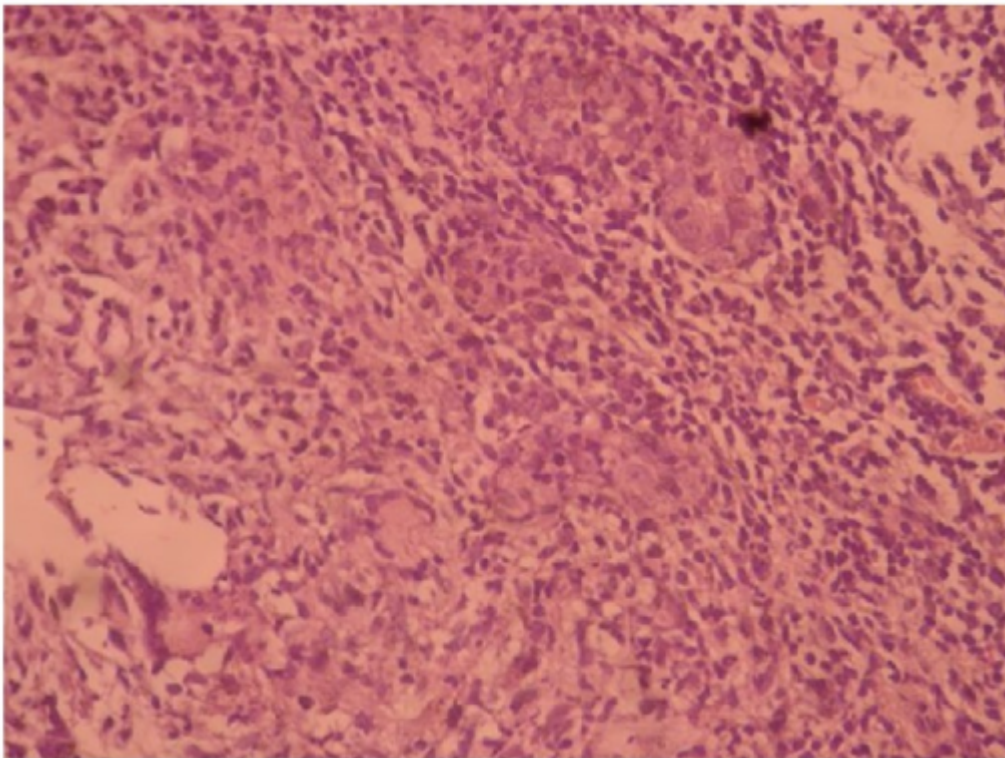


# Hyperprolactinemia — Symptoms and Treatment

[See online here](#)

**Hyperprolactinemia is defined as a condition of high prolactin levels in the blood. Many factors contribute to the development of hyperprolactinemia. Bromocriptine or cabergoline are the first-line drugs for treatment. Refractory cases require surgery, and when hyperprolactinemia is caused by macroprolactinoma, radiation therapy is used. This article discusses possible causes, diagnosis, treatment, and management of hyperprolactinemia.**

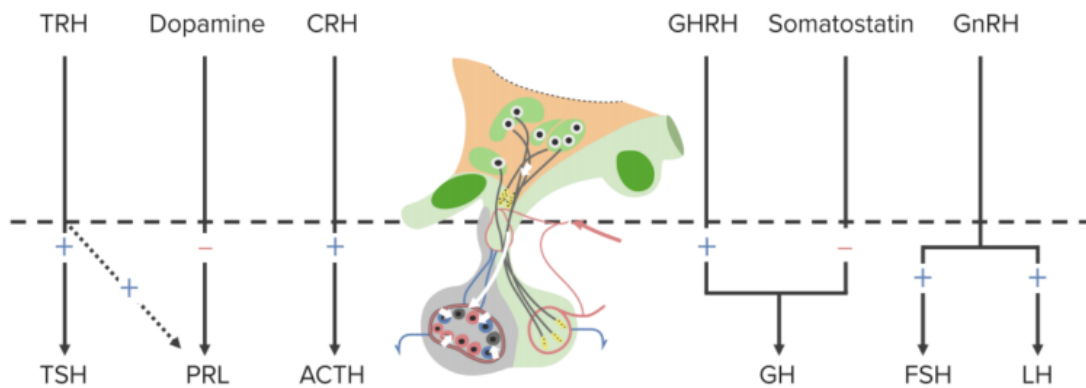


## Definition

Hyperprolactinemia, as the name suggests, **is the hypersecretion of the hormone prolactin, which leads to high prolactin levels in the blood.** Prolactin is a hormone secreted by the anterior pituitary gland. The lactotroph cells of the pituitary gland secrete prolactin into the systemic circulation. Dopamine inhibits prolactin secretion, whereas thyrotropin-releasing hormone (TRH) and estrogen stimulate prolactin secretion.

