Contemporary management of prolactinomas

JAMES K. LIU, M.D., AND WILLIAM T. COULDWELL, M.D., PH.D.

Department of Neurosurgery, University of Utah School of Medicine, Salt Lake City, Utah

Prolactin-secreting pituitary adenomas—prolactinomas—are the most common type of functional pituitary tumor. Treatment of hyperprolactinemia is indicated because of the consequences of infertility, gonadal dysfunction, and osteoporosis. Making the correct diagnosis is important because the first line of therapy is medical management with dopamine agonists. Medical therapy is effective in normalizing prolactin levels in more than 90% of patients, but long-term treatment may be required in some patients. Transsphenoidal surgery is usually indicated in those patients in whom medical therapy fails or cannot be tolerated, or in patients who harbor microprolactinomas. In experienced hands, a hormonal and oncological cure can be achieved in more than 90% of patients after transsphenoidal removal of microprolactinomas with minimal risks. Thus, surgery may be an option for microprolactinomas in a young patient who desires restoration of fertility and avoidance of long-term medical therapy. The authors review the diagnosis and management of prolactinomas, including medical therapy, surgical therapy, and stereotactic radiosurgery.

KEY WORDS • prolactinoma • pituitary tumor • transsphenoidal approach • bromocriptine • cabergoline

Prolactin-secreting adenomas (prolactinomas) account for approximately 30% of pituitary adenomas and 50 to 60% of functional pituitary tumors.¹⁴⁹ They are the most common type of functioning pituitary tumor and are second in frequency to nonfunctioning adenomas in overall incidence.¹⁴⁵ One published estimate of their prevalence is 100 cases per 1 million persons;²¹ however, based on the results of a recent metaanalysis of the literature, one may infer that this may be a gross underdiagnosis. According to this metaanalysis, MR imaging and histological examinations demonstrate that approximately 17% of patients harbor a microadenoma; one third of these tumors stain positive for prolactin, which indicates the potential for secretion in a large number of incidental adenomas (W. T. Couldwell, unpublished observations). Prolactinomas commonly cause reproductive and sexual dysfunction; macroadenomas can cause local mass effect, resulting in visual compromise, cavernous sinus compression, and hypopituitarism.^{91,92,95,98,145} The objectives for treatment of hyperprolactinemia due to prolactinomas are to normalize the hyperprolactinemic state, preserve residual pituitary function, reduce tumor mass, and prevent disease recurrence.

Our understanding of the pathogenesis, clinical presentation, and optimal management strategies of prolactinomas is continually evolving. Significant advances in the last few decades have contributed to the contemporary diagnosis and management of prolactinoma, including

sensitive diagnostic hormone assays, neuroimaging techniques, pharmacological therapies, microsurgical and endoscopic techniques, and stereotactic radiosurgery. Making the correct diagnosis of prolactinoma is critical to implementing proper therapy. Pharmacological therapy with dopamine agonists remains the mainstay of treatment;^{8,94,95,144} however, there may be a role for surgical removal in some instances, especially in the case of microprolactinomas.^{1,31,149} In this paper we will discuss current management strategies for patients with prolactinoma.

CLINICAL MANIFESTATIONS OF PROLACTINOMAS

Patients with prolactinomas can present with the clinical sequelae of hyperprolactinemia, endocrine dysfunction, local mass effect, and/or pituitary apoplexy (Table 1).

The biological effects of hyperprolactinemia work predominantly on the gonadal axis and on breast tissue.^{9,12} Adult patients in their reproductive years who harbor a prolactinoma have an impairment of the gonadal axis because of the central inhibitory effects of hyperprolactinemia on hypothalamic production of gonadotropin-releasing hormone. This results in hypogonadism and infertility. In premenopausal women, hyperprolactinemia may not be detected until after discontinuation of an oral contraceptive regimen.² The signs and symptoms of hypogonadism in children and postmenopausal patients, however, are clinically absent.^{43,88,122} Adolescents can present with delay or failure of sexual/reproductive development.^{5,17,26,41,90}

Abbreviation used in this paper: MR = magnetic resonance.

