Hyperprolactinaemia and Prolactinoma

Hyperprolactinaemia is defined as a raised level of prolactin in the blood. Note that prolactin levels are normally high during pregnancy and lactation, and also in severe stress.

Prolactinomas are benign, prolactin-producing tumours of the pituitary gland.

Prolactin is produced in the lactotroph cells of the anterior pituitary gland, under inhibitory control by dopamine. Prolactin production can be stimulated by various factors: dopamine receptor antagonists, thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide (VIP) or epidermal growth factor, and by suckling an infant.1

Prolactin is also produced outside the pituitary gland (extra-pituitary prolactin), including hair follicles, adipose tissue and immune cells.

Effects of raised prolactin: [2]

- In women, hyperprolactinaemia inhibits gonadotrophin secretion (follicle-stimulating hormone (FSH) and luteinising hormone (LH)), leading to menstrual dysfunction. It also may cause galactorrhoea.
- In men, hyperprolactinaemia has a direct, reversible effect on the hypothalamus, causing secondary hypogonadism which results in reduced libido and erectile dysfunction.

Aetiology[1, 3]

There are various causes - common causes are prolactinomas and hypothyroidism, or drug-induced (eg antipsychotics). Note that high levels of prolactin may be caused directly, by a prolactin-secreting pituitary tumour; or indirectly by a non-secreting pituitary tumour that prevents dopamine (which inhibits prolactin release) from reaching the normal prolactin-producing cells.

Causes of hyperprolactinaemia

'Physiological' causes:

- Pregnancy.
- Puerperium.
- Breast stimulation (including suckling a child).
- Stress - physical (including excessive exercise) or psychological - including venepuncture.
- Non-fasting sample.
- Macroprolactinaemia:
  - This refers to prolactin of high molecular mass, mostly complexes of monomeric prolactin with immunoglobulins (prolactin auto-antibody complexes). These larger molecules have no bioactivity and a prolonged clearance rate similar to that of immunoglobulins. Depending on the immunoassay used, macroprolactinaemia may account for 25% of laboratory documented hyperprolactinaemia. Consider this cause in an asymptomatic patient with hyperprolactinaemia and consult laboratory staff (see 'Investigations', below).

Intracranial causes:
• Pituitary tumours:
  • Abnormally high levels of prolactin may be caused by a prolactin-secreting pituitary tumour or by a non-secreting pituitary tumour that prevents dopamine (prolactin release-inhibiting hormone) from reaching normal prolactin-producing cells.
  • Prolactinomas:
    • Microprolactinomas (the most common, approximately 90%).
    • Macroprolactinomas (>10 mm size - approximately 10%).
    • Pituitary or hypothalamic tumour compressing the pituitary stalk, e.g. craniopharyngioma.
    • Prolactinomas occur in about 20% of patients with multiple endocrine neoplasia type 1.\(^4\)

• Head injury (eg due to disruption of the pituitary stalk).
• Brain surgery and radiotherapy.
• Post-ictal - within hours of a seizure.

Endocrine and metabolic causes:

• Hypothyroidism (due to increased synthesis of TRH).
• Cushing’s syndrome.
• Chronic renal failure.
• Severe liver disease.
• Polycystic ovarian syndrome.
• Coeliac disease (possibly).\(^5\)

Drugs:

• Dopamine receptor antagonists, eg domperidone, metoclopramide, neuroleptics.
• Dopamine-depleting agents, eg methyldopa.
• Antidepressants, e.g tricyclic antidepressants, monoamine-oxidase inhibitors, serotonin reuptake inhibitors.
• Verapamil.
• Opiates.
• Protease inhibitors.
• Bezafibrate.
• Omeprazole.
• H2-receptor antagonists.
• Oestrogens, anti-androgens.
• Cyproheptadine.
• Cocaine.

Other causes

• Chest wall surgery or trauma.
• Sarcoidosis.
• Langerhan’s cell histiocytosis.
• Idiopathic - a diagnosis of exclusion.

