Growth-hormone and prolactin excess

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The treatment of acromegaly and hyperprolactinaemia has been improved by the availability of effective and well-tolerated slow-release somatostatin analogues and dopamine agonists with long-lasting activity, such as cabergoline. The use of these drugs has extended the possibility of treatment to patients who would have responded poorly to the previously available compounds, such as octreotide or bromocriptine, and to those who were intolerant to pharmacotherapy. Moreover, the improvement in the management of acromegaly has enabled the reversal, at least partly, of cardiomyopathy and sleep apnoea, two important risk factors for morbidity and mortality in these patients.

Growth hormone (GH) and prolactin are polypeptide hormones (191 and 199 aminoacids, respectively) produced by specific populations of pituitary cells. The two hormones have 16% structural homology. The clinical consequences of excess production, however, differ substantially: acromegaly from excess of GH is a severe systemic disease that shortens life-expectancy owing to respiratory, metabolic, and cardiovascular complications and malignant disorders;1,2 hyperprolactinaemia from excess of prolactin leads to infertility and gonadal and sexual dysfunction.3 In most patients with prolactin or GH excess, the cause is a pituitary adenoma.4 The availability of effective and well-tolerated somatostatin and dopamine analogues has changed the therapeutic approach to these patients.

GH concentrations can be measured either in µg/L or in mU/L, according to the assay used. We use µg/L. The equivalent ratio of mU/L to µg/L was 2 (2 mU/L=1 µg/L) before January, 1997, and 3 thereafter.

GH excess
Epidemiology

The prevalence of GH-secreting adenomas is 50–80 cases per million per year.1,2 In less than 2% of patients, excessive GH secretion may be the consequence of a hypothalamic or ectopic tumour (gangliocytoma, bronchial, or pancreatic) that produces GH-releasing hormone (GHRH); such tumours lead to somatotroph hyperplasia or a well-defined adenoma. The ectopic secretion of GH itself is even rarer.1

Diagnosis

The clinical features of acromegaly develop insidiously and progressively over many years. The average delay between onset of symptoms and diagnosis is about 6 years.3 In adults, acromegaly due to chronic GH hypersecretion is characterised by local bone overgrowth. In children and adolescents, acromegaly leads to gigantism because the associated secondary hypogonadism delays epiphyseal closure, which allows continued acceleration of linear growth. Other features include fatigue, hyperhydrosis, goitre, osteoarthritis, carpal tunnel syndrome, and other peripheral neuropathies.4–5 An increased risk of large-bowel polyps and cancer has also been reported in large series of patients with acromegaly; thus, screening by colonoscopy is needed.6–8 Moreover, central or obstructive sleep apnoea and cardiomyopathy are important risk factors for morbidity and mortality; both improve after suppression of GH and insulin-like growth factor I (IGF-I).9–10 Menstrual disorders and decreased libido or potency are related to anterior-pituitary insufficiency but also to cosecretion of prolactin in 30–40% of patients9,3–5.

Acromegaly and gigantism are generally clinically clear and can be readily confirmed by measurement of GH concentrations, which in over 90% of patients are more than 10 µg/L.1 Since secretion of GH is pulsatile, single measurements are not reliable. The oral glucose tolerance test is the simplest and most specific dynamic test to diagnose and assess the cure of acromegaly. In healthy people, the oral glucose tolerance test (75–100 g glucose) suppresses GH concentrations to less than 2 µg/L after 2 h, whereas in patients with acromegaly such suppression does not occur, and a paradoxical GH increase is commonly seen.1 Measurement of plasma IGF-I concentrations in one sample was proposed to replace the oral glucose tolerance test7 because IGF-I concentrations are stable and are a function of the integrated 24 h GH concentration.1 Assays of circulating IGF-I-binding protein 3 (IGF-BP3) and free IGF-I do not, however, have a higher diagnostic sensitivity than the measurement of total IGF-I.10,11 The greater sensitivity of the GH assay facilitates the distinction of acromegalic patients and healthy people, as is shown by use of the chemiluminescence GH assay.11 This assay may be useful to show the persistence of GH hypersecretion after surgery or during medical therapy.

