Hyperprolactinaemia and female reproductive function: what does the evidence say?

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Key content
- Raised levels of prolactin are common and can result in the inhibition of ovulation and infertility.
- This review summarises the published evidence on the association between hyperprolactinaemia and fertility in women.
- The evidence on the assessment and treatment of the subfertile woman with clinical or biochemical evidence of hyperprolactinaemia is discussed.
- The management of hyperprolactinaemia in pregnancy is discussed.

Learning objectives
- To understand the effect of prolactin on ovulation and female reproductive function.
- To be able to carry out an initial assessment of the infertile woman presenting with hyperprolactinaemia.
- To understand the management of hyperprolactinaemia in pregnancy.

Ethical issues
- Whether hyperprolactinaemia in the presence of ovulation in the subfertile woman should be treated is debatable.
- There are safety issues regarding the use of dopamine agonists (bromocriptine, cabergoline and quinagolide) in pregnancy.

Keywords dopamine agonist / infertility / macroprolactin / pituitary adenoma / prolactinoma

Introductory physiology

Prolactin is a single-chain polypeptide hormone which has effects on reproduction, lactation and metabolism. It is synthesised by the anterior pituitary lactotrophs and regulated by the hypothalamic–pituitary axis through the release of dopamine, which acts as a prolactin inhibitory factor.1 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.2 Dopamine is the predominant physiological prolactin inhibitory factor. Studies have reported a possible inhibitory effect of a number of factors (gonadotrophin-releasing hormone-associated protein and gamma amino butyric acid) and a possible releasing effect with other factors (thyrotrophin-releasing hormone, gonadotrophin-releasing hormone, growth hormone-releasing hormone, serotonin and some peptides prolactin-releasing peptide, neuroactive peptides, opioid peptides). The physiological significance of these factors remains uncertain and further research is needed to assess their role in this context.1

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 (or ‘big-big prolactin’).3 McNatty in 19744 showed that high levels of prolactin result in anovulation, secondary to inhibition of luteinising 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.4,5 However, ovarian sensitivity to prolactin is very variable and moderately elevated levels may have no effect in some cases but cause anovulation and amenorrhoea in others.6

Hyperprolactinaemia may have a more subtle influence on follicular function and the intra-ovarian hormonal milieu, without necessarily suppressing ovulation. McNatty in 19797 reported on the association between serum prolactin at the time of oophorectomy, the endocrine microenvironment and the developmental status of the antral follicles. Women with raised serum prolactin had significantly higher levels of prolactin in their antral follicular fluid. The high levels of intrafollicular prolactin were associated with a marked reduction in follicle-stimulating hormone (FSH) and estradiol levels in the antral follicular fluid. Furthermore, these follicles
were severely deficient in granulosa cells. It is of note that this marked reduction in intrafollicular activity was not associated with any significant changes in the levels of FSH or estradiol in the peripheral plasma. The author concluded that hyperprolactinaemia is associated with a marked reduction in intra-ovarian activity, the extent of which may not be always apparent from the levels of circulating hormone levels.

In a further study, Demura et al. in 1982 reported on raised prolactin levels and their effect on human gonadal steroid secretion. The study assessed the suppressive effect of prolactin on human gonadal steroid production using an ovarian perfusion technique. Prolactin was noted to directly suppress both progesterone and 17 beta-estradiol secretion by the ovaries, and the authors concluded that this may explain the hypogonadism associated with hyperprolactinaemia.

Macroprolactin is composed of an antigen–antibody complex of monomeric prolactin and immunoglobulin G. It is immunoreactive but biologically inactive. Macroprolactinaemia is generally associated with normal gonadotrophin activity and gonadal function. It has been estimated that approximately 10% of cases of hyperprolactinaemia are attributed directly to macroprolactinaemia, which is generally asymptomatic and not usually associated with pituitary pathology. Hence, it is important to report the concentration of prolactin corrected for macroprolactin in all hyperprolactinaemia cases, to avoid unnecessary investigations and treatment.

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, and diagnosis in such cases is fairly straightforward. 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.

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%. What is more controversial, however, is the association between hyperprolactinaemia and infertility in the presence of ovulation and regular menstrual cycles. The incidence of raised prolactin concentrations in infertility but ovulatory women ranges from 3.8–11.5%. The evidence on this area is limited and conflicting and this is discussed in the next section.

