Hyperprolactinaemia

Diagnostic and management challenges

JESSIE TENG MB BS(Hons), BMedSci
NIRUPA SACHITHANANDAN MB BS(Hons), FRACP, PhD

Pregnancy and medications are the two most common causes of hyperprolactinaemia in the primary care setting. A detailed history and examination is required to exclude secondary causes of the condition. Medical therapy with dopamine agonists is highly effective and the mainstay of treatment in patients with symptomatic hyperprolactinaemia or macroprolactinomas.

Key points

- **Hyperprolactinaemia should be suspected in premenopausal women with menstrual disturbance and/or galactorrhoea and in men with symptomatic hypogonadism.**
- **Drug-induced hyperprolactinaemia is common, and antipsychotics are frequently implicated. A baseline prolactin measurement is recommended before commencement of long-term antipsychotic treatment.**
- **Dopamine agonists are first-line therapy for symptomatic hyperprolactinaemia or macroprolactinomas.**
- **Management of prolactinomas during pregnancy can be challenging and is best co-ordinated in the setting of a multidisciplinary team comprising an endocrinologist, neurosurgeon and obstetrician.**

ENDOCRINOLOGY TODAY 2014; 3(1): 18-24

Dr Teng is an Endocrinology Advanced Trainee and Dr Sachithanandan is an Endocrinologist in the Department of Endocrinology and Diabetes at St Vincent's Hospital, Melbourne, Vic.

Hyperprolactinaemia is frequently encountered in the primary care setting, with a reported prevalence of approximately 20 per 100,000 in men and 90 per 100,000 in women.[1] In women aged 25 to 34 years, the annual incidence of hyperprolactinaemia has been reported to be 23.9 per 100,000 person years.[1] Pregnancy and drugs are the most common causes of hyperprolactinaemia in clinical practice. Prolactinomas are relatively less common, occurring in only 100 per million adult cases, but account for 40% of all pituitary tumours. Regardless of aetiology, hyperprolactinaemia may cause galactorrhoea in premenopausal women and lead to hypogonadism in both men and women.

This article describes common challenges encountered in the diagnosis and management of hyperprolactinaemia in the primary care setting. Although evidence-based guidelines have recently been published, further research in areas such as optimal management of macroprolactinomas during pregnancy is still required.[1,2]

Physiology

Prolactin, whose main function is in lactation, is secreted by lactotrophs in the anterior pituitary gland. Its secretion is mainly under inhibitory control: dopamine produced by the tuberoinfundibular cells in the hypothalamus binds to dopamine type 2 (D2) receptors on lactotrophs and inhibits prolactin release (Figure). In contrast, both thyrotropin-releasing hormone and oestrogen stimulate prolactin secretion. Prolactin is secreted in an episodic manner, with highest levels observed during sleep and lowest between 10 am and noon.

Clinical manifestations of hyperprolactinaemia

Hyperprolactinaemia should be suspected in patients presenting with symptoms of hypogonadism or galactorrhoea. Hypogonadism is common in hyperprolactinaemia because prolactin inhibits the release of gonadotropin-releasing hormone, thus reducing luteinising hormone, follicle-stimulating hormone and ultimately sex hormone synthesis.

In premenopausal women, hyperprolactinaemia-induced hypogonadism manifests as oligomenorrhoea or amenorrhoea, galactorrhoea and infertility. Patients with amenorrhoea secondary to hyperprolactinaemia may have low bone mass due to oestradiol deficiency, which improves with restoration of menses. Mild hyperprolactinaemia can cause infertility in 20% of cases, even with no apparent disruption of menses, due to insufficient progesterone secretion and a shortened luteal phase (anovulatory cycles). In postmenopausal women and men, hyperprolactinaemia very rarely results in galactorrhoea and it is therefore usually only recognised when a macroadenoma exerts mass effect, causing headaches and visual disturbance, or as an incidental finding during brain imaging. Men can also present with symptoms of hypogonadotropic hypogonadism, including reduced energy, poor libido, erectile dysfunction, decreased muscle mass, reduced body hair and low bone mass.

