



Prolactin secretion in women: narrative review

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Background and Objective: The aim of this review is to explore relevant aspects of prolactin physiology and the conditions associated with hyperprolactinemia in women.

Methods: PubMed and Google Scholar were queried using pertinent keywords to retrieve relevant studies with a particular focus on prolactin physiology, hyperprolactinemia, macroprolactinemia, prolactinoma, and general conditions that may displays alterations of prolactin secretion.

Key Content and Findings: Circulating prolactin displays a circadian cycle that disappears during pregnancy, hyperprolactinemia, and prolactinoma. Prolactin is under dopaminergic control and the influence of estrogens during reproductive years. Physical activity is a powerful stimulus for the pituitary release of prolactin. During pregnancy circulating prolactin increases and is present in the amniotic fluid. During lactation, the principal stimulus for prolactin secretion is breast suckling. Hyperprolactinemia may be related to functional causes or due to the presence of tumors producing prolactin (prolactinomas). Hyperprolactinemia may correspond to excessive production of normal (monomeric) prolactin or polymeric molecules (macroprolactinemia).

Conclusions: The use of polyethylene glycol may differentiate the presence of those forms of prolactin. Functional hyperprolactinemia may be treated with dopaminergic agents like bromocriptine or cabergoline. The majority of cases of hyperprolactinemia associated with pituitary tumors correspond to microprolactinomas that may be treated with the same drugs. Macroprolactinoma may be treated with the same compounds, although surgical excision may be needed in some cases. These drugs should be interrupted during pregnancy unless prolactinoma grows or expand out of the sella turcica. A prolactin fragment has been related to the rare peripartum cardiomyopathy that appears during the last month of pregnancy or within the initial five months after delivery. Hyperprolactinemia has been also associated with an increased risk of subclinical atherosclerosis.

Keywords: Hyperprolactinemia; prolactinoma; macroprolactinemia; cabergoline; bromocriptine

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Introduction

Prolactin is a 23 kilodaltons anterior pituitary hormone traditionally related to the maintenance of lactation during the postpartum period, while its function during the menstrual cycle is more subtle and difficult to demonstrate (1,2). Serum prolactin displays circadian variations related to sleep-related increases, and are not synchronized to those of thyrotropin (TSH) or corticotropin (ACTH). This rhythm disappears during the last trimester of pregnancies and in subjects with hyperprolactinemia or prolactinomas. Other factors from the brain (audition, olfaction), light, and stress may also induce pituitary prolactin secretion (3).

Prolactin is the only pituitary hormone that has not specific feedback from a peripheral hormone. Under normal conditions, prolactin exerts direct feedback on hypothalamic neurons that induces an increase in the dopamine tone (4). In experimental conditions, prolactin secretion increases when the pituitary is removed from the hypothalamic control. Prolactin is also present in the central nervous system, the immune system, the uterus, the mammary gland, and the amnios. However, the precise prolactin functions on these tissues and organs are not completely defined (5). The hormone binds to specific prolactin receptors of target genes that regulate proliferation and cell survival (6). These receptors are widely present in different organs and tissues, including the mammary gland, the genital tract, central nervous system, adrenal cortex, bone, pancreas, and lymph glands (7). Pituitary prolactin receptors are probably involved in the auto-regulation of the hormone secretion. In recent years the hormone has been implicated in different clinical conditions.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://gpm.amegroups.com/article/view/10.21037/gpm-21-4/rc>).

Methods

PubMed and Google Scholar were searched (during November 2020) without language restriction, by all authors, using pertinent keywords to retrieve relevant studies with a focus on prolactin physiology, hyperprolactinemia, macroprolactinemia, prolactinoma, and general conditions that may display alterations of prolactin secretion. Searches also included those terms along with menstrual function, amenorrhea, pregnancy, infertility, amniotic fluid, lactation, breastfeeding, bromocriptine, cabergoline, trans-sphenoidal surgery, cardiovascular risk, breast cancer, and atherosclerosis.

Inclusion and exclusion criteria were guided by the paper title and abstract information.

