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Hyperprolactinaemia: A Monster Between the Woman and Her Conception

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Abstract

Prolactin levels in the blood that are unusually high are known as hyperprolactinemia. fewer than 450 ml U/L for males and fewer than 5000 ml U/L [20ng/mL or µg/L] for women are considered normal values. The adenohypophysis, also known as the anterior pituitary, produces the peptide hormone prolactin, which is mainly linked to the production of milk and is essential for the development of the breast during pregnancy. Galactorrhea, or the production and spontaneous ejection of breast milk without pregnancy or delivery, may be brought on by hyperprolactinemia. Additionally, it modifies or interferes with women's regular menstruation cycles. For some women, the menstrual cycle may stop entirely, leading to infertility. It may result in erectile dysfunction in men. The goal of this research is to examine the pathophysiology of the female aberration and its relationship to the hypothalamo-hypophyseal-gonadal system's functioning. The essay also examines how hyperprolactinemia affects a woman's ability to conceive and makes an effort to give a non-surgical treatment for the illness.

Keywords: Galactorrhea, adenohypophysis, hypoeestrogenism, prolactinoma, amenorrhoea, macroprolactin, microprolactin

Introduction

A high blood level of prolactin, or hyperprolactinemia, may be a result of the body's natural physiological changes during pregnancy and lactation. Pathologically, conditions that impact the pituitary and hypothalamus may be the reason. It may also result from medicines, medicinal plants, and heavy metals interfering with the body's natural control of prolactin levels. Diseases of the liver, kidneys, ovaries, and thyroid may also cause hyperprolactinemia [1]. The pituitary gland is a tiny, bean-shaped gland located near the base of the brain. The pituitary gland affects almost every aspect of the human body, despite its little size. Its hormones aid in controlling vital processes including blood pressure, growth, metabolism, and reproduction. Among the hormones is prolactin.

Prolactin is a single-chain polypeptide hormone that affects metabolism, lactation, and reproduction.

The anterior pituitary lactotrophs produce it, and the hypothalamic-pituitary axis controls it by releasing dopamine, which functions as a prolactin inhibitory factor [2].

Prolactin levels in the blood may rise up to 10 times during pregnancy and breastfeeding due to significant lactotroph hyperplasia. The hormonal changes associated with pregnancy, particularly the shift in oestrogen levels, have a secondary impact. Within six months following delivery, prolactin levels then revert to their initial levels [3]. The primary physiological prolactin inhibitory factor is dopamine

[2]. The most powerful biological form of prolactin is monomeric (23 kDa), which makes up around 80–90% of the protein; dimeric (45–50 kDa) makes up 8–20%; and polymeric (150 kDa) makes up 1–5%. Macroprolactin is the term for the later portion [4].

High prolactin levels in women often result in hypoeestrogenism, or low blood oestrogen levels, which may cause anovulatory infertility and irregular menstruation. Menstruation may completely stop in certain women (amenorrhoea). Others may have irregular periods or altered menstrual flow. Breast milk production may start in women who are neither breastfeeding or pregnant. Because prolactin causes tissue changes in the breast, some women may suffer breast soreness and a lack of libido (desire in sex), particularly when prolactin levels start to increase for the first time. Hypoeestrogenism-related vaginal dryness may make sexual relations difficult or unpleasant. Because the enlarged pituitary presses on the nearby optic chiasm, hyperprolactinemia related to pituitary adenoma may induce headaches and impaired vision.

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Reduced libido, sexual dysfunction, erectile dysfunction, infertility, and gynaecomastia are the most typical signs of hyperprolactinemia in males. Many men with hyperprolactinemia brought on by a pituitary adenoma may put off seeing the doctor until they begin experiencing headaches or vision issues because they lack a dependable indication, such as menstruation. They may not be aware of a progressive decline in desire or sexual function. Osteoporosis may result from hyperprolactinemia due to hypoestrogenism and hypoandrogenism.

Causes

Physiological Causes

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

Pathological Causes

Hyperprolactinaemia may result from prolactinoma or other tumours that develop in or close to the pituitary, such as those that cause acromegaly, blocking the dopamine supply from the brain's hypothalamus to the pituitary's prolactin-secreting cells.

When a non-cancerous tumour (adenoma) of the pituitary gland in the brain overproduces the hormone prolactin, it is known as hyperprolactinaemia. Reduced levels of various sex hormones, such as testosterone in males and oestrogen in women, are the main consequence.