Causes of hyperprolactinaemia

The causes of hyperprolactinaemia can be physiological, pharmacological or pathological (Box 1). It is important to exclude secondary causes of hyperprolactinaemia before further investigation.

Physiological causes of hyperprolactinaemia

Serum prolactin levels increase throughout pregnancy, probably due to the effects of increasing oestradiol levels on lactotroph cells. Prolactin levels peak at delivery and normalise by six weeks postpartum. Prolactin release is also increased by nipple stimulation, the magnitude being proportional to the degree of pre-existing lactotroph hyperplasia.[3]

Drug-induced hyperprolactinaemia

A number of drugs cause hyperprolactinaemia, mainly by antagonising the inhibitory effects of dopamine on D2 dopamine receptors. Antipsychotics, antidepressants and antiemetics are the groups most commonly implicated. Therefore, measuring prolactin levels before prescribing an antipsychotic or antidepressant with a view to long-term therapy is often useful as a baseline for later comparison.[4]

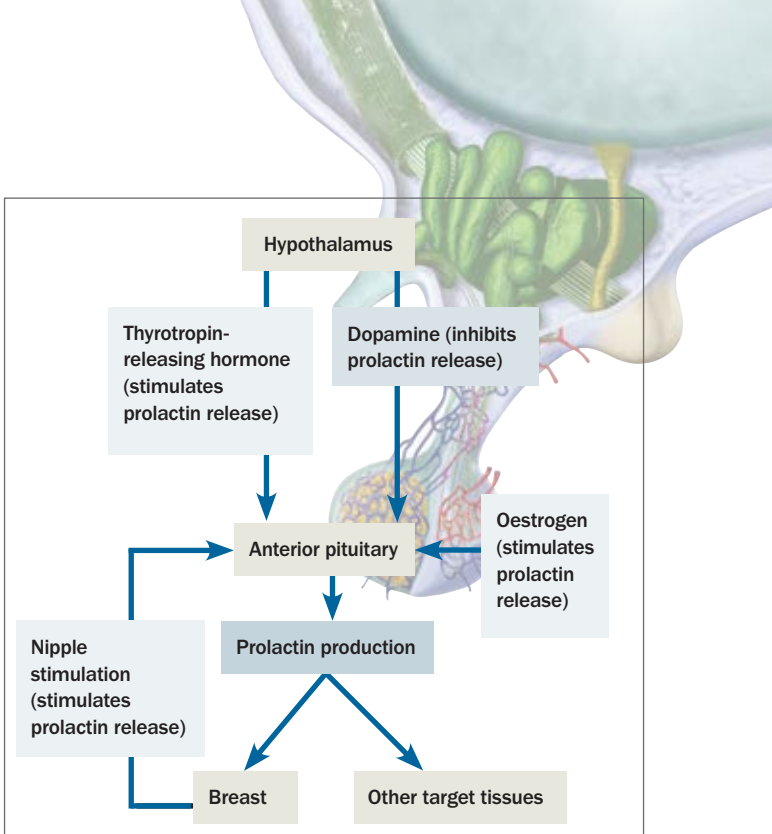


Figure. Regulation of the hypothalamic–pituitary–prolactin axis. Prolactin secretion is mainly under inhibitory control: dopamine produced by the hypothalamus binds to dopamine type 2 receptors on lactotrophs in the anterior pituitary, inhibiting prolactin release. Both nipple stimulation and thyrotropin-releasing hormone increase prolactin release.

