

# Prolactin disorders

Niamh Martin

## Abstract

Hyperprolactinaemia can be physiological, pathological or drug-induced. Elevated serum prolactin concentration can cause secondary hypogonadism via inhibition of hypothalamic gonadotrophin-releasing hormone and pituitary gonadotrophins. Therefore, it is important to determine pathological causes of hyperprolactinaemia, particularly due to a prolactinoma. Female patients can present with galactorrhoea, menstrual irregularity and infertility, whereas men can present with symptoms of secondary hypogonadism. Macroprolactin, representing <5% of circulating prolactin, is a polymeric form of prolactin with limited bioavailability and bioactivity. In patients with a raised prolactin concentration who lack typical features of hyperprolactinaemia, macroprolactinaemia should be suspected and sought. Following confirmation of an elevated serum prolactin and exclusion of other physiological and pathological causes, pituitary magnetic resonance imaging should be performed to investigate the presence of a prolactinoma or non-prolactinoma pituitary tumour. Bromocriptine and cabergoline are the two dopamine agonists used most commonly to correct abnormal serum prolactin concentrations. Both cause tumour shrinkage in prolactinomas and restore gonadal function and fertility, but cabergoline is preferred as it is more effective and better tolerated. Although there are more safety data for bromocriptine than cabergoline, both are considered to be safe in pregnancy.

**Keywords** Bromocriptine; cabergoline; dopamine agonist; hyperprolactinaemia; MRCP; prolactin; prolactinoma

## Introduction

Prolactin, released by anterior pituitary lactotrophs, stimulates lactation. Dopamine is transported via hypophyseal portal vessels from the hypothalamus to the anterior pituitary, where it inhibits prolactin secretion via D<sub>2</sub> receptors expressed by lactotrophs. Disruption of dopamine secretion or transport to the portal vessels can lead to hyperprolactinaemia. Hypersecretion of prolactin causes secondary hypogonadism via inhibitory effects on gonadotrophin-releasing hormone and pituitary gonadotrophins.

## Aetiology and differential diagnosis

Normal serum prolactin concentrations are <625 mU/litre in women and <375 mU/litre in men (reference ranges vary slightly between laboratories). During pregnancy, prolactin rises progressively because of oestrogen-induced lactotroph hyperplasia. The causes of hyperprolactinaemia are outlined in Table 1.

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## Key points

- In patients with a raised serum prolactin who lack typical features of hyperprolactinaemia, macroprolactinaemia should be suspected
- After confirming raised serum prolactin and excluding physiological and iatrogenic causes, pituitary magnetic resonance imaging should be performed to investigate for a prolactinoma or non-prolactinoma pituitary tumour
- Bromocriptine and cabergoline are the two dopamine agonists used most commonly to normalize serum prolactin concentrations and induce tumour shrinkage in prolactinomas. Cabergoline is more effective and better tolerated than bromocriptine
- Although there are more safety data for bromocriptine than cabergoline, both are considered to be safe in pregnancy
- Current evidence does not demonstrate an association between dopamine agonists in doses used to treat hyperprolactinaemia and clinically significant valvular heart disease

Prolactinomas represent approximately 40% of all pituitary adenomas and show a female preponderance. These are classified according to size: microadenomas <1 cm, macroadenomas ≥1 cm in diameter. More than 90% of prolactinomas are microprolactinomas. Generally, prolactin concentrations in patients with prolactinomas parallel tumour size, whereas in disconnection hyperprolactinaemia, where prolactin is raised as a result of pituitary stalk compression by, for example, a non-functioning pituitary adenoma (NFPA), serum prolactin is usually <2,000 mU/litre.<sup>1</sup>

## Clinical features

In premenopausal women, hyperprolactinaemia usually presents with galactorrhoea, menstrual irregularity and infertility. Galactorrhoea is less common in postmenopausal women, in whom there is a reduction in breast glandular tissue caused by lack of oestrogen.

Men can present with symptoms of secondary hypogonadism, such as reduced libido, impotence and infertility. However, men and postmenopausal women often present with signs of tumour compression, such as headache or visual impairment. Chronic hyperprolactinaemia with subsequent secondary hypogonadism can lead to reduced bone mineral density.

