

Hyperprolactinemia: A Systematic Review of Diagnosis and Management

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Abstract

Hyperprolactinemia is a common endocrine disorder that can be associated with significant morbidity. It can result from a number of causes, including use of medication, hypothyroidism and pituitary disorders. Depending on the cause and consequences of hyperprolactinemia, selected patients require treatment considering the underlying cause, age sex, and reproductive status. We describe a systematic review of hyperprolactinemia, including microadenomas and macroadenomas, in various clinical settings, with emphasis on newer diagnostic strategies and the role of various therapeutic options, including treatment with selective dopamine agonists. Through this review, we aimed to compare efficacy and adverse effects of medications, surgery and radiotherapy in the treatment of hyperprolactinemia.

Keywords: *Hyperprolactinemia; diagnostic strategies; therapeutic options.*

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Search strategy

We searched electronic databases, reviewed bibliographies of included articles and sought articles addressing hyperprolactinemia or prolactin-secreting tumours that were treated by dopamine agonists, surgery or radiotherapy, and which focused on outcomes from those treatments. We searched in MEDLINE, The New England Journal of Medicine, Bio Med Central Journal and Pub Med from March 2016 to June 2016. Search was limited to articles published in English.

Introduction

Prolactin is a pituitary-derived hormone that plays a pivotal role in a variety of reproductive functions. It is an essential factor for normal production of breast milk following childbirth. Furthermore, prolactin negatively modulates the secretion of pituitary hormones responsible for gonadal function, including luteinizing hormone and follicle-stimulating hormone. An excess of prolactin, or hyperprolactinemia, is a commonly encountered clinical condition.¹ It is the most common disorder of the hypothalamic-pituitary

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axis. Patients typically present with hypogonadism, infertility or, in the case of macroadenomas, symptoms related to mass effect (headache and visual field defects). Management of this condition depends on the cause and on the effects it has on the patient. Commonly cited indications for treatment of microprolactinomas include infertility, hypogonadism, prevention of bone loss and bothersome galactorrhea.^{2,3} The primary aim of treatment in patients with pituitary macroadenoma is to control the compressive effects of the tumour, including compression of optic chiasm, with a secondary goal to restore gonadal function. However, indications and modalities of treatment of hyperprolactinemia due to pituitary microadenomas are less well defined.² Medications in the form of dopamine agonists are the first line of treatment, with surgery and radiotherapy reserved for refractory and medication-intolerant patients.² Treatment with dopamine agonists can restore normal prolactin levels and gonadal function. However, the choice of which dopamine agonist is most efficacious and produces the least adverse effects is unclear. To provide evidence-based recommendations to practicing clinicians facing these common therapeutic dilemmas, in this review we summarize advances in our understanding of the clinical significance of hyperprolactinemia and its pathogenetic mechanisms, including the influence of concomitant medication use, effects with medications, surgery and radiotherapy in hyperprolactinemic patients.

Prevalence

An excess of prolactin above a reference laboratory's upper limits, or "biochemical hyperprolactinemia," can be identified in up to 10% of the population.¹ The prevalence of hyperprolactinemia ranges from 0.4% in an unselected adult population to as high as 9-17% in women with reproductive diseases. Its prevalence was found to be 5% in a family planning clinic.⁴ Women with oligomenorrhea, amenorrhea,

galactorrhea or infertility, and men with hypogonadism, impotence or infertility must have serum prolactin levels measured.¹ It is estimated at 9% among women with amenorrhea, 17% among women with polycystic ovary syndrome, 25% among women with galactorrhea and as high as 70% among women with amenorrhea and galactorrhea.² The prevalence is about 5% among men who present with impotence or infertility.¹