The last step is to investigate whether an anterior pituitary tumour is present. The refinement of imaging techniques, including high-field magnetic resonance imaging (which produces high signal-to-noise ratios and high spatial resolutions), with high temporal resolution studies has improved the detection of small pituitary or ectopic tumours.

Management

There are five objectives of treatment in acromegaly: removal of the tumour with resolution of its mass effects, preservation of normal residual pituitary function, and...
prevention of recurrences; restoration of normal basal and stimulated GH secretion; relief from symptoms directly caused by GH excess; prevention of disabling long-term consequences (progressive disfigurement, bone expansion, osteoarthrosis, and cardiomyopathy) and risk factors for vascular damage (hypertension, insulin resistance, diabetes mellitus, and lipid abnormalities); and reversal of the poor long-term outcome. Variables that remain unknown are the degree of GH suppression needed to achieve treatment success (especially for the last two objectives), whether the adverse long-term outlook can be reversed by any treatment, and what is the best treatment for suppression of GH, IGF-I, or both.

The currently available treatment options for acromegaly include surgery, irradiation, and pharmacological suppression of GH concentrations by dopamine agonists or somatostatin analogues. The clinical assessment of treatment efficacy for these approaches, alone or combined, is difficult because moderate improvement may occur even with partial decreases in GH concentrations, whereas some residual disease effects may persist once GH concentrations have been lowered. There is, however, no consensus on the criteria defining the cure of acromegaly. The most widely accepted criteria include mean serum GH concentrations of less than 2.5 µg/L (average of at least three to five samples), GH concentrations after suppression with the oral glucose tolerance test of less than 2.0 µg/L, and normal plasma IGF-I concentrations. One preliminary retrospective study reported that normal survival was attained in patients with GH concentrations after treatment of less than 2.5 µg/L, but not in those with higher concentrations. Another study confirmed that the lower the serum GH concentrations after treatment, the lower the mortality. Cure should be followed by restoration of physiological patterns of GH secretion, but there are still questions about whether this approach really offers any practical advantage over basal GH and IGF-I values in routine management of patients with acromegaly. Therefore, although strict definition of biochemical cure may not be necessary, what is essential is to define the GH and IGF-I values that reliably achieve clinical remission and decrease or eliminate long-term morbidity and mortality. This idea has led to the concept of safe values, which is a more realistic concept in clinical practice. After any treatment, basal GH concentrations should be less than 2.5 µg/L or 1.7 µg/L, depending on the GH assay (ie, equivalent to 5 mU/L) with normal IGF-I concentrations for age.

Other pituitary-hormone deficiencies that may be caused by the tumour or its treatment must be treated in the same way as in other types of pituitary tumours.

Surgery

Trans-sphenoidal adenomectomy is the first treatment for GH-secreting tumours. Among 224 consecutive patients, this operation achieved endocrine remission in 72% of microadenomas, 50% of macroadenomas, and only 17% of giant adenomas. IGF-I concentrations within the normal range and GH concentrations of less than 3.0 µg/L or 1.6 µg/L were achieved in 59% and 42%, respectively, of unselected patients. In microadenomas, surgery was successful in 61% of patients. Surgery relieves the compression on adjacent structures such as the optic chiasm and the ventricles. Complications, such as leakage of cerebrospinal fluid, arachnoiditis, and temporary or permanent diabetes insipidus, are rare. Pituitary failure is, however, reported in about 20–30% of patients with macroadenomas. Treatment with octreotide, a long-acting somatostatin analogue, has been reported to induce tumour shrinkage; Fahlbush and colleagues therefore suggested this drug as a preoperative treatment to improve surgical outcome. A controlled study did not support this hypothesis, but treatment for 3–6 months before surgery has been reported to improve metabolic and haemodynamic variables and to decrease substantially the duration of hospital stays for patients with acromegaly. To refine pituitary surgery, a one-nostril endoscopic endonasal trans-sphenoidal procedure has been proposed to decrease damage to the nose and sphenoid sinus and to improve the management of the pituitary fossa.