Antipsychotics differ in their capacity to increase prolactin secretion, and clozapine and aripiprazole only rarely cause hyperprolactinaemia (<5%).[4,5] With chronic antipsychotic use, prolactin levels can remain elevated, resulting in hypogonadism and galactorrhoea. Prolactin levels

1. Causes of hyperprolactinaemia

Physiological
- Pregnancy
- Lactation
- Stress
- Exercise

Pharmacological
- Antipsychotics
- Antidepressants: SSRIs, TCAs, MAOIs
- Antihypertensives: verapamil (not dihydropyridine calcium channel blockers), methyldopa
- Opiates and cocaine
- Gastric motility agents: metoclopramide, domperidone, ranitidine
- Hormones: oestrogen, testosterone (via aromatisation to oestrogen)

Pathological
- Hypothalamic-pituitary stalk damage ('stalk effect')
- Prolactinoma
- Hypothyroidism
- Chronic renal failure
- Chest wall injury

Abbreviations: MAOIs = monoamine oxidase inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

2. Case study: prolactinoma

A 26-year-old woman presented with menstrual irregularity and galactorrhoea. Her prolactin levels were markedly elevated at 3960 mIU/L (198 µg/L; normal, below 620 mIU/L or 31 µg/L). After the exclusion of pregnancy, hypothyroidism, impaired renal function and interfering medications, an MRI of the pituitary was obtained. It showed an 11-mm adenoma (Figure A).

She was commenced on cabergoline, and the hyperprolactinaemia and symptoms resolved within a few weeks. Repeat imaging 12 months later showed significant shrinkage of the tumour (Figure B).

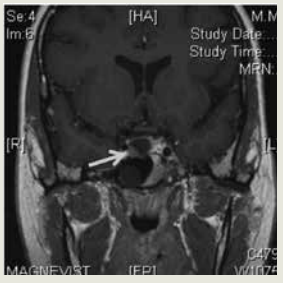


Figure A. The prolactinoma (arrow) before treatment with cabergoline (MRI).

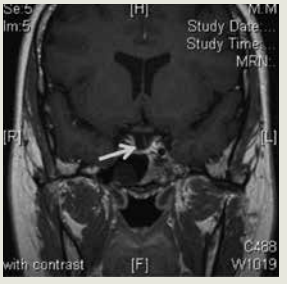


Figure B. The prolactinoma (arrow) 12 months after treatment with cabergoline, showing significant shrinkage of the tumour.

usually normalise within 48 to 96 hours of discontinuing the drug.[6] After commencing therapy, repeat measurement of prolactin levels is indicated only if there are new symptoms consistent with hyperprolactinaemia (hypogonadism, galactorrhoea) or mass effect (headaches, visual disturbance).

Prolactinomas (lactotroph adenomas)

As mentioned earlier, prolactinomas account for 30 to 40% of clinically recognised pituitary adenomas.[2] Most consist solely of lactotroph cells, and 10% also secrete prolactin and growth hormone (GH). In addition, any hypothalamic or pituitary mass that disrupts the dopaminergic neuronal pathway (by compressing the pituitary stalk) can result in hyperprolactinaemia due to loss of the inhibitory effects of dopamine on prolactin secretion – the 'stalk effect'. However, hyperprolactinaemia due to stalk effect is usually mild and prolactin levels rarely exceed 2000 mIU/L.

Prolactinomas are frequently diagnosed at a smaller stage in premenopausal women because of the early disruption of menses (see the case study in Box 2). In men and postmenopausal women, prolactinomas are usually larger at diagnosis due to lack of symptoms and delay in presentation. They are almost always benign tumours, and the cause is not known in most cases (rarely they are due to a genetic mutation).

Other causes of hyperprolactinaemia

Other common causes of hyperprolactinaemia include:

- hypothyroidism, due to the stimulatory effects of thyrotropin-releasing hormone on prolactin secretion
- chronic kidney disease, due to reduced metabolic clearance and increased production as a result of disordered hypothalamic regulation
- chest wall stimulation and psychological stress, presumably due to a neural mechanism.

Clinical evaluation of suspected hyperprolactinaemia

Serum prolactin level, 'hook effect' and macroprolactin

Prolactin levels should be measured in patients with symptoms of hypogonadism or galactorrhoea. A mildly elevated level in patients with few or no symptoms should ideally be confirmed by serial prolactin measurements every 15 to 20 minutes (preferably through an indwelling cannula) to establish persistent hyperprolactinaemia and exclude a stress response from venepuncture.