**Increased levels of prolactin inhibit gonadotropin-releasing hormone (GnRH),** which is synthesized in the hypothalamus, resulting in a decrease in the levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This, in turn, decreases estrogen levels, leading to the cessation of ovulation and menstruation. This is why

women do not menstruate during lactation.



Prolactin. Image by Lecturio

Prolactin is responsible for the production of breast milk. The **primary function of prolactin is to stimulate and maintain lactation in the postpartum period**. It promotes the growth and development of the mammary glands during pregnancy and prepares the breasts to produce milk. It also causes a decrease in sexual drive and reproductive function.

The secretion of prolactin is episodic, and levels vary with age and during the menstrual cycle. Levels increase after sleep and meals. Physiologically, exercise, pregnancy, and stress also cause an increase in prolactin secretion.

## Pathophysiology of Hyperprolactinemia

Prolactin is secreted from the anterior pituitary gland under the direct influence of several hormones that stimulate its secretion (e.g., thyrotropin-releasing hormone, vasoactive intestinal peptide) and dopamine antagonists. Similarly, dopamine tonically inhibits the secretion of prolactin via D2 receptors located on the lactotrophs. Normal values of prolactin range from 0 to 20 ng/mL, based on the laboratory reference value and other factors that influence secretion.

When released into the circulation, prolactin exerts its effects by stimulating breast epithelial cells, thus inducing and maintaining milk production. Estrogen promotes the proliferation of pituitary lactotrophs, thus aiding prolactin secretion. However, estrogen actually inhibits lactation, so there is an increase in breast mass with inhibited lactation during pregnancy when estrogen levels are high. In the postpartum period, there is a rapid decline of estrogen, and lactation begins because prolactin is no longer opposed. This situation is known as puerperal hyperprolactinemia.

Nonpuerperal hyperprolactinemia results from pituitary lactotroph adenomas or any pathology along the hypothalamic-pituitary dopaminergic pathways that produce prolactin.

## Causes of Hyperprolactinemia

Hyperprolactinemia has diverse causes, which can be divided into the following categories.

## Physiological causes

The **most common physiologic cause of increased serum prolactin levels is pregnancy**. A normal pituitary gland grows in size during pregnancy because of estrogen-induced hypertrophy and hyperplasia of the lactotrophs. This eventually leads to a progressive increase in prolactin production and its hypersecretion during pregnancy.

The placenta produces estrogen, which, in turn, stimulates mitosis of the lactotrophs, leading to an increase in serum prolactin, which peaks at the end of pregnancy. The **levels decline rapidly after birth but remain at a slightly increased level** in lactating women for many months.

In infants, prolactin levels are increased approximately 10-fold after birth because of the stimulatory effect of maternal estrogen. The neonatal levels then gradually decrease to normal by approximately 3 months of age. **Other physiologic causes include the following:**

- Lactation
- Coitus
- Nipple stimulation
- Exercise
- Stress
- Sleep
- Pseudocyesis
- Neonatal period

## Systemic disorders

Hyperprolactinemia **can occur because of primary hypothyroidism** due to high thyrotropin-releasing hormone (TRH) levels. This, in turn, stimulates prolactin release and reduces prolactin metabolic clearance.

**Other systemic causes include the following:**

- Severe liver dysfunction/cirrhosis
- End-stage renal disease/chronic renal failure
- Polycystic ovary syndrome
- Chest injury (e.g., trauma, burns) or lesions (e.g., herpes zoster)
- Epilepsy/seizures
- Cranial radiation
- Adrenal insufficiency

## Pharmacological causes

The **most important drugs that cause a rise in serum prolactin levels are dopamine receptor blockers** such as neuroleptics (e.g., haloperidol, sulpiride, chlorpromazine, risperidone, etc.) and antiemetic drugs (e.g., metoclopramide, domperidone).

The classes of drugs\* that produce similar effects are

- Antidepressants/antipsychotics/anticonvulsants
- Antihistamines
- Antihypertensives

- Opioid compounds/cocaine
- Catecholamine depletors
- Protease inhibitors
- Cholinergic agonist
- Estrogen

\* High-yield material for USMLE.