TABLE 1
Clinical manifestations of prolactinomas

hyperprolactinemia
amenorrhea (female patients)
galactorrhea (female patients)
infertility
decreased libido
impotence (male patients)
osteoporosis
delayed puberty (adolescents)
mass effect
headaches
visual acuity & field impairment
cranial nerve palsies
hypothalamic impairment
hydrocephalus
hypopituitarism
pituitary apoplexy

Women commonly present with galactorrhea, amenorrhea, and infertility. Approximately 5% of women with primary amenorrhea and 25% of women with secondary amenorrhea (excluding pregnancy) have a prolactinoma.¹⁵⁴ When galactorrhea accompanies amenorrhea in women, the incidence of a prolactinoma increases to 70 to 80%.⁵¹ Galactorrhea is present in 50 to 80% of women with hyperprolactinemia.^{116,117,137} Although prolactinomas are found to be distributed equally between men and women at autopsy, women are four times more likely to become symptomatic than men. Women generally present earlier in the course of the disease and with smaller tumors (mostly microprolactinomas) at the time of diagnosis. In contrast, men commonly present with larger tumors (mostly macroprolactinomas), which cause local mass effect, and symptoms of visual loss, cranial nerve dysfunction, and/or hypopituitarism.¹⁷ Galactorrhea is extremely rare in men and the hypogonadal manifestations of decreased libido and impotence are often not recognized as a sign of hyperprolactinemia. Approximately 2% of all men with impotence have a prolactinoma.¹⁵⁴ Because most men attribute their sexual dysfunction to the aging process or to functional causes, the presence of a prolactinoma is often not evident until the tumor becomes large and produces local mass effect.

Untreated hyperprolactinemia can also lead to premature osteoporosis in both sexes due to impairment of gonadal function leading to a relative estrogen or testosterone deficiency.^{51,57,60,73,146} These important, but often overlooked effects of hyperprolactinemia are additional arguments for treating patients who may not be concerned about sexual dysfunction. The osteopenia is progressive and correlates with the duration of hypogonadism.¹⁰ Although normalization of prolactin levels halts bone loss, bone density increases to an extent, but does not return to normal baseline values.^{40,72,73,115}

Symptoms from mass effect arise from tumor compression on neighboring structures. Suprasellar extension may cause compression on the optic apparatus, which leads to visual deficits. Less commonly, lateral extension into the cavernous sinus can cause cranial nerve palsies. Compression of the normal pituitary gland can result in hypopituitarism. Extensive macroadenomas can obstruct

the flow of cerebrospinal fluid, resulting in hydrocephalus.

An apoplectic hemorrhage and/or infarction into a prolactinoma (pituitary apoplexy) can cause rapid enlargement of the tumor, resulting in hypopituitarism and acute compression of the sellar and parasellar structures.^{80,83} Clinical signs and symptoms include sudden onset of headache, nausea, vomiting, diplopia, and visual impairment. Headache, the most common symptom, is often described as excruciating and sudden in onset and is frequently associated with nausea and vomiting. When these symptoms are accompanied by meningeal irritation, neck stiffness, and photophobia from a hemorrhage breaking into the subarachnoid space, the clinical picture may mimic an aneurysmal subarachnoid hemorrhage. Pituitary apoplexy often occurs in patients with no history suggestive of a pituitary tumor and may represent the first definite indication that a pituitary tumor is present.

DIFFERENTIAL DIAGNOSIS

The diagnosis of prolactinoma requires that other causes of hyperprolactinemic states and other mass lesions in the sellar and parasellar region are ruled out.^{9,12,91} The cause of hyperprolactinemia can be physiological, pharmacologically induced, or pathological (Table 2). A careful medical history including a list of current medications, results of a physical examination and routine chemical