Prolactin levels less than five times the upper limit of normal (ULN) can occur in patients with any cause of hyperprolactinaemia, whereas markedly elevated values (more than five times ULN) usually suggests the presence of a prolactinoma. The ULN varies with the assay used and the testing laboratory but is generally less than 500 mIU/L (25 µg/L). Microprolactinomas (tumours less than 1 cm in diameter) are typically associated with prolactin levels below 3000 mIU/L (150 µg/L); macroprolactinomas (tumours more than 1 cm in diameter) usually have prolactin values above 5000 mIU/L (250 µg/L).[2] In patients with a large pituitary adenoma but only modestly elevated prolactin levels, the 'hook effect' needs to be excluded. This occurs when very high prolactin levels saturate both the capture and signal antibodies used in immunoradiometric assays, preventing both binding together and resulting in a falsely low prolactin measurement; it can be overcome by repeating the assay using a 1:100 dilution of serum.

Occasionally a larger, glycosylated prolactin called 'macroprolactin' can be detected by the standard prolactin immunoassays, leading to a falsely high prolactin value. This occurs in up to 30% of cases of hyperprolactinaemia.[7,8] Macroprolactin has reduced bioactivity and is usually not associated with symptoms of hyperprolactinaemia or abnormal imaging. Levels of macroprolactin can be measured using polyethylene glycol precipitation, but this test is not performed routinely. Measurement of macroprolactin levels is recommended in cases of asymptomatic hyperprolactinaemia or less typical symptoms, such as headaches or reduced libido in the presence of regular menses.[1,2]

An approach to the diagnosis and management of hyperprolactinaemia is summarised in the flow chart.

History and physical examination

History taking should be targeted at eliciting symptoms and potential causes of hyperprolactinaemia. In premenopausal women, menstrual history and pregnancy should be considered. Medication history is important. Headache and visual disturbance may suggest the presence of a macroadenoma. Enquiry about symptoms of hypothyroidism and other medical problems, including renal disease, is essential.

Physical examination should be directed towards screening for hypothyroidism, hypogonadism and expressible galactorrhoea.

Confrontation visual field testing is helpful in detecting bitemporal hemianopia or other temporal field loss.

Evaluation of drug-induced hyperprolactinaemia

If the patient is taking a drug known to cause hyperprolactinaemia, the drug should be cautiously discontinued where possible (for antipsychotics, this should be done in collaboration with the treating psychiatrist), and prolactin levels remeasured. If the drug cannot be discontinued or the onset of hyperprolactinaemia does not coincide with drug therapy, imaging of the pituitary is recommended to exclude a prolactinoma.[1] Reproductive hormone levels should be checked in all patients with drug-induced hyperprolactinaemia.

Evaluation of nondrug-induced hyperprolactinaemia

All patients with hyperprolactinaemia should have their thyroid, renal and liver functions checked. Reproductive hormone levels should also be checked, including follicle-stimulating hormone, luteinising hormone, oestradiol (in women) and testosterone (in men). Pregnancy should be excluded in all premenopausal women.

Once secondary causes have been excluded, the pituitary should be imaged. Magnetic resonance imaging (MRI) of the pituitary is the best radiological investigation for a structural pituitary lesion. Computed tomography is less sensitive, and not ideal for detecting pituitary microadenomas. Patients reporting headaches or visual disturbance and those found to have a macroadenoma encroaching on the optic chiasm should also have formal visual field testing.

