

# Hyperprolactinaemia: A Monster Between the Woman and Her Conception

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## Abstract

Hyperprolactinaemia is the presence of abnormally high levels of prolactin in the blood. Normal levels are less than 5000 ml U/L [20ng/mL or µg/L] for women, and less than 450 ml U/L for men. Prolactin is a peptide hormone produced by the adenohypophysis (also called anterior pituitary) that is primarily associated with milk production and plays a vital role in breast development during pregnancy. Hyperprolactinaemia may cause galactorrhea (production and spontaneous ejection of breast milk without pregnancy or childbirth). It also alters/disrupts the normal menstrual cycle in women. In other women, menstruation may cease completely, resulting in infertility. In the man, it could cause erectile dysfunction. The present study is to review the pathophysiology of the abnormality in the woman, and how it relates to the functioning of the hypothalamo-hypophyseal-gonadal system. The article also looks at the effect of hyperprolactinaemia on the fertility of the woman, and attempts to proffer non-surgical remedy to the condition.

**Keywords:** Galactorrhea, adenohypophysis, hypoestrogenism, prolactinoma, amenorrhoea, macroprolactin, microprolactin

## INTRODUCTION

Hyperprolactinaemia, which is a high level of prolactin in the blood can be a part of normal physiological changes in the body during pregnancy and breastfeeding. Pathologically, it can be caused by diseases affecting the hypothalamus and pituitary gland. It may also be caused by disruption of the normal regulation of prolactin levels by drugs, medicinal herbs and heavy metals inside the body. Hyperprolactinaemia may also be the result of disease of other organs such as the liver, kidneys, ovaries and thyroid[1].

The pituitary gland is a small bean-shaped gland situated at the base of the brain. Despite its small size, the pituitary gland influences nearly every part of the human body. Its hormones help regulate important functions such as growth, metabolism, blood pressure and reproduction. Prolactin is one of the hormones.

Prolactin is a single-chain polypeptide hormone which has effects on reproduction, lactation and metabolism.

It is synthesized by the anterior pituitary lactotrophs and regulated by the hypothalamic-pituitary axis through the release of dopamine, which acts as a prolactin inhibitory factor[2].

During pregnancy and lactation there is considerable hyperplasia of lactotrophs, resulting in up to a ten-fold increase in the circulating levels of prolactin. This effect is secondary to the hormonal changes of pregnancy, predominantly the change in estrogen levels. Subsequently, prolactin levels return to baseline concentrations within 6 months of delivery [3].

Dopamine is the predominant physiological prolactin inhibitory factor[2].

Approximately 80–90% of prolactin is monomeric (23 kDa), and this is its most potent biological form; 8–20% is dimeric (45–50 kDa); and 1–5% is polymeric (150 kDa). The latter fraction is called macroprolactin[4].

In women, a high blood level of prolactin often causes hypoestrogenism (low level of oestrogen in the

blood) with anovulatory infertility and a decrease in menstruation. In some women, menstruation may disappear altogether (amenorrhoea). In others, menstruation may become irregular or menstrual flow may change. Women who are not pregnant or nursing may begin producing breast milk. Some women may experience a loss of libido (interest in sex) and breast pain, especially when prolactin levels begin to rise for the first time, as the hormone promotes tissue changes in the breast. Intercourse may become difficult or painful because of vaginal dryness due to hypoestrogenism. Hyperprolactinaemia that is secondary to pituitary adenoma may cause headaches and visual blurredness caused by the enlarged pituitary pressing against the adjacent optic chiasm.

In men, the most common symptoms of hyperprolactinaemia are decreased libido, sexual dysfunction, erectile dysfunction, infertility, and gynecomastia. Seeing that men have no reliable indicator such as menstruation to signal the problem, many men with hyperprolactinaemia being caused by a pituitary adenoma may delay going to the doctor until they start having headaches or eye problems. They may not recognize a gradual loss of sexual function or libido.

Because of hypoestrogenism and hypoandrogenism, hyperprolactinaemia can lead to osteoporosis.