Prolactinoma classification\(^3\)

• Microadenomas: <10 mm.
• Macroadenomas: >10 mm.
• Giant pituitary adenomas: >40 mm.
• Malignant prolactinomas (very rare).

Some pituitary tumours may occur as part of a clinical syndrome. In multiple endocrine neoplasia type 1 (MEN 1), an autosomal-dominant genetic disorder, pituitary adenomas (most often prolactinomas) occur in association with tumours of the parathyroid and pancreatic islet cells.

Epidemiology
Prevalence
This is a relatively common problem. The prevalence of hyperprolactinaemia ranges from 0.4% in an unselected normal adult population to as high as 9-17% in women with reproductive disorders.\[6\]

Prolactinoma:
- In one study, the estimated incidence of dopamine agonist-treated prolactinoma was 8.7 per 100,000 person-years for women and 1.4 per 100,000 person-years for men, with the highest incidence (23.9 per 100,000 person-years) in women aged 25-34 years.
- A possible explanation for the higher incidence of prolactinomas in premenopausal women is higher rates of diagnosis, as in this group there will be more obvious symptoms (oligomenorrhea or infertility).\[3\]

Risk factors
There is a significant risk of tumour enlargement in pregnancy, particularly with macroadenoma.

Presentation\[3\]
The behaviour of prolactin-secreting tumours is determined by their size at presentation; microprolactinomas rarely expand to become macroprolactinomas. Endocrine symptoms and signs:

- **Women:**
  - Common symptoms of are amenorrhoea, oligomenorrhea and galactorrhoea.
  - They may also have infertility, hirsutism and reduced libido.

- **Men:**
  - The hormonal effects of raised prolactin levels are subtle and develop slowly.
  - Endocrine symptoms are reduced libido, reduced beard growth and erectile dysfunction.

- **Children:**
  - Growth failure and delayed puberty are possible presentations in children.

Symptoms due to tumour size (usually macroprolactinomas):

- Headache.
- Visual disturbances (classically, a bitemporal hemianopia (lateral visual fields) or upper temporal quadrantanopia).
- Cranial nerve palsies.
- Symptoms and signs of hypopituitarism.
- Rarely, cerebrospinal fluid (CSF) leak or secondary meningitis.

Investigations\[3, 7\]

**Initial investigations**
- TFTs.
- Exclude pregnancy.
- Basal serum prolactin:
  - If prolactin is mildly elevated (eg 400-1000 mU/L, normal range <400 mU/L), it should be repeated before referral.
  - Dynamic prolactin stimulation tests, such as the TRH test, are not required. Measurement of serum prolactin on three separate occasions (at least two hours after rising and when the patient is rested) is sufficient.
  - A prolactin level >5000 mU/L usually indicates a true prolactinoma.

**Further investigations**
- Visual field testing.
- Pituitary imaging (preferably MRI).
Assessment of pituitary function.

Diagnostic pitfalls

- Macroprolactinaemia (see 'Aetiology', above) - suspect this if there is a high prolactin level with no symptoms (eg normal menstrual cycles). The serum sample should be treated with polyethylene glycerol (PEG) to precipitate out the macroprolactin.
- The assay for prolactin has a 'high-dose hook effect' - there may be a falsely low prolactin result due to the behaviour of the assay. Therefore, if a large tumour is found in conjunction with relatively low prolactin levels, the laboratory should perform serial dilutions of the serum to exclude this effect.

Management\(^2,3,7\)

General

- Treat the underlying cause if feasible.
- The goals of treatment are:
  - Relieve symptoms (if present).
  - Prevent complications:
    - Prevent osteoporosis (due to hypogonadism).
    - For macroprolactinomas, shrink the tumour in order to reduce pressure effects, eg vision loss.
  - Restore fertility and sexual function.