Prolactin molecule

Prolactin is a 23 kDa polypeptide hormone (198 amino acids) synthesized in the lactotroph cells of the anterior pituitary gland. Its secretion is pulsatile and increases with sleep, stress, food ingestion, pregnancy, chest wall stimulation, and trauma. Macroprolactinemia denotes the situation in which there is high level of the circulating 'big prolactin' molecules of 50 and 150 kDa (PRL-IgG complexes); which have high immunogenic properties, but poor or no biological effect. When these big variants circulate in large amounts, the condition is referred to as "macroprolactinemia", identified as hyperprolactinemia by the commonly used immune assays. Many commercial assays do not detect macroprolactin. Macroprolactin in the serum can be detected by Polyethylene glycol precipitation.⁴ In these situations even though high levels of circulating prolactin hormone are detected, the biological prolactin is normal and so there are no clinical symptoms, although a smaller proportion of patients with macroprolactinemia may have symptoms.⁵⁻⁸ It should be suspected when typical symptoms of hyperprolactinemia are absent.^{9,10} As macroprolactinemia is common in hyperprolactinemia, routine screening for macroprolactinemia could eliminate unnecessary diagnostic testing as well as treatment in cases of asymptomatic hyperprolactinemic subjects.⁶

Regulation of prolactin secretion

The main biological action of prolactin is inducing and maintaining lactation. However, it also exerts

metabolic effects, takes part in reproductive mammary development and stimulates immune responsiveness.^{11,12} Plenty of mediators of central, pituitary, and peripheral origin take part in regulating prolactin secretion through a direct or indirect effect on lactotroph cells.⁵ Like most anterior pituitary hormones, prolactin is under dual regulation by hypothalamic hormones delivered through the hypothalamic–pituitary portal circulation. The predominant signal is tonic inhibitory control of hypothalamic dopamine which traverses the portal venous system to act upon pituitary lactotroph D2 receptors. Other prolactin inhibiting factors include gamma amino butyric acid (GABA), somatostatin, acetylcholine, and norepinephrine. The second signal is stimulatory which is provided by the hypothalamic peptides, thyrotropin releasing hormone (TRH), vasoactive intestinal peptide (VIP), epidermal growth factor (EGF), and dopamine receptor antagonists.^{13,14} Actual serum prolactin level is the result of a complex balance between positive and negative stimuli derived from both external and endogenous environments. Serotonin physiologically mediates nocturnal surges and suckling-induced prolactin rises and is a potent modulator of prolactin secretion. Histamine inhibits the dopaminergic system and has a predominantly stimulatory effect. Estrogen stimulates pituitary lactotroph proliferation especially during pregnancy. However, during pregnancy lactation is inhibited by high levels of estrogen and progesterone. In the postpartum period, estrogen and progesterone rapidly decline which allows lactation to commence. During lactation and breastfeeding, ovulation may be suppressed due to the suppression of gonadotropins by prolactin, but may resume before menstruation resumes.¹⁵

Causes of hyperprolactinemia

Hyperprolactinemia can be physiological or pathological.

Etiology of hyperprolactinemia¹⁶

1. Physiologic hypersecretion

- Pregnancy
- Lactation
- Chest wall stimulation
- Sleep
- Stress

2. Idiopathic hyperprolactinemia (40%)

3. Hypothalamic-pituitary stalk damage

- Tumours: Craniopharyngioma, meningioma, dysgerminoma, dermoid cyst, pineal gland tumours
- Empty sella
- Lymphocytic hypophysitis
- Rathke's cyst
- Irradiation
- Trauma
- Pituitary stalk lesion
- Suprasellar surgery

4. Pituitary hypersecretion

- Prolactinoma
- Metastatic tumors
- Tuberculosis
- Sarcoidosis
- Histiocytosis
- Acromegaly
- Cushing disease
- Addison's disease

5. Systemic disorders

- Chronic renal failure
- Hypothyroidism
- Ectopic production
- Cirrhosis
- Pseudocyesis
- Epileptic seizures

6. Drug induced

- Dopamin receptor blocker
- Dopamin depleting agents
- Histamin receptor antagonists
- Stimulator of serotonergic pathway
- Estrogens, antiandrogens
- Serotonin reuptake inhibitors
- Calcium channel blockers