TABLE 2
Causes of hyperprolactinemia

physiological
pregnancy
breast feeding (suckling reflex)
stress
exercise
pharmacological
neuroleptic medication (phenothiazines, haloperidol)
atypical antipsychotic medications (clozapine, risperidone)
antidepressant medication (primarily amoxapine and rarely other tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors)
antihypertension medication (α -methyldopa, reserpine, verapamil)
metoclopramide
H-2 blockers (intravenous cimetidine)
sellar/parasellar lesions
prolactinomas
nonfunctioning pituitary macroadenomas w/ stalk effect
germinomas
craniopharyngiomas
meningiomas
primary empty sella syndrome
lymphocytic hypophysitis
histiocytosis X
sarcoidosis
metastasis
other disease states
primary hypothyroidism
chest-wall lesion (trauma, surgery, herpes zoster)
hypothalamic dysfunction
chronic renal failure
cirrhosis
ectopic secretion of prolactin
seizures

analyses, and a thyroid-stimulating hormone level should be obtained. Because prolactin secretion is mediated by dopamine, any process that disrupts dopamine secretion, interferes with dopamine delivery through the portal system, or antagonizes the action of dopamine at its receptor may cause hyperprolactinemia. Prolactin levels lower than 25 ng/ml in women and 20 ng/ml in men are within the normal range.

Physiological hyperprolactinemia can occur from psychological and physical stress, such as exercise, surgery, and hypoglycemia, but the prolactin level rarely exceeds 40 ng/ml in these cases.^{117,118} It is critical to rule out pregnancy in women with hyperprolactinemia because prolactin levels are elevated during the first and second trimesters and peak in the third trimester to several hundred nanograms per milliliter.¹¹² Prolactin levels decrease rapidly after delivery in postpartum women who do not breast feed. In those who do breast feed, however, serum prolactin levels remain elevated for the first few weeks, with sharp surges in prolactin secretion during suckling.⁵⁵ Within a few months, the prolactin levels return to normal, despite continued lactation.

Medications, such as phenothiazines, butyrophenones, and metoclopramide, which antagonize dopamine receptors on lactotrophs are a common cause of hyperprolactinemia.³³ Some antidepressant medications, such as monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors, may also elevate serum prolactin levels.^{33,96,127,140,141} Among antihypertension medications associated with hyperprolactinemia are α -methyldopa, reserpine, and verapamil.^{46,130} Administration of estrogen may also elevate prolactin levels.¹⁵⁹ Medication-induced hyperprolactinemia is associated with levels of prolactin in the range of 25 to 100 ng/ml; it usually resolves in a few days to weeks after cessation of the offending drug.

Hyperprolactinemia can occur in approximately 20 to 30% of patients with primary hypothyroidism.^{58,114,126,136} Severe primary hypothyroidism results in elevated thyrotropin-releasing hormone levels, causing mild-to-moderate elevations in serum prolactin, which can lead to thyrotroph hypertrophy and pituitary hyperplasia. This situation can sometimes be misdiagnosed as a prolactinoma; therefore, it is important to obtain the concentration of thyroid-stimulating hormone to rule out primary hypothyroidism.^{45,129,132} Correction of primary hypothyroidism with hormone replacement almost always leads to normalization of prolactin levels within a few weeks or months. Chronic renal failure can also result in hyperprolactinemia because of decreased renal clearance of serum prolactin.^{79,124}

Masses in the sellar and parasellar region, such as craniopharyngiomas, nonfunctioning macroadenomas, hypothalamic tumors, granulomatous lesions, and lymphocytic hypophysitis, can compress the pituitary stalk and interrupt the dopaminergic inhibition of lactotrophs ("stalk-section effect"); this results in elevated prolactin levels in the range of 50 to 125 ng/ml. The stalk effect rarely causes the serum prolactin level to increase higher than 100 ng/ml, whereas prolactinomas typically generate much higher levels. In some patients with acromegaly, prolactin may be cosecreted with growth hormone.^{3,50,75}

Most causes of hyperprolactinemia can be ruled out on the basis of the patient's medical history and physical examination, a pregnancy test, and thyroid and renal function tests. When other causes of hyperprolactinemia have been ruled out, an MR image with Gd administration should be obtained to confirm the diagnosis of a prolactinoma. Patients with signs and symptoms of visual loss or with neuroimaging-confirmed macroadenomas that extend beyond the sella turcica should undergo formal neuro-ophthalmological testing, including assessments of visual field and acuity. We also obtain serum levels of other pituitary-related hormones (growth hormone, insulin-like growth factor-1, prolactin, fasting morning cortisol, adrenocorticotrophic hormone, luteinizing hormone, follicle stimulating hormone, sex hormones) and thyroid function tests to determine anterior pituitary function in all patients with a neuroimaging-confirmed pituitary adenoma.