Menstrual cycle, fertility, and physical activity

Female fertility is linked to prolactin and cortisol secretion within normal ranges. Hyperprolactinemia is associated with anovulation, amenorrhea, and infertility. Interaction of prolactin and cortisol may also interfere with other hormones directly involved in the menstrual cycle and ovulation (8). Under normal conditions, prolactin is inhibited by the neurotransmitter dopamine released by the hypothalamus which is quite different from other pituitary hormones, like gonadotropins, that are stimulated by hypothalamic neurotransmitters. During the menstrual cycle, prolactin is mildly influenced by ovarian steroids. Estrogen is a key regulator of prolactin that increases the production and secretion of prolactin from the pituitary gland. Acute stress may also increase circulating prolactin in both females and males. The peak levels can be detected 15 minutes after exposure to stressors, and there is a close correlation with corticosterone. However, the prolactin increase is different according to different types of stressors (9). Circulating prolactin levels are low most of the time, and physiological hyperprolactinemia is only achieved during lactation. In addition to dopamine and estrogen, a whole range of other hormones can both increase and decrease the amount of prolactin released in the body, with some examples being thyrotropin-releasing hormone (TRH), oxytocin, and anti-diuretic hormone.

Hyperprolactinemia during reproductive years has been considered a detrimental factor for fertilization. However, new evidence from assisted reproductive technology may change the traditional scenario. Endometrial cells have prolactin receptors that participate in endometrial receptivity and appropriate environment for embryo transfer during *in vitro* fertilization. Kamel *et al.* (10) reported a positive correlation between quality embryo implantation and pregnancy. Zhang *et al.* (11) have studied 3,009 women with prolactin levels below 50 ng/mL submitted to *in vitro* fertilization/intracytoplasmic sperm injection cycles due to tubal or male factor infertility. Women with mean prolactin levels higher than 30 ng/mL were associated with cumulative clinical pregnancy, and cases with levels higher than 40 ng/mL were associated with the cumulative live birth rate. Also, women treated with long protocols of gonadotropin-releasing hormone agonists displayed slight high prolactin levels during the

hyperstimulation, being considered the change an indicator for cumulated pregnancies and live birth rates.

Physical activity and exercise are potent stimulants for prolactin and thyroid hormones (thyroxine and triiodothyronine). This combined hormonal response is mediated by the secretion of hypothalamic TRH which causes the release of both thyroid-stimulating (TSH) and prolactin (12). The prolactin response is proportional to exercise intensity and duration, although prolonged exercise may be related to the elevation of core temperature. The prolactin increase differs according to when exercise is carried out, being the nocturnal prolactin increase higher when the physical activity is at the end of the day. On the other hand, the prolactin response to high-intensity interval training is similar when performed under hyperoxia (increased fraction of inspired oxygen) and normoxic conditions (13).

Pregnancy and lactation

During normal human pregnancy, circulating prolactin levels progressively increase following a similar profile to estradiol. These changes have been related to mammary gland preparation for lactation. The amniotic fluid content of prolactin is higher amounts of prolactin than maternal and fetal compartments (1,2,14,15). These findings are similar in pregnant *Macaca mulatta* (16). It seems that human prolactin amniotic fluid levels are related to the decidual prolactin gene expression activity (17,18). Amniotic prolactin maintains control of the differential secretion of proinflammatory chemokines by human fetal membranes (19). Thus, the high prolactin concentration in amniotic fluid maintains the equilibrium between pro- and anti-inflammatory equilibrium. The high level of PRL in the amniotic cavity is involved in the mechanism by which the fetal-placental unit regulates the equilibrium between pro- and anti-inflammatory modulators (20). Prolactin inhibits the lipopolysaccharide-induced chemokine secretion of fetal membranes (19). Under experimental conditions, intra-amniotic lipopolysaccharide administration induces preterm labor and birth (21). However, it remains to be determined if amniotic fluid prolactin changes are the cause or a secondary phenomenon to the cavity inflammation.

Lactation is a complex process regulated by different hormones, including estrogens, progesterone, prolactin, oxytocin, insulin, and glucocorticoids. In postpartum and lactation, prolactin secretion increases during sustained nipple suction, and there is some degree of infertility (22).

The nipple suckling during breastfeeding stimulates the release of prolactin and oxytocin. The amount of milk production does not correlate with the reached prolactin levels during suckling. Mothers reach higher levels of prolactin and oxytocin during lactation if the child does not receive milk supplements, as compared to those that combine breastfeeding with formula feeding (23). However, when breastfeeding is reduced to three or fewer times/day or lactation is completed with formula feeding, menstrual cycles, and ovulation return.