Physiological hyperprolactinemia is usually mild or moderate. During normal pregnancy, serum prolactin rises progressively to around 200-500 ng/mL. Many common medications cause mild hyperprolactinemia where prolactin levels rise up to less than 100 ng/mL. Pathological hyperprolactinemia can be caused by both hypothalamic-pituitary disease (prolactinomas) as well as non-hypothalamic-pituitary disease. The presence of a secondary cause and fluctuating degrees of hyperprolactinemia should raise the suspicion of a non tumorous cause. Prolactinomas account for 25-30% of functioning pituitary tumours and are the most frequent cause of chronic hyperprolactinemia.¹⁷ Prolactinomas are divided into two groups: (1) microadenomas (smaller than 10 mm) which are more common in premenopausal women, and (2) macroadenomas (10 mm or larger) which are more common in men and postmenopausal women. Pituitary adenomas co-secreting prolactin hormone also raise prolactin levels. Hypothalamus and pituitary stalk lesions such as nonfunctioning adenomas, gliomas, and craniopharyngiomas also result in prolactin elevation.¹⁸ The hyperprolactinemia of hypothyroidism is related to several mechanisms. In response to the hypothyroid state, there is a compensatory increase in the discharge of central hypothalamic thyrotropin releasing hormone which results in increased stimulation of prolactin secretion. Furthermore, prolactin elimination from the systemic circulation is reduced. There may be diffuse pituitary enlargement in primary hypothyroidism, which is reverseible with appropriate thyroid hormone replacement therapy.¹³

Clinical presentations

The clinical manifestations of prolactin excess (Table I) can be categorized into two groups, those that are due to prolactin excess and those representing the consequences of the resulting hypogonadism. The clinical manifestations of conditions vary significantly depending on the age and the sex of the patient and the magnitude of the

prolactin excess. Clinical presentation in women is more obvious and occurs earlier than in men. Women can present with symptoms of oligomenorrhea, amenorrhea, galactorrhea, decreased libido, infertility, and decreased bone mass.

Table I: Clinical presentations of hyperprolactinemia

Pre-menopausal women
<ul style="list-style-type: none"> Marked prolactin excess (>100 µg/L [normally <25 µg/L]) is commonly associated with hypogonadism,* galactorrhea and amenorrhea Moderate prolactin excess (51–75 µg/L) is associated with oligomenorrhea Mild prolactin excess (31–50 µg/L) is associated with short luteal phase, decreased libido and infertility Increased body weight may be associated with prolactin-secreting pituitary tumour¹⁹ Osteopenia is present mainly in people with associated hypogonadism Degree of bone loss is related to duration and severity of hypogonadism*²⁰
Men
<ul style="list-style-type: none"> Hyperprolactinemia presents with decreased libido, impotence, decreased sperm production, infertility, gynecomastia and, rarely, galactorrhea Impotence is unresponsive to testosterone treatment and is associated with decreased muscle mass, body hair and osteoporosis²¹

*The degree of hypogonadism is generally proportionate to the degree of prolactin elevation.

Diagnostic evaluation

Normal serum prolactin levels vary between 5 and 25 ng/mL in females although physiological and diurnal variations occur.²² Serum prolactin levels are higher in the afternoon than in the morning, and hence should preferably be measured in the morning. Hyperprolactinemia is usually defined as fasting levels of above 20 ng/mL in men and above 25 ng/mL in women¹² at least 2 hours after waking up. For evaluation of hyperprolactinemia, physiologic causes, including pregnancy in women of childbearing age should be considered. Interpretation of postpartum hyperprolactinemia depends on interval after delivery and status of lactation. Prolactin levels normalize within approximately 6 months after delivery in nursing mothers and within weeks in non-nursing mothers.²³ Elevations in prolactin levels due to stalk compression rarely exceed 150 µg per liter, but the use of antipsychotic agents or metoclopramide can increase prolactin levels to more than 200 µg per liter. Clinical manifestations of drug-induced hyperprolactinemia are similar to those of prolactinomas, except for tumour mass