### Causes

#### Physiological Causes

Physiological (non-pathological) causes include: pregnancy, breastfeeding, and mental stress.

#### Pathological Causes

Prolactinoma or other tumours arising in or near the pituitary — such as those that cause acromegaly may block the flow of dopamine from the brain (hypothalamus) to the prolactin-secreting cells of pituitary thereby hyperprolactinaemia.

hyperprolactinaemia is a condition in which a non-cancerous tumor (adenoma) of the pituitary gland in the brain overproduces the hormone prolactin. The major effect is decreased levels of some sex hormones — estrogen in women and testosterone in men.

Although prolactinoma isn't life-threatening, it can impair vision, cause infertility and produce other effects. Prolactinoma is the most common type of hormone-producing tumor that can develop in the pituitary gland.

Likewise, an abnormality of a division of the pituitary stalk could also cause hyperprolactinaemia. Other causes include chronic renal failure, hypothyroidism, bronchogenic carcinoma and sarcoidosis. Some women with polycystic ovary syndrome may have mildly-elevated prolactin levels.

Non-puerperal mastitis may induce transient hyperprolactinemia (neurogenic hyperprolactinemia) of about three weeks' duration; conversely, hyperprolactinemia may contribute to non-puerperal mastitis[5].

Prolactinoma could also be a tumor that develops in the pituitary gland with an unknown cause.

Apart from diagnosing hyperprolactinaemia and hypopituitarism, prolactin levels are often checked by physicians in patients that have suffered a seizure, when there is doubt as to whether they have had an epileptic seizure or a non-epileptic seizure. Shortly after epileptic seizures, prolactin levels often rise, whereas they are normal in non-epileptic seizures.

### Medical Causes

Prolactin secretion in the pituitary is normally suppressed by the brain chemical dopamine. Drugs that block the effects of dopamine at the pituitary or deplete dopamine storage in the brain may cause the pituitary to secrete more prolactin. These drugs include the typical antipsychotics: phenothiazines such as chlorpromazine (Thorazine), and butyrophenones such as haloperidol (Haldol); atypical antipsychotics such as risperidone (Risperdal) and paliperidone (Invega); gastroprokinetic drugs used to treat gastro-oesophageal reflux and medication-induced nausea (such as that from chemotherapy).

In particular, the dopamine antagonists metoclopramide and domperidone are both powerful prolactin stimulators and have been used to stimulate breast milk secretion for decades. However, since prolactin is antagonized by dopamine and the body depends on the two being in balance, the risk of prolactin stimulation is generally present with all drugs that deplete dopamine, either directly or indirectly.

### Symptoms of Hyperprolactinaemia

There may be no noticeable signs or symptoms from prolactinoma. However, signs and symptoms can result from excessive prolactin in your blood

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(hyperprolactinemia) or from pressure on surrounding tissues from a large tumor. Because elevated prolactin can disrupt the reproductive system (hypogonadism), some of the signs and symptoms of prolactinoma are specific to females or males.

In females, prolactinoma can cause: Irregular menstrual periods (oligomenorrhea) or no menstrual periods (amenorrhea), Milky discharge from the breasts (galactorrhea) when not pregnant or breast-feeding, Painful intercourse due to vaginal dryness, Acne and excessive body and facial hair, and hair growth (hirsutism).

In males, prolactinoma can cause: Erectile dysfunction, Decreased body and facial hair, and enlarged breasts (gynecomastia)

In both sexes, prolactinoma can cause: Low bone density, Reduction of other hormone production by the pituitary gland (hypopituitarism) as a result of tumor pressure, Loss of interest in sexual activities, Headaches, and Visual disturbances, and Infertility

Women tend to notice signs and symptoms earlier than men do, when tumors are smaller in size, probably because they're alerted by missed or irregular menstrual periods. Men tend to notice signs and symptoms later, when tumors are larger and more likely to cause headache or vision problems.

