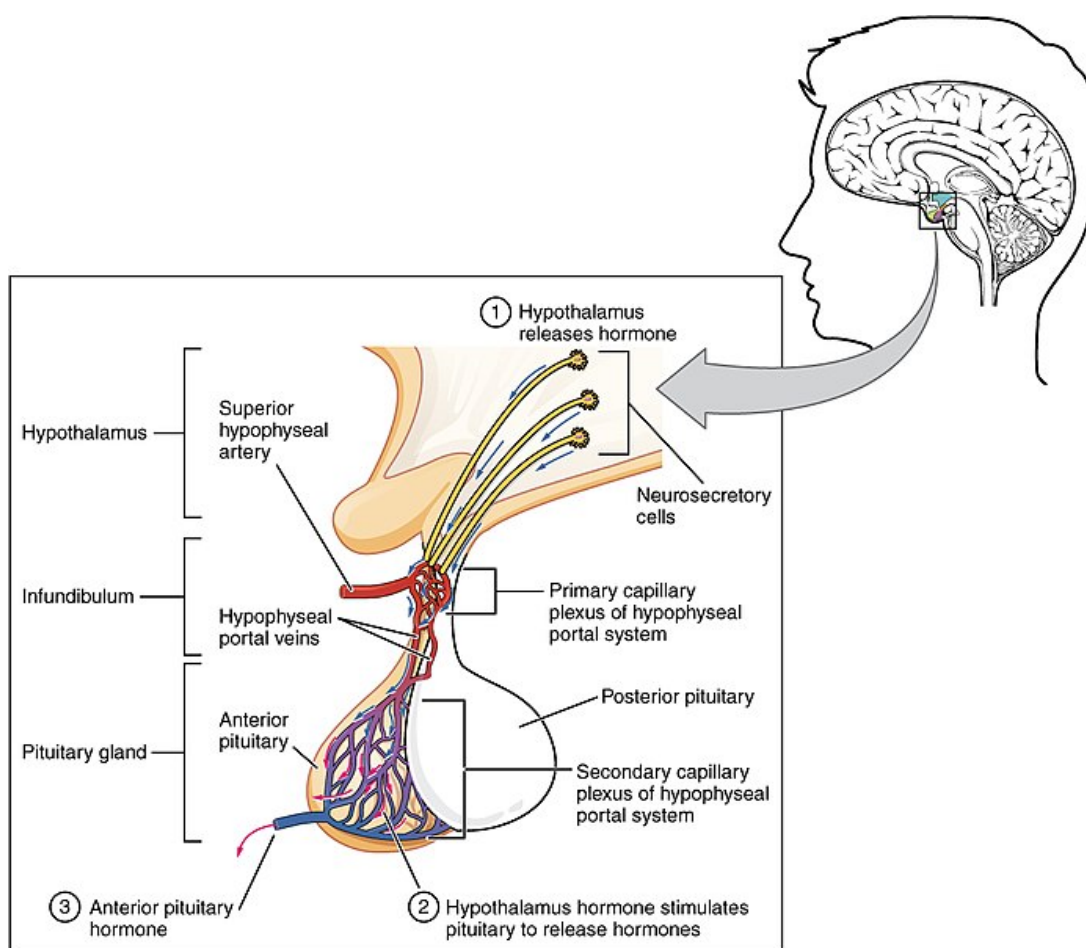


Prolactinoma – Diagnosis and Treatment

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Prolactinomas are benign hormone-secreting pituitary tumors. They can cause symptoms secondary to prolactin secretion as well as space-occupying lesion effects. The management of prolactinomas in pregnancy differs from that in the non-pregnant state. In this article, the etiology, pathophysiology, epidemiology, symptoms, diagnosis, differential diagnosis, management, and treatment of prolactinomas in men and women (pregnant and non-pregnant) are described.



Definition of Prolactinomas

Prolactinomas are the most common hormone-secreting pituitary tumors that occur due to the neoplastic transformation of the anterior pituitary lactotrophs. They are benign, non-cancerous tumors and rarely become malignant.

Depending on their size, they are classified as follows:

- **Microprolactinomas:** tumors < 10 mm in diameter, which are common in

pre-menopausal women

- **Macroprolactinomas:** tumors > **10 mm in** diameter, which are common in **men** and **post-menopausal** women

Epidemiology of Prolactinoma

Prolactinomas account for 25-40% of all pituitary adenomas in the USA. They occur in child-bearing years (second and third decade of life). Microprolactinomas are more common than macroprolactinomas. They can cause significant morbidity (local mass effect of a macroprolactinoma), although mortality is unlikely.