effects.^{24,25} Most patients with prolactin levels more than 150 µg per liter have associated symptoms though the symptoms do not correlate well with prolactin levels. Macroprolactin, can cause spurious hyperprolactinemia because of delayed clearance.⁶ Unless the prolactin levels are markedly elevated, the investigation should be repeated before labeling the patient as hyperprolactinemic. Even one normal value should be considered as normal and an isolated raised one should be discarded as spurious. Other common conditions which must be excluded when considering raised prolactin levels are non-fasting sample, excessive exercise, history of drug intake, chest wall surgery or trauma, renal disease, cirrhosis, and seizure within 1-2 hours. These conditions usually cause prolactin elevation of <50 ng/mL. Plain radiographs have been replaced by cross-sectional imaging techniques such as CT scanning and MRI. Currently, MRI remains the method of choice for evaluation of pituitary tumors. Lesions that are iso-dense with surrounding structures may not be identified well with CT scan.²⁶ In patients with microadenomas pituitary function is typically normal. In amenorrhagic women, serum levels of follicle-stimulating hormone should be measured to rule out primary ovarian failure, and serum testosterone levels should be assessed in men with hyperprolactinemia; infertility (in patients desiring fertility) is an indication for therapy. Bone density should be evaluated in patients with hypogonadism. Patients with macroadenomas adjacent to the optic chiasm or compressing it require visual-field testing as visual compromise needs rapid treatment.²⁷ The hyperprolactinemia is referred to as “idiopathic” in cases where other causes of hyperprolactinemia have been excluded and no adenoma can be visualized with MRI (Figure 1).²⁸

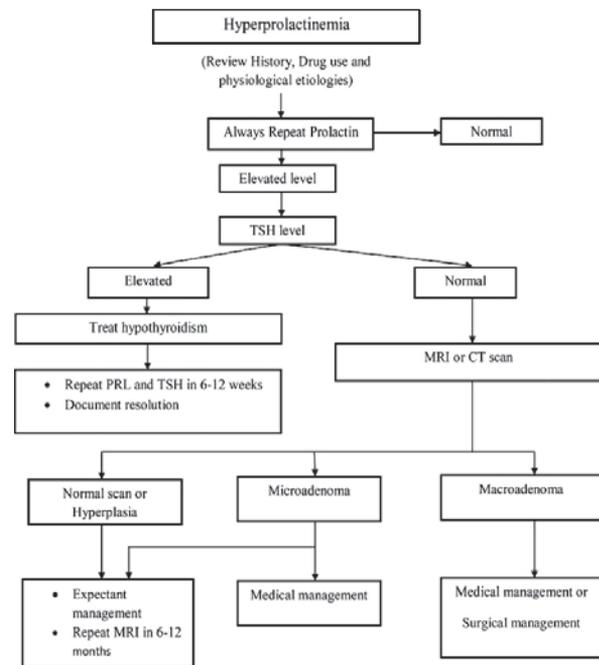


Fig 1: Overview of diagnosis and management of hyperprolactinemia

Management

The objective of hyperprolactinemia treatment is to correct the biochemical consequences of the hormonal excess.

Objectives of treatment of hyperprolactinemia²⁹

- Restoration and maintenance of normal gonadal function.
- Restoration of normal fertility.
- Prevention of osteoporosis.
- If a pituitary tumour is present:
 - Correction of visual or neurological abnormalities.
 - Reduction or removal of tumour mass.
 - Preservation of normal pituitary function.
 - Prevention of progression of pituitary or hypothalamic disease.

For management purpose, hyperprolactinemics can be broadly divided into three groups.

Management of hyperprolactinemia based on etiology³⁰

Group 1

Dopamine agonist is the mainstay of management in patients desiring fertility, with symptoms of estrogen deprivation or with galactorrhea.