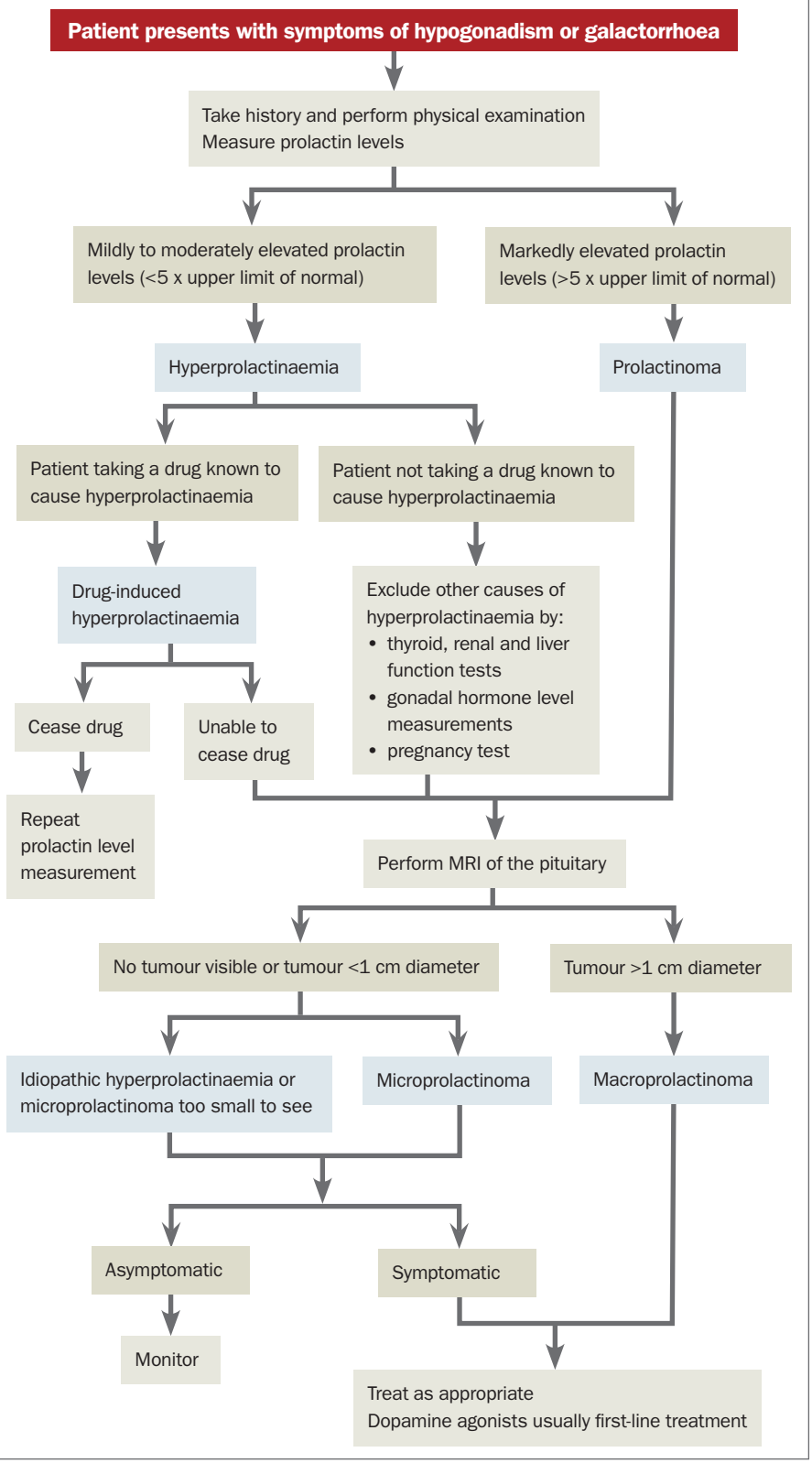
If a pituitary mass is found, the potential diagnoses include a prolactinoma or hyperprolactinaemia due to the stalk effect and loss of dopamine inhibition. Evaluation of other pituitary hormones should be made to assess for insufficiency and oversecretion (GH and prolactin co-secretion should be excluded with an insulin-like growth factor 1 measurement). If a pituitary mass is not evident on MRI, the patient could have idiopathic hyperprolactinaemia or a microprolactinoma that is too small to be visualised on such imaging, and the patient will then need to be monitored with serial prolactin measurements and imaging.