Prolactinomas are classified as microadenomas (< 10 mm in diameter) and macroadenomas (>10 mm in diameter) and it is estimated that 10% of healthy unselected people will have radiological evidence of pituitary adenomas.6[Serri O]

Pituitary imaging should be considered before starting treatment, as this can result in reduction in the size of microprolactinomas and underdiagnosis. Many authorities suggest, however, that pituitary MRI is not necessary if the prolactin level is < 1000 mIU/l and no other clinical or biochemical features of pituitary disease are present.

Management of prolactin excess Indications for treatment can be divided into those related to the effects of hyperprolactinaemia (anovulation and infertility/ reduced bone density/ galactorrhoea) and those related to the mass effect of the prolactinoma (visual field defects due to pressure on the optic chiasma/ hypopituitarism/ cranial nerve defects/ headaches) [7;8].

### Risk Factors

Most prolactinomas occur in women between 20 and 34 years old, but can occur in both sexes at any age. The disorder is rare in children.

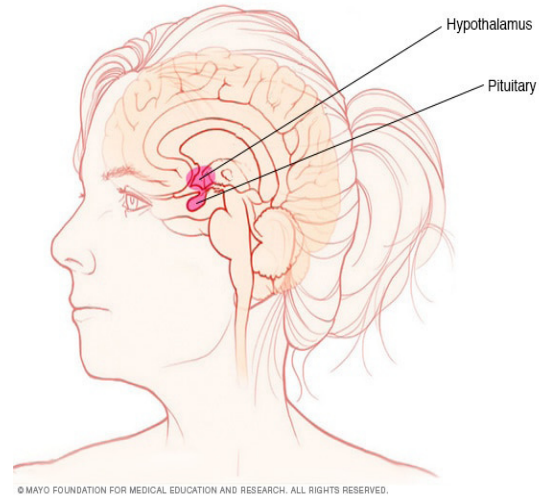


Figure1. Showing the positions of the hypothalamus and the pituitary gland

### Complications

Complications of prolactinoma may include:

- **Vision loss.** Left untreated, a prolactinoma may grow large enough to compress the optic nerve.
- **Hypopituitarism.** With larger prolactinomas, pressure on the normal pituitary gland can cause dysfunction of other hormones controlled by the pituitary, resulting in hypothyroidism, adrenal insufficiency and growth hormone deficiency.
- **Bone loss (osteoporosis).** Too much prolactin can reduce production of the hormones estrogen and testosterone, resulting in decreased bone density and an increased risk of osteoporosis.
- **Pregnancy complications.** During a normal pregnancy, the production of estrogen increases. In the event of pregnancy and presence of a large prolactinoma, the high levels of estrogen may cause tumor growth and associated signs and symptoms, such as headaches and changes in vision.

### Management

Treatment is usually medical or surgical and, very rarely, radiotherapy.

### Medical Treatment

Correction of hyperprolactinaemia using dopamine agonists has been reported to restore ovulation in approximately 90% of women with anovulation secondary to hyperprolactinaemia and result in pregnancy in 80–85% [8;12].

Dopamine agonists are the first-line treatment for both microprolactinomas and macroprolactinomas; the preparations commonly used are bromocriptine and cabergoline.

Treatment is usually medication with dopamine agonists such as cabergoline[12], bromocriptine (often preferred when pregnancy is possible) [13; 8] and less frequently lisuride. A new drug in use is norprolac[14]with the active ingredient quinagolide. Terguride is also used.

*Vitexagnus-castus* extract can be tried in cases of mild hyperprolactinaemia[15].

### Bromocriptine

This dopamine agonist has been used in clinical practice for more than 25 years. Bromocriptine has a relatively short half-life and is, therefore, taken 1–3 times/day [8].It has been shown to restore ovulation in 80–90% of women and to reduce the size of prolactinomas in 70% of cases [8].

It has also been reported to improve visual field defects and headache symptoms within days of treatment. Bromocriptine has a high prevalence of adverse gastrointestinal effects (nausea 30%, vomiting 20%) and postural hypotension (25%). [8].