Idiopathic hyperprolactinemia

Bromocriptine is the first option for this condition and is the drug used for the longest period of time. It is best to give as continuous therapy and prolactin levels reduce in about a week; ovulation and menstruation resumes in 4-8 weeks. Most popular method to confirm resumption of ovulatory function in oligo or amenorrhic women is weekly assessment of progesterone. Ovulation rates achieved by medical therapy with dopamine agonist alone are approximately 80-90% if there is no other cause for anovulation other than hyperprolactinemia.^{30,31} In the remaining women, exogenous gonadotropin stimulation can be added along with dopamine agonist to achieve ovulation.

Microadenoma with hyperprolactinemia

Medical management can be continued for 18 months to 6 or more years. Tumour expansion may occur during pregnancy in less than 2% of cases. No treatment is required in asymptomatic and very slow growing tumours which do not metastasize. Follow-up is mandatory with yearly estimation of prolactin levels, MRI, and visual fields. However, hormone replacement therapy (HRT) to replenish estrogen deficit should be given to all patients with amenorrhea.

Medical therapeutic options for the management of hyperprolactinemia

Medical therapy has traditionally involved agonists of the physiologic inhibitor of prolactin, dopamine (Table II).²⁸

Table II: Advantages, disadvantages and cost of various dopamine agonist agents available

Agent	Main advantages	Disadvantages	Typical dose
Bromocriptine	Longest track record	High frequency of gastrointestinal upset and sedation	2.5 mg/day
Cabergoline	High efficacy; less adverse events; indicated in cases of bromocriptine resistance or intolerance	Experience during pregnancy relatively limited	0.5 mg/week
Quinagolide	Pituitary selectivity; indicated in cases of bromocriptine resistance or intolerance	Daily use; limited access	0.075 mg/day
Pergolide	Occasionally beneficial in resistant cases	High frequency of adverse events	0.25 mg/day

Dopamine agonists have been in clinical use for many years and remain the cornerstone for therapy of prolactinomas.^{30,31} All (except quinagolide) are ergot alkaloids. Current recommendations advocate dopamine agonist therapy according to patient's requirement. Most commonly used dopamine agonists are bromocriptine and cabergoline. Others are lisuride, pergolide, quinagolide, terguride, and metergoline. Patients who are intolerant or fail to respond to one agent may do well with another.

Side effects associated with these drugs are nausea, vomiting, headache, constipation, dizziness, faintness, depression, postural hypotension, digital vasospasm, and nasal stuffiness. These symptoms are most likely to occur with initiation of treatment or when the dose is increased. One rare but notable side effect is neuropsychiatric symptoms which present as auditory hallucinations, delusion, and mood changes. It quickly resolves with discontinuation of the drug.³² Previous concerns about valvular heart disease with the use of these agents have largely been disproved by more recent reports.³³⁻³⁶

Bromocriptine is a lysergic acid derivative with a bromine substitute at position 2.³⁷ It is a strong dopamine agonist which binds to dopamine receptor and directly inhibits PRL secretion. It decreases prolactin synthesis, DNA synthesis, cell multiplication, and overall size of prolactinoma. It

has a short half-life and so it requires twice daily administration to maintain optimal suppression of prolactin levels. Intolerance to bromocriptine is common and it is the main indication of using an alternative drug. Tolerance is better when started with the lowest possible dose of 1.25 mg/day after dinner and then increased gradually by 1.25 mg each week until prolactin levels are normal or a dose of 2.5 mg twice daily is reached which is effective in 66% cases.³⁸ However, one can start with 7.5 mg/day dosage to save time and 90% will respond.