Prolactinoma may cause infertility, eyesight impairment, and other side effects, although it is not life-threatening. The most prevalent kind of tumour that produces hormones in the pituitary gland is called a prolactinoma.

Similarly, hyperprolactinemia may also result from an anomaly in a pituitary stalk division. Sarcoidosis, bronchogenic cancer, hypothyroidism, and chronic renal failure are further factors. Prolactin levels may be somewhat raised in certain individuals with polycystic ovary syndrome.

On the other hand, hyperprolactinemia may contribute to non-puerperal mastitis, and non-puerperal mastitis may cause temporary hyperprolactinemia (neurogenic hyperprolactinemia) lasting around three weeks [5].

An unidentified tumour that grows in the pituitary gland may alternatively be called a prolactinoma.

In addition to identifying hyperprolactinemia and hypopituitarism, doctors often measure prolactin levels in patients who have had a seizure when it's unclear whether the patient had an epileptic or non-epileptic seizure. Prolactin levels are typical in non-epileptic seizures, although they often increase shortly after epileptic episodes.

Medical Causes

Dopamine generally suppresses the pituitary's production of prolactin. The pituitary may release more prolactin if medications impede dopamine's actions at the pituitary or reduce the amount of dopamine stored in the brain. These

medications include gastroprokinetic medications used to treat gastro-oesophageal reflux and medication-induced nausea (such as that from chemotherapy); atypical antipsychotics like risperidone (Risperdal) and paliperidone (Invega); and typical antipsychotics like phenothiazines like chlorpromazine (Thorazine) and butyrophenones like haloperidol (Haldol).

Specifically, the dopamine antagonists domperidone and metoclopramide are potent prolactin stimulators and have been used for decades to increase the production of breast milk. However, all medications that deplete dopamine, either directly or indirectly, carry the risk of prolactin stimulation since dopamine antagonises prolactin and the body relies on the two being in balance.

Symptoms of Hyperprolactinaemia

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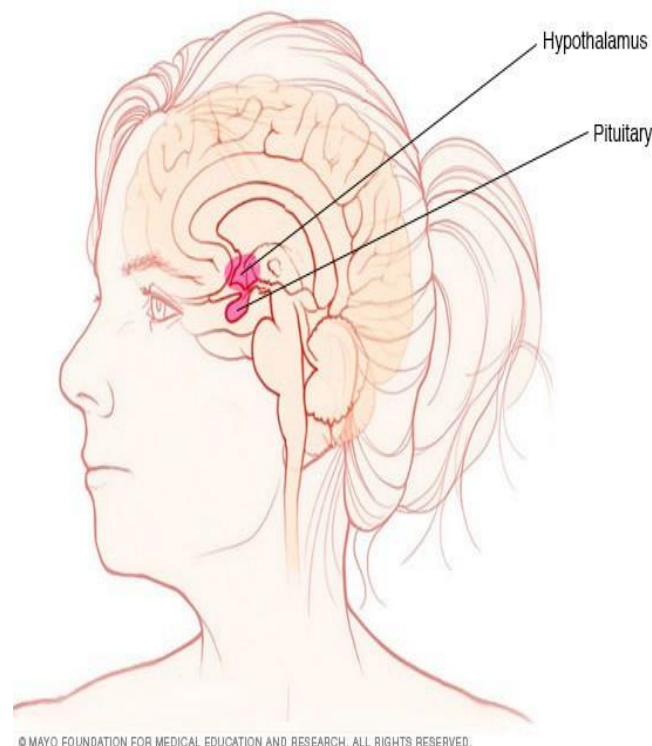
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Prolactinoma may not show any symptoms at all. However, hyperprolactinemia, or too much prolactin in the blood, or pressure from a big tumour on surrounding tissues might cause symptoms. Certain indications and symptoms of prolactinoma are unique to either men or females since high prolactin might interfere with the reproductive system (hypogonadism).

Prolactinoma in women

may result in: When not pregnant or nursing, milky discharge from the breasts (galactorrhea), irregular menstrual cycles (oligomenorrhea) or none at all (amenorrhoea), Sex that hurts because of vaginal dryness Hirsutism, acne, and extensive body and face treatments. Prolactinoma in men may result in decreased face and body hair, larger breasts (gynaecomastia), and erectile dysfunction. Prolactinoma in both sexes may result in: Low bone density, hypopituitarism, a condition when the pituitary gland produces less hormones due to tumour pressure, Infertility, headaches, loss of interest in sexual activities, and visual problems When tumours are smaller in size, women often detect signs and symptoms earlier than men do. This is likely due to overlooked or risk factors.