Gender ratio

Both men and women are equally affected. **About 90% of women and 60% of men present with macroprolactinomas.** This discrepancy is because symptoms, such as menstrual irregularities, are common in women; upon seeking medical consultation, the prolactinoma is diagnosed. On the other hand, fewer men tend to be diagnosed with macroprolactinomas as the symptoms of hypogonadism are non-specific initially, which delays this diagnosis.

Most men seek medical advice when they develop complications of space-occupying lesions. By then, the tumor has usually enlarged to form a macroprolactinoma. These tumors rarely occur in children.

Etiology of Prolactinoma

The etiology of prolactinomas is obscure. Most prolactinomas occur sporadically; however, they may sometimes be caused due to a genetic condition. **Prolactinomas can develop as an outcome of multiple endocrine neoplasia, type 1 (MEN 1) along with pancreatic islet cell tumors** and parathyroid tumors. It is an autosomal-dominant genetic disorder. Familial isolated pituitary adenoma (FIPA) has an autosomal-dominant inheritance and accounts for 2-3% of pituitary tumors.

A mutation in the aryl hydrocarbon interaction protein gene has been identified in 25% of FIPA family members; these adenomas are predominantly prolactinomas and somatotropinomas.

Pathophysiology of Prolactinoma

Prolactin, a polypeptide hormone, is secreted by the lactotrophs of the anterior pituitary gland. Prolactinoma is an anterior pituitary lactotroph tumor that results in the increased synthesis and secretion of prolactin. This tumor is a true neoplasm that has monoclonal cell origin.

Prolactin acts on the mammary glands and facilitates mammogenesis (growth and development of the mammary gland), lactogenesis (secretion of milk), and galactopoiesis (maintenance of milk secretion). It participates in the synthesis of progesterone and in luteal cell hypertrophy during pregnancy and influences reproductive behavior. **Prolactin plays an important role in homeostasis by regulating the immune system,** maintaining osmotic balance, and facilitating angiogenesis.

Prolactin-releasing factors (PRFs) and prolactin inhibitory factors (PIFs) are the hypothalamic factors that regulate prolactin secretion. **Dopamine is the most**

important PIF that causes tonic inhibition of prolactin secretion. This is contrary to the other anterior pituitary hormones that are controlled by hypothalamic releasing factors. Thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide stimulate prolactin secretion.

It is hypothesized that **dopamine may have a role in the pathogenesis of prolactinomas.** Certain antipsychotic drugs deplete the dopamine stores in the brain or interfere with the effects of dopamine in the pituitary gland resulting in the secretion of prolactin.

Note: Dopamine inhibits the secretion of prolactin, which forms the basis of the treatment of prolactinomas.

Hyperprolactinemia is a state where there is an increase in prolactin levels. In addition to a prolactinoma, hyperprolactinemia can be caused by a pathological problem of the hypothalamic-pituitary-dopaminergic pathway or due to the effect of certain drugs. Idiopathic hyperprolactinemia is a possibility and its diagnosis is based on the exclusion of other conditions. Several drugs, including trifluoperazine, haloperidol, risperidone, molindone, metoclopramide, and verapamil can cause hyperprolactinemia.

Symptoms of Prolactinoma

Prolactinoma can cause symptoms either due to the effects of increased prolactin levels or due to complications arising from space-occupying lesions. Symptoms depend on the size of the prolactinoma as well as the age and gender of the patient.

Hormonal symptoms

Women of reproductive age commonly present with menstrual disturbances such as oligomenorrhea or amenorrhea. Infertility may result in the long run due to the suppression of gonadotropin-releasing hormone (GnRH) by prolactin.

Galactorrhea is seen in 30–80% of women. It can be spontaneous or expressive (observed only when the nipples are squeezed). This is due to the direct physiological effect of prolactin on breast epithelial cells.