Studies investigating the role of prolactin in subfertile women with regular menstrual cycles

We carried out a literature search on MEDLINE and Google Scholar to identify studies assessing the reproductive outcomes in ovulatory subfertile women with hyperprolactinaemia. We identified no studies that assessed the role of dopamine agonist treatment in this group, but three studies reported on the hormone profiles and conception rates in this group of women. These studies are summarised as follows.

Hyperprolactinaemia and changes in hormone profiles in women with ovulatory menstrual cycles

Ranta et al. in 1979 reported on the 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. The prolactin concentrations were significantly higher in the infertile group compared with the control group and the progesterone concentrations were lower.

Vanrell and Balasch in 1983 reported on the prevalence of hyperprolactinaemia in infertile women who had regular menstrual cycles and 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, and the authors concluded that the evidence for usefulness of serum prolactin measurement in the evaluation of luteal function in infertility was scanty.

Stratford et al. in 1999 reported on the serum prolactin concentrations in a series of 315 infertile women. The median prolactin level was 221 mIU/l and the range was 77–1629 mIU/l. A total of 22 (7%) women had raised prolactin levels of >500 mIU/l (generally considered as above the normal range); of these, two women had prolactin levels of >800 mIU/l and irregular menstrual cycles, whereas 20 women had levels of 500–800 mIU/l. All but one of the 20 women had ovulation confirmed by mid-luteal progesterone assessment and ultrasound and had normal follicular phase estradiol concentrations. The authors concluded that the prevalence of
Hyperprolactinaemia in infertile women is low, and that women with significantly increased plasma prolactin concentrations can be predicted by their history or clinical symptoms, and are unlikely to be missed by a policy of selective testing. However, the number of women with raised prolactin levels in the study was small and the authors did not comment on reproductive outcomes.

Hyperprolactinaemia and conception rates in women with ovulatory menstrual cycles
Glazner et al. in 1987\(^8\) reported on prolactin levels in 188 infertile women with regular menstrual cycles: 47 had prolactin levels of \(\leq 200\) mIU/l, 100 of 201–400 mIU/l, 18 of \(\leq 600\) mIU/l, 16 of \(\leq 800\) mIU/l and 7 of \(>800\) mIU/l. The conception rates were lower in the 600–800 mIU/l group compared with the other groups (including those with lower or higher prolactin levels), but the differences were not statistically significant. For women with prolactin levels of \(\leq 600\) mIU/l, the conception rates at 6 and 12 months were 38% and 48%, respectively. The respective figures for women with levels of 600–800 mIU/l were 26% and 26%, and those for the 7 women with levels of \(>800\) mIU/l were 43% and 62%. There was no statistically significant difference between the groups in either their mid-luteal progesterone levels or conception rates and the authors concluded that prolactin measurement is generally of no value in normally menstruating women. The study did not comment on the pregnancy outcomes and included only small numbers of women with raised prolactin levels.

The National Institute for Health and Clinical Excellence (NICE) guidelines on infertility (2004)\(^14\) state that fertility investigations should not routinely include assessment of prolactin levels and that this should only be offered to women with ovulatory disorders, galactorrhoea or pituitary tumours.

However, the published reports on prolactin and female fertility included small numbers of women, with no reference to macroprolactin levels, as many of these were older investigations conducted before the introduction of macroprolactin measurement. In addition, they did not provide sufficient details on pregnancy outcomes; this area warrants further evaluation in adequately powered studies.

Hyperprolactinaemia and miscarriage
The evidence on the association between hyperprolactinaemia and pregnancy loss is also limited. A randomised trial\(^19\) reported on the treatment of hyperprolactinaemia in ovulatory women who had experienced more than two miscarriages. In the group treated with bromocriptine, 18/21 (86%) women had a successful pregnancy compared with 11/21 (52%) who had no treatment. Bromocriptine was started before conception in a dosage of 2.5–5.0 mg/day and continued until the end of the ninth week of gestation. However, the study had a small sample size and there was criticism of the criteria used to define raised prolactin levels.