## Pituitary causes

Pituitary adenomas (prolactinomas) are the **most common cause of pathologic hyperprolactinemia**. Approximately 40% of patients with acromegaly have hyperprolactinemia due to hypersecretion of growth hormone and prolactin. Other pituitary causes include:

- Cushing's disease
- Empty sella syndrome
- Lymphocytic hypophysitis

## Hypothalamic causes

Prolactin hypersecretion after impaired hypothalamic/tuberoinfundibular dopamine secretion may be caused by the following:

- Tumors, such as craniopharyngioma, meningioma, dysgerminoma, etc.
- Suprasellar surgery
- Rathke's cyst
- Sarcoidosis

## Diagnosis of Hyperprolactinemia

For women, the normal prolactin range is 0 to 20  $\mu\text{g/L}$ , and for men it is 0 to 15  $\mu\text{g/L}$ .

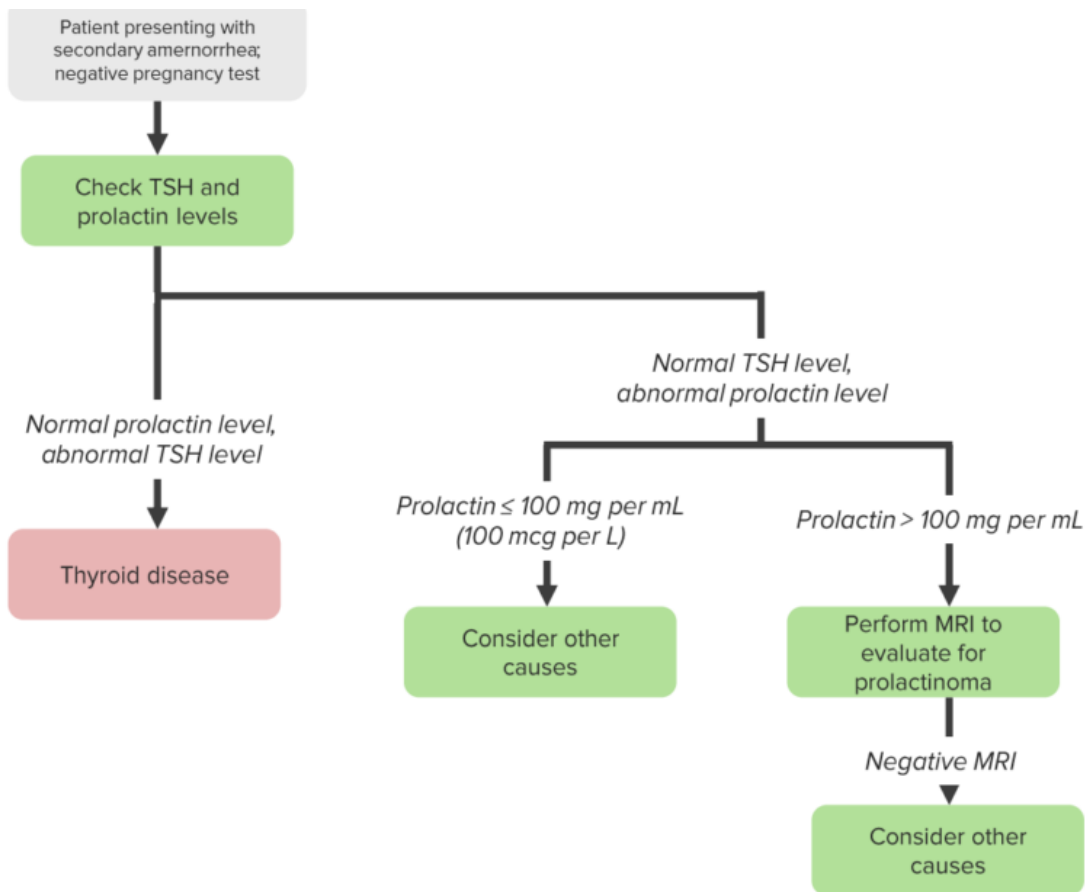
**Serum prolactin level:** A serum prolactin level higher than the upper limit of the normal range confirms the diagnosis, provided there is no venipuncture stress. Thus, **serum prolactin level of greater than 20  $\mu\text{g/L}$  (20  $\text{ng/mL}$ ) indicates a diagnosis of hyperprolactinemia.**

Depending on the results of history and thorough examination, once the diagnosis is confirmed, **further investigations are required to determine the underlying cause**. Examples of such investigations are

- Pregnancy test
- Thyroid function test
- Kidney function test
- Liver function test
- Imaging studies, such as pituitary imaging and magnetic resonance imaging
- Pituitary function test

During the diagnostic work-up of hyperprolactinemia, pregnancy,\* lactation, hypothyroidism, and medications should be considered first.