Other symptoms in women are as follows:

- Vaginal dryness due to low estrogen levels
- Delayed **menarche** in young girls
- Induction of other hormonal diseases due to compression of the hormone-secreting cells of the pituitary, which release TSH and GH

The following symptoms are observed in men:

- **Decreased libido, erectile dysfunction, or infertility**
- Galactorrhea or gynecomastia (rare)
- Loss of musculature and body hair
- In pre-pubertal boys, prolactinoma may result in small testicles and female body habitus
- Vision disturbances and headache until the appearance of symptoms of space-occupying lesions

Sexual dysfunction could be either due to hyperprolactinemia or a combination of hyperprolactinemia and low testosterone levels (secondary hypogonadism). **High prolactin levels suppress GnRH, leading to a decrease in FSH and LH secretion,**

thereby leading to decreased testosterone levels. Sexual dysfunction is seen both in men and women.

Elevated prolactin levels lead to low bone mineral density causing osteopenia or osteoporosis. Elevated prolactin level has a direct effect on bone and leads to increased bone turnover in both genders.

Symptoms caused due to space-occupying lesions

Symptoms mainly occur in individuals with macroprolactinoma. Symptoms and complications arising from space-occupying lesions of prolactinomas are **similar to those observed in other brain tumors**. Patients commonly present with headache and visual field defects. When the tumor compresses the optic chiasma, it results in bitemporal hemianopia, a common visual disturbance in individuals with prolactinomas.

Note: Blurred vision or complete blindness may occur if the prolactinoma grows inwards and compresses the optic nerve. Ophthalmoplegia occurs when the tumor compresses cranial nerves 3, 4, or 6.

Macroprolactinoma can also compress the surrounding normally functioning pituitary tissue, resulting in a deficiency of TSH, GH, or ACTH.

Diagnosis of Prolactinomas

Blood tests

- **Determination of prolactin levels:** The greater the size of the adenoma, the higher the prolactin level. Usually, a fasting sample is required. If only modest levels of the hormone are observed, the test should be repeated. Normally, the prolactin level is > 250 ng/mL; levels > 500 ng/mL are indicative of macroprolactinomas.
- **Determination of growth hormone levels,** since prolactinomas tend to secrete this hormone.
- **Urine or serum pregnancy tests** are performed to determine if the patient is pregnant.
- Serum TSH may be increased and prolactin may be elevated secondary to increased TRH. **Free T4 levels** should also be determined.
- FSH, LH, and **testosterone levels** may be decreased.
- If adrenal insufficiency is suspected, **basal and cosyntropin-stimulated cortisol levels** are measured.
- If a patient has symptoms of acromegaly, levels of insulin-like growth factor-1 are measured.
- **Liver function tests;** serum urea and creatinine are measured to assess liver or kidney failure.

Imaging studies

1. **Magnetic resonance imaging (MRI)** with gadolinium enhancement can identify small lesions (as small as 3–5 mm) and is recommended for soft tissue delineation.
2. **Computed tomography (CT)** with contrast is useful in identifying bone destruction.

A biopsy of the lesion is indicated when there is diagnostic uncertainty.

Differential diagnosis for hyperprolactinemia

- Pregnancy and puerperium
- Primary hypothyroidism
- Drug use: phenothiazines, haloperidol, metoclopramide, tricyclic antidepressants, cocaine, opiate abuse, methyldopa, reserpine, and verapamil
- Adrenal insufficiency
- Chronic renal failure
- Liver cirrhosis
- Breast stimulation
- Chest wall lesions due to trauma or surgery
- Spinal cord lesions
- Hypothalamic or pituitary causes: growth hormone-secreting adenoma, non-functioning adenoma, pituitary stalk compression, meningioma, craniopharyngioma, and dysgerminoma
- Previous radiation to the hypothalamic or pituitary regions
- Idiopathic causes

Treatment of Prolactinoma

Most microprolactinomas (up to 95%) do not progress to macroprolactinomas;

however, the prolactin levels of patients with microprolactinomas having minimal symptoms should be closely monitored; patients should be indicated annual CT/MRI scans. On the other hand, if a patient with microprolactinoma is symptomatic, then the condition needs to be treated. Patients with macroprolactinoma need treatment as the tumor may compress the surrounding structures.

Medical management

Bromocriptine is a dopamine agonist that decreases the synthesis and secretion of prolactin. It reduces the rate of tumor cell division and also decreases cell growth. A twice-daily oral dose of 1.25 mg is recommended, which can be gradually increased over time. Doses > 7.5 mg are not needed except in the case of macroadenomas. Side effects include nausea, nasal stuffiness, depression, psychosis, and orthostatic hypotension.

Women intolerant to oral bromocriptine may be prescribed intravaginal bromocriptine as it is equally effective.