Interpreting Serum Prolactin Levels

Interpreting serum prolactin levels in conjunction with neuroimages is important in making the correct diagnosis of a prolactinoma to ensure proper treatment. In most cases, serum prolactin levels correlate with the size of the prolactinomas. Patients with microprolactinomas (size < 10 mm) are generally found to have serum prolactin levels that range between 100 and 250 ng/ml, although these levels may be higher. In those patients who harbor macroprolactinomas (size > 10 mm), the serum prolactin level is typically higher than 250 ng/ml. When the tumor has invaded the cavernous sinus, the serum prolactin level may be several thousand nanograms per milliliter. In macroadenomas associated with a mildly elevated prolactin level, approximately 50 to 125 ng/ml, the hyperprolactinemia can be attributed to the stalk-section effect from a nonfunctioning adenoma. Nevertheless, one should be aware of falsely low serum prolactin levels (25–150 ng/ml) in the face of a giant and invasive prolactinoma (> 3 cm); this is known as the high-dose "hook effect."^{6,28,52,131} The hook effect occurs when radioimmunoassays are performed using the two-site (monoclonal "sandwich") technique. At extremely high levels of serum prolactin, as in the presence of giant and invasive prolactinomas, the binding sites of the primary (capture) antibody and the secondary (signal) antibody become saturated and the true prolactin level is not accurately measured. The antibody binding curve is no longer proportional to the amount of serum prolactin, and the measured prolactin declines or hooks downward. This may be resolved by performing serial dilutions of the serum samples to overcome the hook effect.

MEDICAL TREATMENT

General Principles

The general objectives of the treatment of hyperprolactinemia are to suppress excessive hormone secretion and its clinical consequences, restore fertility, remove tumor mass, preserve residual pituitary function, and prevent disease recurrence or progression. In the treatment of microprolactinomas (tumors < 10 mm), removal of the

tumor mass is of secondary importance because the tumor is not likely to produce symptoms by mass effect.

Pharmacological therapy with a dopamine agonist is the first consideration for the treatment of prolactinomas.^{20,24} The dopamine agonists approved for use in the US are bromocriptine and cabergoline. They are both very effective in normalizing serum prolactin levels, shrinking tumor mass, and restoring gonadal function.

Bromocriptine should be used whenever pregnancy is a desired goal. Cabergoline is more expensive than bromocriptine, but easier to administer, usually better tolerated, and effective in patients who do not have a response to bromocriptine. If the prolactin level does not normalize or if the patient cannot tolerate bromocriptine, a change to cabergoline may be effective. Patients with macroprolactinomas generally require higher doses of bromocriptine or cabergoline than patients with microprolactinomas. Both dopamine agonists decrease the serum prolactin levels within days (Figs. 1 and 2) and result in a decrease in the size of the tumor and restoration of anterior pituitary function. Visual-field testing should be repeated 1 month after initiation of therapy, and MR imaging should be repeated at 6 weeks and again at 6 months after initiation of treatment. Serum prolactin levels should be monitored yearly.