Radiation therapy

This treatment should be considered for patients with contraindications to surgery or whose operation has failed. Tumour response to radiotherapy is slow and up to 5 years may elapse before a clinically significant decrease in GH is achieved. Serum GH concentrations fall exponentially after irradiation, reportedly reaching less than 5 µg/L in 40–80% of patients. Decreases of GH concentrations to less than 2.5 µg/L occur in fewer patients, and achievement of normal IGF-I concentrations is rare. The risks of complications such as optic-nerve damage, cranial-nerve palsy, impaired memory, lethargy, and local tissue necrosis have been decreased through improved, precise isocentric simulators and accurate dosing techniques. Radiation damage to the surrounding normal pituitary tissue, however, leads to hypopituitarism in most patients within 10 years. The risk of malignant disorders of the central nervous system developing after radiotherapy should be considered. Brada and colleagues reported that 2.4% of patients developed a second tumour, which suggests an actuarial risk of 1.3% at 10 years and 1.9% at 20 years, but no increased incidence of second tumours has been reported. γ-Knife radiosurgery is currently being investigated, but it seems not to improve the efficacy of conventional radiotherapy, and its long-term side-effects are unknown.

Pharmacotherapy

Dopamine agonists and somatostatin analogues are used alone or in combination in selected patients to treat acromegaly. In healthy people, dopamine agonists stimulate GH secretion by a mechanism mediated through the central nervous system. By contrast, in about 50% of patients with acromegaly, dopamine agonists inhibit GH secretion, presumably through the stimulation of D2 receptors. Dopamine agonists are primarily effective in GH-secreting tumours that also secrete prolactin or that show immunostaining for prolactin. All dopamine agonists, except quinagolide, are ergoline-derived compounds and are given orally. The frequency of administration varies from every 8–12 h (bromocriptine) to once weekly (cabergoline). In a collection of 28 series including more than 500 patients with acromegaly, bromocriptine lowered GH concentrations to less than 10 µg/L in 50% of cases, but to less than 5 µg/L in only 10–20%. Symptoms improved in up to 70% of patients but tumour shrinkage occurred in only
10–15%. Side-effects, such as nausea, vomiting, hypotension, nasal congestion, and depression, in most patients can be prevented if lower doses are used at first. Since high doses are needed for therapeutic efficacy, however, side-effects are commonly a limiting factor. The published evidence does not suggest that any other dopamine agonist is more effective than bromocriptine or has different therapeutic/toxic ratios. Variable results have been reported with two selective D2-receptor agonists: cabergoline and quinagolide.31,32

Somatostatin suppresses GH concentrations in healthy people and patients with acromegaly, but its potential application in treating GH excess is limited by its short half-life (1–3 min). Octreotide is a long-acting synthetic somatostatin analogue with a half-life of 80–100 min. In several studies, octreotide lowered GH in 94% and achieved normal IGF-I concentrations in about 70% of patients.1,2,35 A combined analysis of 466 patients treated worldwide showed that octreotide administration lowered GH concentrations to less than 2·5 µg/L in 29·2% of patients, achieved normal IGF-I concentrations in 39·9%, and achieved tumour shrinkage (>20% decrease in size) in 38·6% (table 1). Soon after administration of octreotide, clinical signs and symptoms, especially headache, hyperhidrosis, and joint pain, are relieved. Octreotide treatment improves obstructive and central sleep apnoea (decrease in the number of apnoeic episodes and degree of blood oxygen desaturation) and significantly decreases left-ventricular mass (without improving cardiac performance), prostate size, and joint thickness. Despite the wide range of positive effects of this treatment, including the evidence that tachyphylaxis does not occur even after 10 years of treatment, octreotide is still reserved for patients whose surgery fails or for control of symptoms during radiotherapy. The main reasons for the limited use of octreotide are its cost, the need for multiple daily injections, and its side-effects, especially on the gastrointestinal tract. Gallbladder abnormalities (sediment, sludge, microtholithiasis, and gallstones) occur in about 20% of patients and are associated with low morbidity. Generally, these effects disappear spontaneously or after treatment with ursodeoxycholic acid in the absence of signs of symptomatic cholelithiasis or cholecystitis. In patients with symptomatic cholelithiasis, withdrawal of octreotide treatment is advisable.