Prolactinomas may affect both sexes at any age, however most typically affect women between the ages of 20 and 34. In children, the condition is uncommon.



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

Complications

Prolactinoma complications might include:

irregular bouts of menstruation. When tumours are bigger and more likely to cause headaches or visual issues,

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men often discover signs and symptoms later.

loss of vision. A prolactinoma may grow to the point where it compresses the optic nerve if treatment is not received.

Hypopituitarism.

When prolactinomas are bigger, It is anticipated that 10% of healthy, unselected individuals will have radiographic evidence of pituitary adenomas. Prolactinomas are categorised as microadenomas (less than 10 mm in diameter) and macroadenomas (more than 10 mm in diameter).6 [Serri O]

Before beginning therapy, pituitary imaging should be taken into account since it may cause microprolactinomas to shrink and underdiagnose. osteoporosis, or loss of bone. Prolactin overproduction may lower the synthesis of the hormones testosterone and oestrogen, which lowers bone density and raises the risk of osteoporosis.

essential if the prolactin level is less than 1000 mIU/l and difficulties during pregnancy.

There are no further biochemical or clinical signs of pituitary illness during a normal period.

Control of high prolactin Treatment indications can be separated into those associated with the mass effect of the prolactinoma (visual field defects due to pressure on the optic chiasma, hypopituitarism, cranial nerve defects, headaches) and those associated with the effects of hyperprolactinemia (anovulation and infertility, decreased bone density, galactorrhea) [7;8].

Oestrogen production rises throughout pregnancy. When a big prolactinoma is present during pregnancy, the increased oestrogen levels may lead to tumour development and related symptoms such headaches and visual problems.

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

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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 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 supracellular 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

Infertility has often been reported in female patients with hyperprolactinemia. The link between hyperprolactinemia and infertility in the context of ovulation and normal menstrual cycles is even more contentious [9]. Between 3.8 and 11.5% of infertile yet ovulatory women had elevated prolactin levels [7].

Prolactin concentrations were significantly higher in the infertile group compared to the control group, while progesterone concentrations were lower, according to a study that examined the luteal phase serum prolactin and progesterone concentrations in 31 ovulatory women who presented with infertility and compared them with those

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in 58 women who had intrauterine contraceptive devices [10].

The hormone profiles and luteal endometrial histology of infertile women with regular menstrual cycles were associated with those of infertile women with normal prolactin levels in another investigation on the frequency of hyperprolactinemia. Of the 130 infertile women with normal menstrual cycles and no galactorrhea, 15 (11.5%) had hyperprolactinemia. Women with elevated serum prolactin did not have a higher incidence of insufficient luteal phase, as determined by histology. The findings indicated that there was little proof of the value of measuring blood prolactin in assessing luteal function in infertility [11].

Discussion and Conclusion

Discussion

Anovulation is caused by high prolactin levels, which limit the pulsatility of luteinizing hormone. Increased prolactin levels have also been linked to impaired follicular growth and decreased corpus luteal sensitivity to luteinizing hormone, which may lead to a decrease in progesterone release [9;19].

Ovarian sensitivity to prolactin, however, varies greatly; in some situations, fairly high levels may have little impact, while in others, they may result in amenorrhoea and anovulation [20].

Without necessarily inhibiting ovulation, hyperprolactinemia may have a more modest effect on follicular activity and the intra-ovarian hormonal milieu [9]. Antral follicular fluid prolactin levels were much higher in women with elevated serum prolactin. Follicle-stimulating hormone (FSH) and oestradiol levels in the antral follicular fluid were significantly lower when intra-follicular prolactin levels were elevated.

Granulosa cells showed substantial deficiencies in both female reproductive function and hyperprolactinemia. It is noteworthy that there were no appreciable changes in the levels of FSH or oestradiol in the peripheral plasma in relation to this notable decrease in intra-follicular activity. As a result, hyperprolactinemia is linked to a significant decrease in intra-ovarian activity, the degree of which may not always be evident from circulating hormone levels.

Prolactin was shown to directly decrease progesterone and 17 in a research by Demura et al. to address the problems with conception brought on by high blood prolactin levels and other related health issues.

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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

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