Bromocriptine

Dopamine agonists bind to dopamine D2 receptors on the membrane of the lactotroph, inhibit prolactin synthesis and release, and reduce tumor volume.^{24,95} Bromocriptine, an ergot derivative, has been used effectively to treat hyperprolactinemia caused by prolactinomas since its approval by the US Food and Drug Administration in 1978.¹⁴⁴ Bromocriptine has a high degree of potency and its use has resulted in the normalization of prolactin levels in more than 90% of cases and a significant reduction of tumor mass in approximately 85% of cases.^{8,18,32,156} Tumor shrinkage occurs rapidly within several days and is effective in decompression of the visual apparatus in patients with macroprolactinomas who present with visual deficits

Serum Prolactin Response to Dopamine Agonist Therapy

Fig. 2. Graph showing changes in the serum prolactin level during dopamine agonist therapy received by the patient shown in Fig. 1. Note that the hormone levels decreased significantly within 1 week and normalized within 1 to 2 months after initiation of therapy.

(Fig. 1).^{32,133,154} Some tumors are very responsive to bromocriptine and shrink by more than 80% within 6 weeks after the initiation of therapy.^{133,145} In some instances, the tumor will shrink sufficiently to become undetectable on neuroimaging studies.¹⁴⁹ Bromocriptine has also been reported to restore gonadal and anterior pituitary functions in more than 80% of patients. Most female patients begin menstruation within 6 months after initiating therapy.

Bromocriptine dosage is started at 1.25 to 2.5 mg orally once a day and increased over 2 to 3 weeks to 5 to 10 mg daily in divided doses. After normalization of serum prolactin levels, bromocriptine can be reduced to the lowest effective dosage. Cessation of the drug usually results in recurrent hyperprolactinemia and reexpansion of the tumor,^{102,134,160} although some studies show evidence of sustained normoprolactinemia following cessation of treatment.^{64,105} Approximately 10 to 25% of patients are partially or totally resistant to bromocriptine.^{14,15,106} Five

Fig. 1. Coronal Gd-enhanced T₁-weighted MR images. *Left:* Image obtained in a 40-year-old man who presented with headaches, deterioration of vision, and loss of libido due to a macroadenoma with cavernous sinus extension. The patient's initial serum prolactin level was 3652 ng/ml, which confirmed the diagnosis of a macroprolactinoma. The patient was treated with bromocriptine, which was eventually changed to cabergoline because the man experienced intolerable side effects. *Center and Right:* Images obtained at 2 (*center*) and 6 (*right*) months after initiation of dopamine agonist therapy, demonstrating significant shrinking of the tumor with normalization of serum prolactin levels (5.5 ng/ml at 2 months and 2.6 ng/ml at 6 months).

to 10 percent of patients may not be able to tolerate bromocriptine treatment because of drug-related effects, including dizziness, nausea, arrhythmias, and gastrointestinal discomfort; orthostatic hypotension can also limit its tolerance in some patients. The incidence of orthostatic hypotension may be decreased by increasing the dose slowly or administering the drug at night.¹⁵⁵ In some women, intravaginal administration (2.5–5 mg daily) may reduce gastrointestinal side effects;⁶⁸ although some vaginal irritation may occur, this is generally well tolerated.^{63,68,71} Cardiovascular disease is a relative contraindication for bromocriptine administration.^{59,128} Dopamine agonists may precipitate psychotic episodes in patients requiring neuroleptic medications.¹⁰⁷ At high doses, cold-induced vasospasm of the digits has also been reported.⁴²

Other clinicians have reported that tumor reduction is not likely to occur if it is not evident within 3 months after bromocriptine therapy is begun.^{133,145} It has been our observation that patients who do not respond by 6 weeks are unlikely to respond by 3 months and, therefore, our current practice is to obtain an MR image 6 weeks after initiating medical therapy to document tumor reduction. In the bromocriptine-treated patient who responds to medication, but experiences a failure in normalization of his or her serum prolactin levels and does not achieve restoration of gonadal function, consideration should be given to cabergoline therapy.²⁵ A combined medical and surgical therapy may be indicated if the patient fails to respond to cabergoline administration. After surgical debulking of the lesion, hyperprolactinemia is often more responsive to medical therapy, requiring lower doses for control of serum prolactin. Because some patients may have persistent hyperprolactinemia and tumor progression during bromocriptine therapy, close monitoring of serum prolactin levels and serial MR images is mandatory.