Depot preparations have been developed to avoid the need for three injections of octreotide per day. Such preparations were developed to allow injections only once or twice every month and to achieve stable tumour concentrations of the drug, good clinical control of symptoms and signs, sustained GH and IGF-I suppression, and good compliance. At present, two depot preparations of long-acting somatostatin analogues are available in several European countries. The first is a slow-release form of the cyclic octapeptide, lanreotide. Studies have reported that slow-release lanreotide is effective in patients previously responsive to octreotide but is better tolerated and improves compliance.13,41 13 of 22 acromegalic patients treated with slow-release lanreotide for 3 years had normal GH and IGF-I concentrations after treatment. Nine of these patients, however, had to increase the injection frequency to one every 10 days for optimum control. Loose stools, nausea, abdominal pain, or a combination of symptoms were reported by 11 of the patients for the first 2 days after injection, and four patients developed new gallstones.40

The second depot preparation is the slow-release form of octreotide incorporated in microspheres of a biodegradable polymer, poly-(DL-lactide-co-glycolide) (SLD). Decreases in GH concentrations to below 5 µg/L were recorded in 86–100%, to below 2 µg/L in 39–75%, and to below 1 µg/L in 24–40% in different series of patients with acromegaly including a total number of 175 cases. Normal plasma IGF-I concentrations were achieved in 65–95% after the last injection.42 Tumour shrinkage by more than 20% was recorded in 71–86% of patients. After up to 34 months of therapy, there was no evidence of tachyphylaxis. This slow-release octreotide preparation was well tolerated; up to 50% of patients experienced mild to moderate side-effects but they were of short duration and generally subsided with continued drug administration.43 The rate of gallbladder abnormalities was higher among patients who had previously undergone long-term treatment with subcutaneous octreotide than among those who had not.43

<table>
<thead>
<tr>
<th>Study</th>
<th>Number with past treatment</th>
<th>Number of cases</th>
<th>GH &lt;5 µg/L (10 µM/L)</th>
<th>GH &lt;2·5 µg/L (5 µM/L)</th>
<th>Normal IGF-I</th>
<th>Tumour shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>466</td>
<td>232</td>
<td>63/216</td>
<td>144/361</td>
<td>54/140</td>
<td></td>
</tr>
</tbody>
</table>

NA=not assessed.

Table 1: Effects of octreotide therapy
present. The results of trials of somatotroph-specific cytotoxic agents (targeted by an agonist or antibody to the GH-releasing-hormone receptor) for selective elimination of residual tumour cells, and GH-receptor antagonists to block the peripheral effects of GH will soon be available.

**Prolactin excess**

**Epidemiology**

The aetiology of pathological hyperprolactinaemia is diverse (panel). Any process interfering with dopamine synthesis, its transport to the pituitary gland, or its action at lactotroph dopamine receptors can lead to hyperprolactinaemia.\(^1\) Once drugs are excluded, microprolactinomas (<10 mm) or macroprolactinomas (>10 mm) are the most common causes of hyperprolactinaemia. The prevalence of prolactinomas is unknown; in necropsy series, the rate varies between 23% and 27% for microadenomas.\(^44,45\) Macroadenomas are less common than microadenomas, and occur more often in men than in women. This finding is probably related to duration of disease and the gradual development of symptoms, which primarily involve sexual and gonadal function in both sexes. Natural-history studies suggest, however, that more than 90% of microadenomas remain small and only a small proportion become macroadenomas.\(^46\) Macroadenomas may, therefore, be biologically different from microadenomas.