Assessment of the subfertile woman with clinical or biochemical evidence of hyperprolactinaemia
A clinical evaluation, including a medication history, is required to exclude physiological and secondary causes of hyperprolactinaemia. These causes are summarised in Box 1. Repeat testing for confirmation of raised levels should be carried out before proceeding with pituitary imaging. Assessment for macroprolactin is required to exclude this as a cause of hyperprolactinaemia. Care must be taken in interpreting low levels of prolactin in the presence of macroadenomas, as this can be due to a high-dose ‘hook’ effect,\(^20\) where very high prolactin levels saturate the antibodies in the assay and prevent the formation of a prolactin–antibody complex, resulting in false low readings. In such cases prolactin levels should be measured in both undiluted and diluted serum.

It is important to differentiate disconnection hyperprolactinaemia from hyperprolactinaemia caused by a prolactin-secreting adenoma. In disconnection hyperprolactinaemia raised prolactin levels are secondary to disruption of the dopaminergic inhibition of the pituitary lactotrophs, caused by non-functioning adenomas. Prolactin levels in cases of disconnection hyperprolactinaemia are usually \(\leq 2000\) mIU/l; higher levels are suggestive of a prolactin-secreting tumour.
Hyperprolactinaemia and female reproductive function

Disconnection hyperprolactinaemia should be differentiated from a prolactin-secreting adenoma, to facilitate planning the appropriate therapy, as the former is unlikely to benefit from medical treatment.\(^{21}\) It is also necessary to assess thyroid-stimulating hormone, as this can be associated with hyperprolactinaemia, probably through direct stimulation of lactotrophs by thyrotrophin-releasing hormone (Box 1).

Pituitary magnetic resonance imaging (MRI) is the imaging investigation of choice in assessing for pituitary adenomas.\(^{22}\) 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.\(^{23}\) 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). Treatment is usually medical or surgical and, very rarely, radiotherapy.\(^{10,13}\)

Medical treatment

Dopamine agonists are the first-line treatment for both microprolactinomas and macroprolactinomas; the preparations commonly used are bromocriptine and cabergoline. Both of these conventional preparations are discussed in detail below.

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.\(^{24}\) It has been shown to restore ovulation in 80–90% of women and to reduce the size of prolactinomas in 70% of cases.\(^{24}\) 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%).\(^{24}\) 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.\(^{25}\)

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\(^{26,27}\) 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.\(^{26}\)

The drug has a very long elimination half-life and can, therefore, be administered once or twice a week. It has been shown\(^{13}\) 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.\(^{28}\)

Quinagolide

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.\(^{13}\)

Surgery

In the past three decades, with the introduction of dopamine agonists, medical treatment has become the first-line treatment
for prolactinomas. Indications for surgery include the following:

- failure of medical therapy
- expanding prolactinomas with progressive neurological and ophthalmological deficits not responding to dopamine agonist treatment
- pituitary apoplexy, a potentially life-threatening situation where infarction or haemorrhage into a prolactinoma results in sudden visual disturbance, severe headache, altered consciousness and vascular collapse.

Studies have suggested that in cases of apoplexy where the visual field impairment is stable, medical treatment with careful monitoring is still a suitable option.

Surgery is usually carried out using a trans-sphenoidal approach, which provides sufficient access to microprolactinomas and most macroprolactinomas. Craniotomy is rarely performed and is usually reserved for prolactinomas that are inaccessible via the trans-sphenoidal approach. It has been reported that surgery is successful in controlling 74–75% of microprolactinomas and 34–38% of macroprolactinomas.

Radiotherapy

The role of radiotherapy in the treatment of prolactinomas has become very limited and is restricted to those resistant to dopamine agonists and surgery. Adverse effects of radiotherapy include: hypopituitarism (70%), radiation necrosis to the surrounding brain tissue (<1%), cranial neuropathy and damage to the optic apparatus (1%). Secondary intracranial malignancies have been reported after radiotherapy, but are less likely to occur with single-dose radiation.

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. Reports have suggested a 1.5-fold increased risk of fetal loss with surgery in the first trimester and this increases to five-fold in the second trimester of pregnancy.

Bromocriptine is usually discontinued early in pregnancy in women with microprolactinaemia and most will have a very low risk of tumour expansion during the pregnancy. 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 so 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.

Conclusion

Hyperprolactinaemia is common and classically presents with galactorrhoea 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. Relatively few data are available to guide decision making and 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.

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