After initiating treatment, prolactin levels return to normal within a few days to weeks in 80–90% of patients with microprolactinomas.

Bromocriptine treatment results in the shrinkage of tumors in about 80–85% of patients along with the recovery of gonadal functions. Contrary to the observation in patients with macroprolactinomas, prolactin levels do not return to normal in patients with microprolactinomas following bromocriptine treatment. Further, the shrinkage of the tumor does not correlate well with prolactin levels. As the tumor shrinks, pituitary function improves as evidenced by increased serum testosterone levels and sperm counts. The patient should be regularly monitored for clinical symptoms, prolactin levels, and radiological changes.

The adverse reactions of bromocriptine include dizziness, nausea, nasal congestion, and orthostatic hypotension.

Patients unresponsive or intolerant to bromocriptine may be prescribed cabergoline at a twice-weekly dose owing to its long half-life. It is more efficacious than bromocriptine in reducing prolactin levels and achieving tumor shrinkage. Cabergoline has fewer side effects compared to bromocriptine and includes nausea, headache, fatigue, and dizziness.

Note: Due to the above reasons, cabergoline is the first-line drug in the management of prolactinomas.

In women presenting with infertility secondary to a prolactinoma, **gonadal functions recover and menstrual cycles resume within a few months as prolactin levels normalize**. Sometimes, pregnancy may occur even before the appearance of the menstrual cycle; therefore patients should be advised to use barrier methods of contraception until the resumption of normal menstrual cycles. This helps assess the timing of conception and also helps the physician to withhold medical therapy upon conception.

Surgery

Trans-sphenoidal pituitary adenectomy is the surgical treatment of choice in patients with dopamine agonist treatment-resistant microprolactinomas (despite being treated with the maximum tolerated dose), macroprolactinoma, or large cystic or hemorrhagic tumors. Transcranial resection of a pituitary tumor is indicated only in patients with significant extrasellar extension.

Radiation treatment

Radiation is rarely used as a primary treatment to manage prolactinoma. It is only used when there is a **rapid tumor regrowth** despite medical and surgical intervention, or in the case of malignant prolactinomas. Complications include hypopituitarism (12–80% of cases), optic nerve damage, and neurologic dysfunction.

Management of resistant prolactinoma

For patients with resistant prolactinomas and persistent hyperprolactinemia despite medical treatment, surgical debulking with or without radiation therapy and temozolomide (for malignant prolactinoma) are indicated. Temozolomide is a chemotherapeutic alkylating agent that has been shown to reduce prolactin levels and reduce tumor growth.

Even after regression of the tumor, periodic monitoring of prolactin levels is suggested to the patient to prevent tumor regrowth.

Prolactinoma in Pregnancy

During pregnancy the pituitary gland doubles in size and prolactin levels increase 10-fold; hence, it is not advisable to check prolactin levels during this phase with the aim of treating prolactinomas.

Management of prolactinoma should commence prior to conception and the couple should be appropriately counseled. The anticipated risks are an enlargement of the prolactinoma and exposure of the fetus to dopamine agonists.

The risk of enlargement of macroprolactinomas during pregnancy is low. On the other

hand, **macroprolactinomas can enlarge during pregnancy due to the hormonal stimulation of lactotrophs**. Hence, the tumor should be shrunk by resorting to therapy with dopamine agonists or a transsphenoidal adenectomy prior to pregnancy.

Bromocriptine has a relatively safe profile and can be used until pregnancy is confirmed. Dopamine-agonist therapy should be stopped once pregnancy is confirmed as these drugs can cross the placenta. Their safety profiles during pregnancy have not been studied extensively.

During pregnancy, women with prolactinomas should be followed-up every three months and specifically asked about headaches and vision disturbances. If an enlarged prolactinoma (macroprolactinoma) is revealed in an MRI and the patient's vision is affected, they may be started on bromocriptine for the rest of the pregnancy.

If the adenoma does not respond to bromocriptine, cabergoline can be prescribed, since it is more efficacious and better tolerated than bromocriptine in the treatment of prolactinomas in pregnancy. If the patient is non-responsive to cabergoline and if the vision is severely compromised, then transsphenoidal surgery should be performed in the second trimester. If the patient is already in the third trimester, then surgery should be deferred until delivery.

Breastfeeding can be advised as there is no evidence that breastfeeding stimulates tumor growth. Dopamine agonists must be withheld in women who wish to breastfeed, as these drugs impair lactation.

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