**Diagnosis**

Secretion of prolactin is pulsatile, and at least three measurements are needed for the diagnosis to be made correctly. In rare cases, patients have an increased amount of high-molecular-weight prolactin (150–170 kDa), but the clinical implications of hyperprolactinaemia due to this molecular form of prolactin are still uncertain. During the past 20 years, many pharmacological tests have been used to distinguish tumoral from non-tumoral hyperprolactinaemia, with controversial results.\(^7\) These tests are no longer used, because of the poor reliability in differential diagnosis. Generally, prolactin concentrations are correlated with tumour size.\(^1\) Neuroradiological studies are mandatory to complete the diagnostic protocol.

**Management**

The objectives of the treatment of hyperprolactinaemia are: suppression of excessive hormone secretion and its clinical consequences (particularly infertility, sexual dysfunction, and osteoporosis); tumour removal and relief of any disturbance in vision and cranial-nerve function; preservation of the residual pituitary function; and, if possible, prevention of disease recurrence or progression. Before medical treatment became available, therapy consisted of surgical removal with or without pituitary irradiation. Since the early 1970s, surgery and radiotherapy have been progressively replaced by dopamine agonists. There is controversy over the primary therapy (medical or surgical) of tumour-related hyperprolactinaemia, and over the treatment of women who wish to become pregnant.

**Surgery**

For microprolactinomas, trans-sphenoidal microsurgical resection restores normal prolactin concentrations and normal menses and eliminates galactorrhoea in 85–90% of patients.\(^3,47\) Success rates are higher in patients who have prolactin concentrations of less than 200 mg/L and who have had amenorrhoea for less than 5 years.\(^3\) The risks of complications and hypopituitarism are small. Recurrence rates vary substantially between different series.\(^3,47–50\) In one report,\(^3\) 71% of patients with microprolactinoma were initially cured by means of surgery with a subsequent recurrence rate of 17% and a long-term cure rate of 59%. In another series,\(^48\) the long-term cure rate was 74% (initial cure in 90%, recurrence rate 16%). For macroprolactinomas, trans-sphenoidal surgery was less successful; 32% of patients were cured initially, with a 19% recurrence rate and a long-term cure rate of only 26%.\(^48\) Long-term recurrence rates of 33-3% and 12-0% were reported in macroprolactinomas.\(^3,49,50\) Despite these disappointing results, some centres still recommend surgery to debulk the tumour to protect vital structures such as the optic chiasm.\(^3\) Rapid tumour shrinkage is, however, achieved with dopamine-agonist treatment in most patients.

**Radiotherapy**

Radiotherapy is applied in large invasive macroprolactinomas when medical treatment fails to suppress prolactin concentrations or induce tumour shrinkage. Radiotherapy gradually decreases prolactin concentrations, generally reaching normal values within 10 years.\(^51\) Radiotherapy prevents further growth of the tumour but is less effective in promoting a prompt

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**Aetiology of hyperprolactinaemia**

**Hypothalamic disorders**

Tumours—craniopharyngioma, germinoma, third-ventricle tumour, cyst, glioma, hamartoma, metastasis

Infiltrative diseases—sarcoidosis, tuberculosis, Langerhans-cell histiocytosis

Pseudotumour cerebri

Cranial irradiation

**Pituitary disorders**

Microprolactinoma or macroprolactinoma

Acromegaly

Cushing’s disease

Pituitary-stalk section

Empty-sella syndrome

Pseudoprolactinomas—non-functioning adenoma, meningioma, intrasellar germinoma, metastasis that may produce functional stalk section

Infiltrative diseases—giant-cell granuloma, sarcoidosis

**Drugs**

Neuroleptics—perphenazine, fluphenazine, thorazine, promazine, trifluoperazine, haloperidol, chlorpromazine, dopamine-receptor blockers (such as metoclopramide, sulpiride, domperidone, cimetidine)