Hyperprolactinemia and macroprolactinemia

In addition to the ordinary monomeric 23 kilodaltons prolactin, there are different variants of plasma and pituitary prolactin and referred to as “big” and “big big” prolactins, or macroprolactins. These macromolecules without pathological significance have nil or minimal biological activity (24), and can be separated by polyethylene glycol precipitation from the monomeric hormone to obtain a real concentration of the bioactive hormone (25,26). Subjects with macroprolactinemia usually have normal monomeric circulating prolactin levels after the separation of macroprolactins. The big prolactin molecules are synthesized by glycosylation, aggregation, and molecule binding. Some three-quarters of macroprolactinemia cases have anti-prolactin antibodies (25). The prevalence of macroprolactinemia is 18.9%, with higher prevalence among Africans (30.3%), Europeans (17.5%), and lowest rates among subjects from the Western Pacific region (12.6%) (27).

The duration of treatment with dopaminergic drugs is a matter of controversy. Xia *et al.* (28) conducted a meta-analysis to assess the optimal timing of dopaminergic drug withdrawal in patients with hyperprolactinemia. It seems that the cabergoline interruption maintains better normoprolactinemia than that of bromocriptine, especially among patients with idiopathic hyperprolactinemia and when a low dose of cabergoline produced a significant reduction of tumor size (29).

Prolactinomas

Prolactinoma is the most frequent pituitary tumor, and the majority of cases is a small tumor of few millimeters (microprolactinoma). In a few cases, larger tumors reach several centimeters (macroprolactinoma). Symptoms include menstrual disorders or amenorrhea, galactorrhea, infertility, and/or neurological symptoms if growing. A high

level of serum prolactin and magnetic resonance imaging are the ways for diagnosis and periodic control of treatment and evolution. Computed tomography is also useful, although is less sensitive than magnetic resonance imaging. In some cases, the eye exam with measurements of the visual field may be convenient. It seems that prolactinomas have different gender characteristics, being tumors larger, more frequently invasive, resistant to dopaminergic drugs, and with a high risk of recurrence and malignancy in men. The tumor aggressiveness can be differentiated by the expression of growth factors (vascular endothelial growth factor and epidermal growth factor), differentiation and proliferation, adhesion molecules, matrix metalloproteinase 9, and chromosome abnormalities (30). The different aggressiveness involves the need for individualized follow-up protocols.

The majority of prolactinomas can be managed with pharmacologic dopaminergic agents such as bromocriptine or cabergoline. Cabergoline is the current ordinary pharmacologic treatment that allows reduction of serum prolactin levels and size reduction of the tumor. This drug is more effective and has fewer adverse effects than bromocriptine. The duration of treatment with dopaminergic drugs is a matter of controversy. The risk of pregnancies during dopaminergic-induced ovulation may affect pregnancy; therefore, the therapy should be interrupted as early as pregnancy is diagnosed in cases of macroprolactinomas and intrasellar macroprolactinomas. Both compounds can be used during pregnancy. In macroprolactinomas expanded out of the sella turcica, dopaminergic treatment should be maintained with periodic sellar MRI control.

In some prolactinomas, cabergoline treatment may be needed for long periods, and normalization of hormone levels is associated with visible remnant tumour. In a large series of prolactinomas, the majority of patients treated with cabergoline for one year, continued to have normal prolactin levels after drug withdrawal. However, some patients develop hyperprolactinemia after one or several years of termination of the initial therapy (31). The rate of recurrence was associated with cavernous sinus invasion at diagnosis. The hyperprolactinemia recurrence reaches 65% of patients with prolactinoma, and the cabergoline dose reduction to the lowest level before the withdrawal was associated with less rate of recurrences (29). Those cases with a significant reduction of tumor size before treatment interruption achieve better results than the abrupt interruption.

Pregnancy in women with prolactinoma needs strict management before conception and during pregnancy. In microprolactinoma and small (intrasellar) macroprolactinoma, dopaminergic drugs should be interrupted as soon as pregnancy is confirmed. However, in some intrasellar macroprolactinomas that spread out of the sella turcica, or if the tumor size increase during pregnancy, dopaminergic treatment may be necessary and should be maintained during pregnancy (32). In these cases, dopaminergic treatment should be maintained with periodic sellar magnetic resonance imaging (MRI) control. In this population, bromocriptine is the elective treatment during pregnancy since the shorter half-life and more number of treated patients as compared to cabergoline.