Management of prolactinoma\(^4\)

Asymptomatic patients with prolactinomas do not have an absolute requirement for treatment of their prolactinomas. Indications for treatment are:

- Adverse effects of tumour size.
- Adverse effects of hyperprolactinaemia.

Usually, treat with dopamine agonists (cabergoline, or bromocriptine - but see 'Note' below re monitoring).

- These reduce prolactin levels, allowing oestrogen levels to normalise.
- They are effective in most patients.
- Usually, they need to be continued on a long-term basis; in some patients with microprolactinomas withdrawal of treatment can be trialled after three years, but follow-up is essential.

Note: with dopamine agonists, cautions are:\(^8\)

- Exclude cardiac valve fibrosis and pulmonary fibrosis before starting treatment, then monitor for cardiac/retroperitoneal/pulmonary fibrosis (for details see the British National Formulary).
- Be aware that excess or sudden sleepiness is a possible side-effect.
- Hypotensive reactions can occur when starting treatment.

If dopamine agonists are ineffective, further treatment is by the following:

- Surgery - to reduce tumour size.
- Radiotherapy - to reduce the chance of recurrence (rarely needed).
- Women with hypogonadism and microprolactinomas may be treated for their hypogonadism with oral contraceptives, as long as their prolactin levels do not increase substantially and there is no evidence of tumour enlargement.\(^4,9\)

During pregnancy:

- There is a small risk of tumour enlargement, particularly with macroadenomas. Refer urgently if there are headaches or visual disturbance.
- Patients should be under an endocrinologist (ideally for pre-conception counselling too).


- Depending on the individual situation, management may be:
  - Omitting dopamine agonists for the duration of pregnancy and during lactation.
  - If treatment is required, bromocriptine and cabergoline appear to be safe during pregnancy - bromocriptine is the most 'tried and tested' in this scenario.

**Drug-induced hyperprolactinaemia**
- This may be treated by withdrawing the drug (if feasible), with oestrogen or testosterone replacement, or with a cautious trial of a dopamine agonist.\[10\]

**Macroprolactinaemia**
- This condition usually requires no treatment, and does not generally cause infertility.\[1\]

**Good practice points**
- Refer to hospital urgently if vision deteriorates.
- Remember that successful treatment usually restores fertility - so contraception must be used in patients wishing to avoid pregnancy.
- Ask about erectile function. Provide reassurance that it is part of the disease and that it can be treated.
- Prevent osteoporosis.

**Complications\[^4,7\]**
These will depend on the underlying cause, endocrine function and the tumour size (if due to a pituitary tumour). Possible complications are:

- Complications of hypogonadism:
  - Osteoporosis.
  - Reduced fertility.
  - Erectile dysfunction, and infertility.

- Complications relating to tumour size:
  - Visual loss.
  - Headache.
  - **Pituitary apoplexy:**\[^11\]
    - This is the sudden onset of neurological symptoms (headache, visual symptoms, altered mental status) and hormonal dysfunction due to acute haemorrhage or infarction of a pituitary gland.
    - May develop in patients with giant prolactinomas if their tumours do not reduce in size substantially with a chosen form of therapy.

  - **CSF rhinorrhoea** may occur with rapid size reductions in large prolactinomas that are highly sensitive to dopamine agonist therapy.
  - Very rarely, prolactinomas may be malignant.

**Prognosis**
This depends on the underlying cause.

Microprolactinomas spontaneously resolve in around a third of women, especially after the menopause or pregnancy. Treatment should be discontinued intermittently to see if it is still needed.\[^4\] The treatment dose may be decreased slowly over time. It is reasonable to attempt dopamine agonist withdrawal in patients who have been treated for 2-3 years, if prolactin levels are normal and the tumour volume has reduced. However, there are high rates of recurrence, so follow-up is essential.\[^9\]

**Further reading & references**
• Molitch ME; The cabergoline-resistant prolactinoma patient: new challenges. J Clin Endocrinol Metab. 2008 Dec;93(12):4643-5.

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