\*High-yield material for USMLE.



Diagnosis of hyperprolactinemia. Image by Lecturio

## Clinical Presentation of Hyperprolactinemia

The **condition may be asymptomatic**. In men and premenopausal women, hyperprolactinemia presents with typical symptoms that include:

- Hypogonadism
- Infertility-like symptoms
- Menstrual abnormalities such as amenorrhea or oligomenorrhea (in women)
- Galactorrhea (less often, but more common in women)
- Decrease in sexual function (poor libido)
- Headache
- Visual defects
- Secondary bone loss

Other signs include

- Erectile dysfunction (in men)
- Gynaecomastia (in men)
- Hirsutism (in women)

## Differential Diagnosis of Hyperprolactinemia

Differential diagnosis includes

- Pituitary adenomas
- Prolactinoma

- Acute kidney injury

For more information on the differential diagnosis of hyperprolactinemia, refer to the article on [prolactinomas](#).

## Management of Hyperprolactinemia

Patients with hyperprolactinemia **do not necessarily need treatment**. Asymptomatic patients with microprolactinomas and no interest in fertility can be observed and have routine monitoring through serial prolactin level measurements and annual imaging scans.

### Patients indicated for treatment are

- Patients with macroprolactinomas or growing macroprolactinomas (as shown on serial imaging follow-ups)
- Patients with complaints of hypogonadism or who desire fertility
- Patients with complaints of galactorrhea or gynecomastia

## Treatment of Hyperprolactinemia

### Goals

- To control the tumor (or reduce the size of the tumor in the case of macroprolactinomas)
- To restore fertility and eugonadism
- To relieve symptoms of galactorrhea or gynecomastia
- To relieve symptoms caused by tumor mass effect

### Lines of treatment

- Medication is generally the first choice of treatment.
- For patients who do not respond to or cannot tolerate medication, surgery is the second choice of treatment.
- When medication and surgical procedures do not achieve the desired results, radiotherapy is the third choice of treatment.

### Medication therapy

**Dopamine agonists, such as bromocriptine or cabergoline, are the first-line drugs used** in medication therapy for hyperprolactinemia.\* The therapy usually continues for 1 to 2 years (depending on the tumor size or symptoms). Once prolactin levels return to the normal range, medication is stopped. Approximately **one-sixth of patients maintain normal prolactin levels after** medication therapy has ended.

\*High-yield material for USMLE. For more on bromocriptine and cabergoline, refer to the article on [prolactinomas](#). Another dopamine agonist, pergolide, was previously used for the treatment of hyperprolactinemia. Pergolide was withdrawn from the US market on March 29, 2007, because of heart valve damage leading to cardiac valve regurgitation.

### Surgical therapy

With the advent of surgical microscopes, **transsphenoidal pituitary surgery became the preferred choice for surgical treatment**. More recently, endonasal endoscopic surgery, which seems to reduce hospitalization time, has become available. These recent developments have made the selective removal of a pituitary adenoma possible with few

complications and low mortality rates.

In addition to normalizing prolactin levels, surgery **aims to eliminate or diminish the mass effect of macroadenomas**, often relieving neurologic and visual manifestations. For tumors with extrasellar locations expanding out of the midline, a transcranial surgical approach is followed.

### Radiation therapy

In patients for whom the tumor cannot be controlled with medication or surgery, **radiation therapy is used (rare)**. Radiotherapy can be given in one of the following ways:

- Conventional external-beam radiation therapy
- Stereotactic radiation therapy (photon beam, gamma knife, linear accelerator [LINAC], or proton beam)

### Hormonal therapy

In patients with microprolactinoma, if the dopamine agonists are not tolerated or are contraindicated for any reason, **hormonal replacement is a valid alternative** for relieving symptoms related to hypogonadism. This is considered for patients who are not interested in fertility and want to eliminate symptoms such as menstrual abnormalities, sexual dysfunction, etc. Testosterone is used for men, and oral contraceptives are used for premenopausal women. There may be a slight increase in prolactin levels in these patients. It is **important to be careful: use low doses of estradiol** ( $\leq 30 \mu\text{g/day}$ ) and closely monitor prolactin levels and tumor growth in these patients.

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