A recent meta-analysis compared dopaminergic drugs and surgical treatment of prolactinomas, reporting that long-term remission after dopamine agonist interruption of treatment was 34% and after surgical treatment 67%. In the subgroup of microprolactinoma, disease remission was 36% after dopaminergic drugs and 83% after surgery (33). Transsphenoidal surgery was associated with 2% of permanent diabetes insipidus and 3% of cerebrospinal fluid leakage. The endoscopic microscope-assisted and endoscopic surgical techniques are not devoid of side effects (34). During the post-menopause years, prolactinomas have a benign evolution as compared to the reproductive years. Besides, they respond to conventional pharmacological treatment (35).

Prolactin and other clinical conditions

Prolactin has been related to some common conditions. Women with endometriosis and infertility display high prolactin levels and low anti-müllerian hormone as compared with infertile women without endometriosis. Also, the highest prolactin levels were found in women with ovarian endometriomas (36). Pellicer *et al.* (37) revised the effects of different dopaminergic drugs (quinagolide, bromocriptine, and cabergoline) on angiogenesis in women with endometriosis to reduce the size of endometriosis lesions and pain, maintaining ovulation. The dopaminergic agent bromocriptine has been also reported to improve moderate to severe pain in women with adenomyosis (38), although it is not clear if the effect is independent or mediated by changes in prolactin.

There are controversial results concerning prolactin associations with other clinical conditions. Prolactin has been related to mammary carcinogenesis and as a

factor in tumor progression (39). However, no consistent data is supporting an increased risk of breast cancer in hyperprolactinemic women (40,41).

Prolactin and cardiovascular risks

The peripartum cardiomyopathy is a rare form of heart failure that displays clinical symptoms during the last month of pregnancy or within the initial 5 months of the postpartum period (without an identifiable cause). However, a link between that rare disease with preeclampsia and prolactin has been suggested since placenta-derived antiangiogenic factor soluble Fms-like tyrosine kinase 1. A prolactin fragment has been postulated as cardiotoxic while bromocriptine was considered standard adjuvant therapy for this rare disease (42,43).

In patients with chronic kidney disease, increased prolactin levels are associated with endothelial dysfunction, stiffness, and increased cardiovascular events (44). The prolactin increase may be related to a reduction of its metabolism, increased secretion associated with the uremic state, or reduced dopamine availability, and is not associated with macroprolactinemia (45).

Some evidence suggests that prolactin may be involved in the development of essential hypertension, atherosclerosis, and coronary and ischemic syndromes (46-49). Thus, hyperprolactinemia has been associated with a preclinical increase in carotid intima-media thickness, directly or by indirect mechanisms, including insulin resistance, low-grade inflammation, and carotid dysfunction. Another outcome related to preclinical atherosclerosis is flow-mediated dilation (50). In postmenopausal women, hyperprolactinemia has been reported associated with preclinical atherosclerosis aortic systolic and diastolic blood pressure and pulse wave velocity (51).

Different endocrine disorders have been related to an increased risk of atherosclerosis and cardiovascular disease. Hormones may induce metabolic alterations that contribute to atherogenesis, hypertension, insulin resistance, and dyslipidemia that are relevant to atherogenesis, plaque formation, and thrombosis (52). Preclinical and laboratory studies suggest the correlation between prolactin levels and hypertension. Zhang *et al.* (53) reported the association of increased circulating prolactin and the risk of hypertension in postmenopausal women followed during 8 years in the Nurses' Health Study. As compared to women with prolactin levels of 8 ng/mL or below, As compared to women with prolactin levels of 8 ng/mL or below, patients

with higher concentration have an increased relative risk of hypertension.

Summary

Prolactin is a labile hormone under the influence of the hypothalamus and steroid hormones. Prolactin participates in fertilization and lactation, whereas hyperprolactinemia may be associated with amenorrhea and infertility. However, prolactin is also involved in metabolic alterations, subclinical atherosclerosis, and some forms of hypertension. Authentic hyperprolactinemia should be differentiated from those cases of macroprolactinemia. The treatment of hyperprolactinemia includes cabergoline or bromocriptine. Some macroprolactinomas should be treated by transphenoidal surgery.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://gpm.amegroups.com/article/view/10.21037/gpm-21-4/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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