Antidepressants—amoxapine, imipramine, amitriptyline

Antihypertensives—\(\alpha\)-methyldopa, reserpine

Oestrogens

Opioids

Phenytoin or sodium valproate

**Primary hypothyroidism**

**Chronic renal failure**

**Cirrhosis**

**Neurogenic**

Chest wall or spinal-cord lesions, breast stimulation

**Stress physical or psychological**

**Idiopathic**

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**Pharmacological tests**

Antihypertensives—\(\alpha\)-methyldopa, reserpine

Opioids

Phenytoin or sodium valproate

**Neuroleptics**—perphenazine, fluphenazine, thorazine, promazine, trifluoperazine, haloperidol, chlorpromazine, dopamine-receptor blockers (such as metoclopramide, sulpiride, domperidone, cimetidine)

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Antihypertensives—\(\alpha\)-methyldopa, reserpine

Oestrogens

Opioids

Phenytoin or sodium valproate
decrease in prolactin concentrations.\textsuperscript{52} Radiobiological damage rarely occurs as long as a linear accelerator is used, therapy is delivered through three fields, and a fractionated dose of less than 2 Gy daily is delivered to a total dose of 45 Gy.\textsuperscript{53} Owing to the high success rate of pharmacotherapy, however, radiotherapy is rarely applied to prolactinomas.

\textbf{Pharmacotherapy}

For more than 20 years dopamine agonists, especially bromocriptine, but also pergolide and lisuride, have been the standard drugs for hyperprolactinaemia. They inhibit prolactin synthesis and secretion and decrease cellular DNA synthesis and tumour growth. Restoration of normal prolactin concentrations and tumour shrinkage after bromocriptine 2.5–5.0 mg daily are observed in about 80\% of prolactinomas.\textsuperscript{1,2,5} Side-effects (nausea, dizziness, and orthostatic hypotension) are limiting factors in continuing the treatment in 5–10\% of patients.\textsuperscript{1,2,5} 1–3\% of patients are reported to have developed psychosis.\textsuperscript{5} Complete or partial resistance to bromocriptine treatment is seen in a few patients (about 5\%). Such resistance is thought to be the consequence of abnormalities of the dopamine D2 receptor or post-receptor abnormalities.\textsuperscript{51} Quinagolide and cabergoline, two selective D2 receptor agonists, are effective in some resistant patients.\textsuperscript{55,56}

There is evidence that weekly administration of cabergoline is more effective and better tolerated than daily bromocriptine. In a randomised multicentre study of 459 women with hyperprolactinaemia, stable normal prolactin concentrations were achieved in 83\% of patients treated with cabergoline compared with 50\% of those treated with bromocriptine.\textsuperscript{52} Ovarian cycles or pregnancies were recorded in 72\% of women treated with cabergoline and in 52\% of those treated with bromocriptine.\textsuperscript{57} A further advantage is that side-effects were substantially less frequent, less severe, and shorter-lived (especially nausea and vomiting) with cabergoline than with bromocriptine.\textsuperscript{57} Moreover, cabergoline treatment at weekly low doses induced substantial tumour shrinkage.\textsuperscript{54,60}

To overcome poor tolerability of the oral formulation of bromocriptine, a depot intramuscular injectable preparation of cabergoline was developed. This formulation (given at doses of 50–150 mg every 4 weeks) was well tolerated,\textsuperscript{61} and initial side-effects could be prevented by administration of oral prednisone.\textsuperscript{62} This preparation seems to be especially useful for patients who previously experienced severe side-effects from oral therapy.\textsuperscript{53} Striking tumour shrinkage and consequent improvement of visual field were reported as early as 1–2 weeks from the first injection.\textsuperscript{41} To decrease gastrointestinal side-effects, intravaginal administration of bromocriptine was also tested with partial efficacy.\textsuperscript{45} Bromocriptine, cabergoline, and quinagolide have not been associated with any adverse effect on fetal development or pregnancy outcome (table 2). Experience with bromocriptine is, however, wider than that with the other two drugs. Therefore, for women who want to retain fertility, this drug remains the treatment of choice in most centres, whereas cabergoline and quinagolide are acceptable second-line drugs in patients intolerant or resistant to bromocriptine. Current opinion is to stop treatment if patients with microprolactinomas become pregnant, whereas continued treatment is preferable in those with macroprolactinomas to avoid the risk of tumour enlargement. In this case sellar magnetic resonance imaging is essential.