Another alternative is vaginal usage of the same drug which is well tolerated. Vaginal absorption is nearly complete and lower therapeutic dosing is possible as it avoids the liver first pass metabolism.³⁹ It is also available in a long acting form (depot-bromocriptine) for intramuscular injection and a slow release oral form.^{40,41} Bromocriptine has good treatment results but after discontinuation of treatment prolactin returns to elevated levels in 75% of patients and there is no clinical or laboratory assessment to predict long-term beneficial result.⁴²

Cabergoline shares many characteristics and adverse effects of bromocriptine but has a very long half-life allowing weekly dosing. This is more effective in suppressing prolactin and reducing tumour size.³⁰ The low rate of side effects and the weekly dosage make cabergoline a better choice for initial treatment. It can also be given vaginally if nausea occurs when taken orally.⁴³ A dose of 0.25 mg twice per week is usually adequate for hyperprolactinemia. Maximum dose that can be given is 1 mg twice a week.

Though both drugs have been found to be safe in pregnancy, the number of reports studying bromocriptine in pregnancy far exceeds that of cabergoline.³⁸

Group 2

Macroadenoma with hyperprolactinemia

The aim of the treatment is reduction in tumour mass along with the correction of the biochemical consequences of the hormonal excess including restoration of fertility, prevention of bone loss, and suppression of galactorrhea.³

Dopamine agonists are the first line of treatment with surgery and radiotherapy reserved for refractory and medication intolerant patients.⁴⁴ Macroprolactinomas regress with medication but the response is variable. Some show prompt shrinkage with low doses while others may require prolonged treatment with higher dosage. Reduction in tumour size can take place in several days to weeks.^{17,45}

Surgical removal of tumours associated with prolactin excess requires careful consideration of treatment objectives. It is indicated in patients with nonfunctional pituitary adenomas or other non-lactotroph adenomas associated with hyperprolactinemia and in patients in whom medical therapy has been unsuccessful or poorly tolerated.

Indications for pituitary surgery in patients with hyperprolactinemia²⁷

- Increasing tumour size despite optimal medical therapy.
- Pituitary apoplexy.
- Inability to tolerate dopamine agonist therapy.
- Dopamine agonist-resistant macroadenoma.
- Dopamine agonist-resistant microadenoma in a woman seeking fertility.
- If ovulation induction is not appropriate.
- Persistent chiasmal compression despite optimal medical therapy.

- In women seeking fertility, macroadenoma in close proximity to optic chiasm despite optimal medical therapy (pre pregnancy debulking recommended).
- Cerebrospinal fluid leak during administration of dopamine agonist.
- Macroadenoma in a patient with a psychiatric condition for which dopamine agonists are contraindicated.

Transnasal transsphenoidal microsurgical excision of prolactinoma is a widely chosen as it is a safe procedure. It is usually recommended for very large tumours, those with suprasellar and frontal extension, and visual impairment persisting after medications. Besides the usual surgical risks, hypopituitarism is a potential long-term effect of surgery and patients should be counseled properly beforehand. Unfortunately, relapse is common as excision is often incomplete but prolactin levels are lower than before. Prolactin levels should be monitored regularly. First after 4 weeks of starting therapy and then repeated after 3-6 months depending on symptom reversal. Repeat MRI is done after 6 months of normalization of prolactin levels. Further evaluation is done with 6 monthly prolactin levels. Scanning should be repeated only if symptoms reappear or exacerbate.

There are several possible explanations for the recurrence or persistence of hyperprolactinemia after surgery as listed below:

- a. Tumour may be multifocal in origin
- b. Complete resection is difficult because prolactin producing tumour looks like the surrounding normal pituitary
- c. There may be continuing abnormality of the hypothalamus giving rise to chronic stimulation of the lactotrophs and recurrent hyperplasia. However, pituitary tumours are monoclonal in origin as indicated by molecular biology studies.⁴⁶

External radiation therapy is only reserved for residual tumour in patients who have undergone surgery and there is incomplete resection. It is of very limited benefit since the response is typically quite modest and delayed.⁴⁷ There is also a risk of developing hypopituitarism. Bromocriptine has been used in patients where surgery or combined surgery and radiation therapy is failed.