Treatment of hyperprolactinaemia

Treatment of prolactinoma

For patients with prolactinomas, treatment is usually initiated when there are symptoms due to hyperprolactinaemia or the size of the adenoma. Up to 95% of microprolactinomas do not enlarge, and

An approach to the diagnosis and management of hyperprolactinaemia



may be monitored without therapy.[9] In premenopausal women with microprolactinomas who do not desire fertility and do not have problematic galactorrhoea, oestrogen replacement therapy with the oral contraceptive pill is appropriate to avoid the long-term effects of hypogonadism on bone health. For macroprolactinomas, treatment is essential if headache, visual impairment or other neurological symptoms are present. If the tumour extends beyond the sella, abuts the optic chiasm or invades the cavernous sinuses, treatment is usually pre-emptively initiated to prevent complications due to tumour growth.

Dopamine agonists are usually the first-line treatment for any cause of hyperprolactinaemia, including prolactinomas. The aim of therapy is to normalise serum prolactin, restore gonadal function and reduce or stabilise pituitary tumour size. Cabergoline is an ergot dopamine agonist that is orally administered once or twice per week, starting at 0.25 to 0.5 mg weekly. The dose is gradually titrated by increments of 0.25 to 0.5 mg per week based on response (fall in prolactin, resolution of symptoms and stabilisation or shrinkage of tumour). Bromocriptine is another ergot derivative and can be started at 1.25 mg orally at night with food, increasing to a maximum dose of 15 mg daily. Intolerance to bromocriptine is much more common than to cabergoline, and is usually due to gastrointestinal disturbance. In patients who are unable to tolerate bromocriptine or cabergoline, treatment with quinagolide, a nonergot dopamine agonist, may be considered. Other side effects of dopamine agonists include postural hypotension, nasal stuffiness, constipation and, very rarely, disorders of impulse control such as sex addiction and gambling.[10] Dopamine agonist-related cardiac valvulopathy (which is usually seen in patients with Parkinson's disease treated with very high doses of ergot-derived dopamine agonists) is rarely seen in patients with prolactinoma, who are usually treated with much smaller doses of these drugs.[11]

Almost 85% of prolactinomas respond

well to medical therapy, and treatment can be gradually tapered with monitoring. When starting dopaminergic treatment it is important to warn women that restoration of fertility may be imminent (even before the first menstruation); contraception should be advised if pregnancy is not desired.

Removal of the tumour via transsphenoidal surgery should be considered if the prolactinoma is resistant to medical therapy, visual disturbance does not correct within a month or the patient is intolerant of dopamine agonists. In these situations, the patient should be managed in a neurosurgical unit specialising in pituitary surgery.

Treatment of drug-induced hyperprolactinaemia

For chronic asymptomatic drug-induced hyperprolactinaemia, hormonal replacement therapy (oestrogen or testosterone) should be considered where necessary to prevent the long-term effects of hypogonadism, including osteoporosis. For symptomatic patients, where possible the offending drug should be ceased or changed to an alternative agent without hyperprolactinaemic side effects. If this is not feasible or if fertility is desired, a dopamine agonist or, in the case of an antipsychotic-induced hyperprolactinaemia, the substitution of aripripazole (which rarely causes hyperprolactinaemia) could be considered, with close monitoring of the patient's mental state and tight collaboration between the primary care physician, psychiatrist and endocrinologist.[4]

Management of prolactinomas in pregnancy

The management of women with prolactinomas who are pregnant or wish to become pregnant can be challenging. Premenopausal women with macroprolactinomas should be offered preconception counselling and transsphenoidal surgery should be considered if appropriate.[12] About 2% of microprolactinomas and 30% of macroprolactinomas grow throughout pregnancy, and could compromise visual fields. As prolactin levels during pregnancy do not necessarily reflect tumour growth, there is no role for routine monitoring of prolactin during pregnancy. Women with macroadenomas should have regular formal visual field assessments each trimester during pregnancy. An MRI is indicated if new visual field abnormalities or headaches develop. As microprolactinomas rarely grow during pregnancy, formal visual field testing is not indicated in this setting.