## Investigations

A single prolactin measurement is usually sufficient to diagnose hyperprolactinaemia. In cases of mild hyperprolactinaemia, it can be worth obtaining several sequential prolactin measurements separated by at least 20 minutes, using an indwelling cannula to minimize venepuncture stress. Secondary causes

## Causes of hyperprolactinaemia

### Physiological

Pregnancy and lactation

Nipple stimulation, including chest wall injury (e.g. Herpes zoster)

Stress

- Venepuncture
- Hypoglycaemia
- Exercise
- Surgery
- Trauma
- Sexual intercourse

### Pathological

Hypothalamic–pituitary disease

- Secretion by tumour (e.g. prolactinoma), sometimes with other pituitary hormones (e.g. growth hormone)
- Pituitary stalk compression impeding dopamine transport to lactotrophs (disconnection hyperprolactinaemia)

Polycystic ovary syndrome

Primary hypothyroidism

Chronic renal failure

Cirrhosis

### Iatrogenic

Antipsychotics

- Typical (e.g. phenothiazines)
- Atypical (e.g. risperidone, clozapine)

Antidepressants

- Tricyclics
- Monoamine oxidase inhibitors
- Selective serotonin reuptake inhibitors

Opiates

Antiemetics

- Metoclopramide
- Domperidone

High-dose oestrogens

Other

- Verapamil
- Cimetidine

**Table 1**

should be excluded by a careful history, examination, pregnancy test, renal function and thyroid function tests.

Once pathological hyperprolactinaemia is confirmed, a gadolinium-enhanced pituitary magnetic resonance imaging (MRI) scan should be performed. Patients with macroprolactinomas or NFPAs, particularly with suprasellar extension, should undergo formal visual field examination using perimetry, and assessment of the remainder of their pituitary function.

In patients with a prolactinoma who are young (<30 years) or have a family history of pituitary adenoma, a diagnosis of familial pituitary adenoma should be considered. This can be in the context of a genetic predisposition to tumour development in a number of organs, for example multiple endocrine neoplasia type 1, or limited to only pituitary tumour development with no other

syndromic features (familial isolated pituitary adenomas). These individuals should be offered genetic screening.

## Diagnostic pitfalls in measuring serum prolactin

### Macroprolactin

Most circulating prolactin (80–90%) is monomeric and biologically active. Macroprolactin is a polymeric form, consisting of an antigen–antibody complex of monomeric prolactin and immunoglobulin G. This usually represents <5% of circulating prolactin. Macroprolactin has limited bioavailability and bioactivity. Macroprolactinaemia should be suspected when a patient has a raised prolactin concentration without the typical features of hyperprolactinaemia. Standard laboratory prolactin immunoassays do not reliably detect macroprolactin, and its presence needs to be confirmed by other methods, such as polyethylene glycol precipitation.

### Hook effect

Very high prolactin concentrations, for example in giant prolactinomas, can saturate the antibodies used in immunoradiometric assays to measure prolactin, preventing formation of the prolactin antibody ‘sandwich’. The resultant loss of labelled antibody leads to falsely low values for prolactin and is termed the ‘hook effect’. The effect can be overcome by performing serial dilutions of serum/plasma before assaying for prolactin.

### Management

The treatment goal in prolactinomas is to normalize serum prolactin concentrations, restoring gonadal function and fertility. In macroprolactinomas, the additional aim is tumour shrinkage.

### Pharmacological options: dopamine agonist treatment

Bromocriptine and cabergoline are the two dopamine agonists used most commonly for the treatment of hyperprolactinaemia and prolactinomas. In disconnection hyperprolactinaemia, only small doses are required to normalize serum prolactin concentrations, whereas in prolactinomas, gradual titration of dosage based on sequential prolactin measurements is usually required.

Bromocriptine was the first medical treatment introduced for prolactinomas. Its relatively short elimination half-life usually necessitates dosing 2–3 times a day, and adverse effects include nausea and postural hypotension. Cabergoline is superior to bromocriptine to control hyperprolactinaemia and restore gonadal function, and is better tolerated.<sup>2</sup> The longer half-life of cabergoline results in a more convenient dosing schedule, and patients usually require 2 mg or less per week. The typical initial dosage of cabergoline is 250–500 µg per week, which is gradually titrated upwards with reference to serum prolactin concentration and tumour size. Quinagolide is an alternative, non-ergot-derived dopamine agonist, although data directly comparing its efficacy to cabergoline in the treatment of hyperprolactinaemia are limited.

Current recommendations are consideration of a trial of dopamine agonist withdrawal in patients with stable normal prolactin concentration and no or a minimal visible tumour

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