In women with microprolactinomas who do not want to retain fertility, oestrogen-replacement therapy is an option, since it does not increase tumour size.\textsuperscript{44} The possibility of tumour enlargement in patients with oestrogen-sensitive tumours should, however, be monitored by serial magnetic resonance imaging.

Much information is available on the recovery of menses and fertility in hyperprolactinaemic women, but there are few data for male patients. Impairment of gonadal function in men seems to be a functional modification and can be reversed by long-term quinagolide, bromocriptine, or cabergoline.\textsuperscript{55,66} Restoration of normal sperm morphology and function occurred faster with cabergoline than with bromocriptine treatment.\textsuperscript{46} In patients with large tumours, irreversible damage to the pituitary gonadotrophs can occur.

In both sexes osteoporosis can occur with hyperprolactinaemia; this disorder has been attributed to the concomitant hypogonadism rather than to hyperprolactinaemia per se, since the extent of bone loss is strictly related to the duration of hypogonadism.\textsuperscript{53,66} Treatment with dopamine agonists restores gonadal function and increases vertebral bone-mineral density in most hyperprolactinaemic women.\textsuperscript{57} Few data are available in men, but one study showed that 18 months of treatment with bromocriptine, quinagolide, or cabergoline did not completely eliminate osteopenia/osteoporosis in hyperprolactinaemic men, and a longer period of treatment may be necessary.\textsuperscript{59}

\textbf{Conclusions}

Medical treatment with dopamine agonists is the most appropriate first-line treatment for macroprolactinomas except in poorly responsive or resistant patients. Dopamine agonists shrink tumours and can lead to tumour disappearance.\textsuperscript{51,56–60} Visual-field defects substantially improve in most patients, in many cases without need for surgical tumour debulking. Theoretically, pharmacotherapy should be continued indefinitely, but the dose can be decreased over the years.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Pregnancy outcome} & \textbf{Number of pregnancies with outcome} & \textbf{Bromocriptine} & \textbf{Cabergoline} & \textbf{Quinagolide} \\
& & (n=1410) & (n=199) & (n=176) \\
\hline
\textbf{Normal birth} & 1236 (87.7\%) & 136 (68.3\%) & 128 (72.7\%) \\
\hline
\textbf{Multiple birth} & & & & \\
Twins & 28 (2.0\%) & - & - \\
Triplets & 3 (0.2\%) & - & - \\
\hline
\textbf{Abnormalities at birth} & & & & \\
5 (0.4\%) & 7 (3.5\%) & - & - \\
\hline
\textbf{Miscarriage} & 157 (11.1\%) & 23 (11.6\%) & 24 (14.0\%) \\
\hline
\textbf{Extratruine pregnancy} & 12 (0.8\%) & 1 (0.5\%) & 1 (0.5\%) \\
\hline
\textbf{Termination of pregnancy} & & & & \\
Total & 59 (4.1\%) & 4 (2.0\%) & 14 (7.9\%) \\
Major malformations & 20 & 3 & - \\
Minor malformations & 36 & - & - \\
Hydraliform mole & 3 & - & - \\
Chromosomal abnormalities & - & 3 & - \\
Other & - & - & 10 \\
\hline
\textbf{Fetal death in utero} & - & 1 (0.5\%) & - \\
\hline
\end{tabular}
\caption{Pregnancy outcome in women treated with bromocriptine, cabergoline, or quinagolide}
\end{table}

in 10–20% of patients drug discontinuation does not lead to recurrence of hyperprolactinaemia or rapid tumour regrowth. In microprolactinomas, the treatment strategy could be reconsidered on the basis of the high cure rate of trans-sphenoidal adenomectomy, which might be further improved by use of new endoscopic techniques. Surgery should also be recommended for patients who are severely intolerant to dopamine agonists.

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References


Further reading

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Further reading

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