Although the use of both bromocriptine and cabergoline have not been shown to increase fetal adverse events, dopamine agonists do cross the placental barrier.[13,14] It is therefore recommended that dopamine agonists be ceased in patients with microprolactinomas once pregnancy is confirmed.[2] Treatment of women with macroprolactinomas during pregnancy should be individualised. In this situation, dopamine agonists may be continued without interruption or stopped with close surveillance. If tumour growth is confirmed on MRI (without gadolinium) and is symptomatic, dopamine agonists can be recommenced. If medical therapy fails, options include delivery of the fetus if the pregnancy is sufficiently advanced, or removal of the tumour via transsphenoidal surgery. Women wishing to breastfeed should not be treated with dopamine agonists because the resulting fall in prolactin level will impair lactation.

Summary

Hyperprolactinaemia can present a diagnostic challenge. A detailed history targeted at symptoms and secondary causes is helpful in avoiding unnecessary investigations. Antipsychotic drug-induced hyperprolactinaemia is common, and close collaboration between the GP, psychiatrist and endocrinologist is required when caring for there patients. Management of prolactinomas in pregnancy can be challenging and often requires a specialised team. **ET**

References

1. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 273-288.
2. Casanueva FF, Molitch ME, Schlechte JA, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf) 2006; 65: 265-273.
3. Tyson JE, Hwang P, Guyda H, Friesen HG. Studies of prolactin secretion in human pregnancy. Am J Obstet Gynecol 1972; 113: 14-20.
4. Inder WJ, Castle D. Antipsychotic-induced hyperprolactinaemia. Aust N Z J Psychiatry 2011; 45: 830-837.
5. Bushe C, Yeomans D, Floyd T, Smith SM. Categorical prevalence and severity of hyperprolactinaemia in two UK cohorts of patients with severe mental illness during treatment with antipsychotics. J Psychopharmacol 2008; 22(2 Suppl): 56-62.
6. Rivera JL, Lal S, Ettigi P, Hontela S, Muller HF, Friesen HG. Effect of acute and chronic neuroleptic therapy on serum prolactin levels in men and women of different age groups. Clin Endocrinol (Oxf) 1976; 5: 273-282.
7. Radavelli-Bagatini S, Lhullier FL, Mallmann ES, Spritzer PM. Macroprolactinemia in women with hyperprolactinemia: a 10-year follow-up. Neuro Endocrinol Lett 2013; 34: 207-211.
8. Vallette-Kasic S, Morange-Ramos I, Selim A, et al. Macroprolactinemia revisited: a study on 106 patients. J Clin Endocrinol Metab 2002; 87: 581-588.
9. Schlechte J, Dolan K, Sherman B, Chapler F, Luciano A. The natural history of untreated hyperprolactinemia: a prospective analysis. J Clin Endocrinol Metab 1989; 68: 412-418.
10. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. Drug Saf 1996; 14: 228-238.
11. Auriemma RS, Pivonello R, Perone Y, et al. Safety of long-term treatment with cabergoline on cardiac valve disease in patients with prolactinomas. Eur J Endoocrinol 2013; 169: 359-366.
12. Ikeda H, Watanabe K, Tominaga T, Yoshimoto T. Transsphenoidal microsurgical results of female patients with prolactinomas. Clin Neurol Neurosurg 2013; 115: 1621-1625.
13. Krupp P, Monka C. Bromocriptine in pregnancy: safety aspects. Klin Wochenschr 1987; 65: 823-827.
14. Lebbe M, Hubinont C, Bernard P, Maiter D. Outcome of 100 pregnancies initiated under treatment with cabergoline in hyperprolactinaemic women. Clin Endocrinol (Oxf) 2010; 73: 236-242.

COMPETING INTERESTS: None.