Group 3

Around 40% patients with primary hypothyroidism have mild elevation of PRL levels that can be normalized by thyroid hormone replacement.¹⁶ Medications that can cause hyperprolactinemia should be discontinued for 48-72 hours if it is safe to do so and serum prolactin level repeated. Sometimes the causative agent is essential for the patient's health (for e.g., a psychotropic agent) but it may cause symptomatic hypogonadism. In these patients, treatment with a dopamine agonist should be avoided since it might compromise the effectiveness of the psychotropic drug and the patient should simply be treated with replacement of sex steroids.

About 30% patients with chronic renal failure and up to 80% patients on hemodialysis have raised prolactin levels. This is probably due to either decreased clearance or increased production of prolactin as a result of disordered hypothalamic regulation of prolactin secretion. Correction of the renal failure by transplantation results in normal PRL levels.

Management of hyperprolactinemia in pregnancy

The collaboration of various specialists, including an obstetrician, is required for the careful planning of pregnancy in women with hyperprolactinemia. Ideally, this should occur before conception, to permit a full assessment of the risks and benefits of dopamine agonist therapy during pregnancy.

Management of hyperprolactinemia in pregnancy^{48,49}

There is no evidence of increased teratogenicity associated with bromocriptine or cabergoline use during pregnancy

- Similarly, there is no evidence of increased risk of abortion or multiple pregnancies with dopamine agonist use
- If the tumour size before pregnancy is <10 mm, dopamine agonist therapy is stopped during pregnancy because the risk of tumour expansion is low
- If the tumour size before pregnancy is ≥ 10 mm before pregnancy, bromocriptine use is advised during pregnancy to avoid significant tumour expansion
- All patients should be evaluated every 2 months during pregnancy
- Formal visual field testing is indicated in patients with symptoms or a history of macroadenoma
- If visual field defects develop despite dopamine agonist treatment, early delivery or pituitary surgery should be considered

In most women with prolactinomas, hyperprolactinemia persists after delivery; although spontaneous resumption of menses and remission of hyperprolactinemia can occur.⁵⁰ Prolactin levels and tumour size typically remain stable during nursing. In patients with a macroadenoma requiring treatment after delivery, dopamine agonists are administered, and therefore, nursing is not possible.

Monitoring and Follow-up

Biochemical and clinical improvements in response to dopamine agonist therapy are readily apparent in most patients. In addition, tumour shrinkage can be expected in about 80% of macroadenomas.⁵⁰ However, a major drawback

of medical therapy is the potential need for lifelong treatment. The Pituitary Society has published guidelines for the diagnosis and management of prolactinomas.² These guidelines suggest that discontinuation of dopamine agonist therapy can be attempted in selected patients who have had normal prolactin levels for at least 2 years and minimal residual tumour volume. However, such patients need to be followed carefully, since tumour recurrence is common, particularly in the case of macroadenomas. Unless there is evidence of growth of a prolactinoma or related symptoms, such as headache, there is no indication to continue dopamine agonist therapy after menopause.⁴² After discontinuation of treatment, regular monitoring of clinical symptoms and prolactin levels is recommended. Given the propensity for early recurrence, prolactin levels should be measured monthly for the first 3 months and every 6 months thereafter.

Conclusion

It is important to establish the pathological relevance of hyperprolactinemia before commencing treatment for this endocrinological disorder. Pituitary function should be tested in patients with macroadenomas, and visual-field testing is mandatory when tumours are adjacent to the optic chiasm. Although microadenomas may or may not require therapy, macroadenomas do require therapy. Most cases of true hyperprolactinemia are associated with amenorrhea or hormone deprivation in premenopausal women and can be managed by dopamine agonist or hormone replacement therapy respectively. If a normal prolactin level is maintained and if there is minimal residual tumour during medical therapy, available data suggest that it may be reasonable to discontinue therapy after 2 years, although recurrence rates are high and close follow-up is necessary.

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