The drug has a well-established safety profile in pregnancy and long-term follow-up data up to 9 years, of children born to mothers treated with bromocriptine in early pregnancy, are very reassuring [16].

### Cabergoline

This has been shown to be more effective than bromocriptine in lowering prolactin levels, with substantially fewer adverse effects and higher patient compliance. A potentially significant shortcoming is the possible negative effect on cardiac valvular disease. A number of reports [17;13] have described cardiac valvular insufficiency in people who received high doses of cabergoline, i.e. a total daily dosage of 4 mg in Parkinson's disease, which is much higher than that used for the treatment of hyperprolactinaemia.

The echocardiographic and microscopic features in these cases were similar to those seen in cardiac valvular disorders associated with ergot alkaloids, suggesting causation by the ergot features of cabergoline. A possible explanation is that cabergoline has a high affinity for the 5-hydroxytryptamine receptors 2B (HTR2B) located on the heart valves and that activation of these receptors may lead to mitogenesis and fibroblast proliferation. Caution is, therefore, required with higher doses of ergot-derived dopamine agonist, and the Committee on Safety of Medicines (UK) guidance recommends 6–12 monthly echocardiography for people receiving cabergoline[17].

The drug has a very long elimination half-life and can, therefore, be administered once or twice a week. It has been shown [8]to result in resumption of ovulation in 95% of cases and reduction of tumour size in 80% of cases.

No data have shown cabergoline to be unsafe for women wishing to become pregnant, but there are insufficient safety data available and it is yet to be approved for use in this context.

Data on fetal exposure to cabergoline in early pregnancy have been reported in over 350 cases, with no increase in adverse outcomes[18].

### Quinagolide (Terguride)

This is a non-ergot dopamine agonist that has been reported to have similar efficacy to bromocriptine in reducing prolactin levels and the treatment of galactorrhoea, as well as restoring menses and fertility. It has a long half-life and is, therefore, administered once daily. It has a better adverse-effect profile than bromocriptine, and as a non-ergot derived dopamine agonist, the risk of valvular abnormalities is likely to be lower.

Given the efficacy and better adverse-effect profile of quinagolide and the concerns regarding valvular heart disease with cabergoline, many centres now use quinagolide as the dopamine agonist of choice in the treatment of hyperprolactinaemia. However, there are much fewer safety data on its use in pregnancy, although no teratogenic effects have been documented [8].

### Surgical Management

Surgical Management involves the removal of



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prolactinoma (tumour) by surgery. Details of this is not within the scope of this article.

### *Management of Hyperprolactinaemia and pregnancy*

Treatment of hyperprolactinaemia in women who wish to have a pregnancy is dependent on the size of the prolactinoma and the clinical presentation. Medical treatment is preferred to surgery where possible and will generally provide optimal control in most cases with microprolactinomas or macroprolactinomas with no supracellar extension. Because of its better established safety profile, bromocriptine is generally the first line of treatment. One reason for failure of medical treatment in macroprolactinomas is that these tumours may have a substantial cystic element which causes a mass effect, which will not shrink with dopamine agonist treatment and which will require surgical decompression.

The risk of clinically significant enlargement of microprolactinomas in pregnancy is low (approximately 2.6%). However, this risk is much higher with macroprolactinomas (30–35%) and 8.5% of these may require surgery [7;8].

An MRI should be performed if the woman develops visual symptoms of mass expansion. The risk of tumour expansion during pregnancy in women with macroprolactinomas is quite high that many centres recommend continuation of medical treatment throughout the pregnancy with monitoring of visual fields at least each trimester. Some women with prolactinoma experience persistent breast milk production after they cease breastfeeding, and dopamine agonist therapy may have to be recommenced in such cases.

### **HYPERPROLACTINAEMIA AND FEMALE REPRODUCTIVE FUNCTION**

Female patients with hyperprolactinaemia have severely presented infertility. What is even more controversial is the association between hyperprolactinaemia and infertility in the presence of ovulation and regular menstrual cycles [9].

The incidence of raised prolactin concentrations in infertile but ovulatory women ranges from 3.8–11.5% [7].

A study revealed that luteal phase serum prolactin and progesterone concentrations in 31 ovulatory

women presenting with infertility and compared the levels with those in 58 women who had intrauterine contraceptive devices showed that the prolactin concentrations were significantly higher in the infertile group compared with the control group and the progesterone concentrations were lower [10].

Another study on the prevalence of hyperprolactinaemia in infertile women who had regular menstrual cycles correlated their hormone profiles and luteal endometrial histology with those of infertile women with normal prolactin levels. Hyperprolactinaemia was noted in 15 of 130 infertile women (11.5%) with regular menstrual cycles and no galactorrhoea. There was no increase in the incidence of inadequate luteal phase, diagnosed histologically, in women who had raised serum prolactin. Result showed that the evidence for usefulness of serum prolactin measurement in the evaluation of luteal function in infertility was scanty [11].

## **DISCUSSION AND CONCLUSION**

### **Discussion**

High levels of prolactin result in anovulation, secondary to inhibition of luteinizing hormone pulsatility. It has been suggested that raised prolactin levels can also compromise follicular development and reduce corpus luteal sensitivity to luteinising hormone with a resulting reduction in progesterone secretion [9;19].

However, ovarian sensitivity to prolactin is very variable; moderately elevated levels may have no effect in some cases but cause anovulation and amenorrhoea in others [20].

Hyperprolactinaemia may have a more subtle influence on follicular function and the intra-ovarian hormonal milieu, without necessarily suppressing ovulation [9]. Women with raised serum prolactin had significantly higher levels of prolactin in their antral follicular fluid. The high levels of intra-follicular prolactin were associated with a marked reduction in follicle-stimulating hormone (FSH) and estradiol levels in the antral follicular fluid.

Hyperprolactinaemia and female reproductive function were severely deficient in granulosa cells. It is of note that this marked reduction in intra-follicular activity was not associated with any significant changes in the levels of FSH or estradiol in the peripheral plasma. Hyperprolactinaemia is therefore associated with a marked reduction in intra-ovarian activity, the extent

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of which may not be always apparent from the levels of circulating hormone levels.

In a study by *Demura et al*, prolactin was noted to directly suppress both progesterone and 17 beta-estradiol secretion by the ovaries [21]. This may explain the hypogonadism associated with hyperprolactinaemia.

### Hyperprolactinaemia and Female Infertility

Raised levels of prolactin can result in suppression of luteinising hormone secretion and inhibition of ovulation and thus be associated with infertility. This usually manifests with oligomenorrhoea or amenorrhoea [7].

The pulsatile secretion of luteinising hormone is reduced in frequency and amplitude, possibly through a direct inhibitory effect of prolactin on the hypothalamus. On the other hand, women with polycystic ovary syndrome have been reported to have a higher prevalence of hyperprolactinaemia in addition to, typically having elevated luteinising hormone levels. The causation of this association is poorly understood. One suggested theory is that the chronically unopposed estrogen results in increased secretion of luteinising hormone in addition to stimulating the lactotrophs to secrete more prolactin. In addition, it has been suggested that women with polycystic ovary syndrome may have reduced dopamine production from the hypothalamus and subsequently have elevated prolactin concentrations [22;23].

### Conclusion

Hyperprolactinaemia is common and classically presents with galactorrhoea, oligomenorrhoea and amenorrhoea. Whether modest elevation of serum prolactin without disturbance of menstrual regularity has adverse consequences for women seeking pregnancy remains unclear. Current guidance does not advocate measurement of prolactin or use of prolactin-lowering dopamine agonists in such circumstances. High elevation would interfere with the fertility of the woman and disturb conception process. Prolactin-lowering dopamine agonists may be very useful in this case. Many specialists have developed a low threshold for treating to achieve normal-range prolactin in women with a history of unsuccessful assisted reproduction or recurrent miscarriage. This has helped, in no small measure,

to solve the conception challenges associated with elevated level of serum prolactin and other attendant health challenges.

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