Cabergoline and Other Dopamine Agonists

Cabergoline is a long-lasting, ergot derivative, selective dopamine D2 receptor agonist that has been used effectively in the treatment of both microprolactinomas and macroprolactinomas.^{21–23,29,35,48,49,89,94} Although more expensive than bromocriptine, cabergoline is associated with less frequent and less severe side effects. This drug appears to be superior to bromocriptine in normalizing prolactin levels, restoring gonadal function, and decreasing the size of the tumor.^{23,38,39} It is very useful in patients who become resistant to or cannot tolerate the adverse effects of bromocriptine.²⁵ This favorable profile enables escalation of doses to achieve normal serum prolactin levels in approximately 85% of patients with microadenomas and, more importantly, in a proportion of bromocriptine-resistant patients.^{37,153}

Cabergoline may be administered at doses ranging between 0.5 and 1.5 mg once or twice per week. Because the drug dosing is less frequent and the drug is more tolerable, patient compliance may be better with cabergoline than with bromocriptine.

The results of an important recent study have indicated that the majority of patients who respond to cabergoline with normalization of prolactin levels and a reduction in tumor size may experience remission of hyperprolactinemia following discontinuation of the drug.²¹ This indicates a potential for a curative treatment of many prolactinomas when using this agent (see later discussion).

Pergolide, lisuride, and quinagolide are other new agents that have been shown to suppress serum prolactin levels and decrease tumor size in patients with prolactinomas.^{27,34,36,47,99–101,119,151,152} These agents, however, have not been approved by the Food and Drug Administration for the treatment of prolactinomas.¹²⁰ A recent cross-over study, in which cabergoline and quinagolide were compared, demonstrated a similar efficacy of better than 90% biochemical cure rates and a slightly better cost effectiveness with cabergoline.³⁹

Medical Therapy During Pregnancy

If pregnancy is a desired goal of the patient, bromocriptine should be used whenever possible because of its safety record in pregnancy.^{93,109} Although according to some reports cabergoline does not increase the risk of teratogenesis, experience in this area has been limited.^{111,113} Cabergoline should not be used as a primary therapy for infertility until there is more evidence supporting its safety during pregnancy. Approximately 90% of women treated with bromocriptine will resume menses within 6 months after the start of therapy.^{144,155} The subsequent pregnancy rates are the same as those of healthy women in the same age group.^{56,125} Women should be advised to use a mechanical form of contraception until their menstrual cycle is restored. Normal conception and pregnancy may then follow. Once a menstrual cycle has been missed, a pregnancy test should be obtained and bromocriptine should be discontinued immediately.¹¹⁷ Using bromocriptine in this manner has not been associated with an increased incidence of spontaneous abortion, ectopic pregnancy, or congenital malformation.⁹⁷

Elevation of estrogen levels during pregnancy stimulates DNA synthesis and mitosis in lactotrophs in the pituitary, resulting in tumor enlargement.^{135,147} These changes are usually transient and resolve after delivery. Nevertheless, the patient should be monitored closely for signs and symptoms of tumor expansion. The risk of symptomatic tumor enlargement is related to the initial size of the tumor before pregnancy. The risk of symptomatic tumor enlargement of a microadenoma during pregnancy ranges from 0.5 to 1%.^{133,145} Formal visual-field testing and serial MR imaging are usually not necessary unless the patient becomes symptomatic. For patients with macroadenomas, the risk of symptomatic tumor enlargement ranges from 15 to 35%.⁹⁷ These patients may experience visual loss and symptoms of increased intracranial pressure. Women who harbor macroadenomas with suprasellar extension may be offered surgical debulking before conception.^{1,154} Patients with asymptomatic macroadenomas should undergo close monitoring with visual-field testing once every 3 months. An MR imaging study should be repeated if symptoms of tumor enlargement develop. If the patient experiences symptomatic tumor enlargement, bromocriptine therapy can be safely initiated during pregnancy.^{7,16,74,142} There does not appear to be an increased risk of congenital anomalies or spontaneous abortions associated with the use of bromocriptine during pregnancy. Alternatively, surgical decompression may be an option.

Withdrawal of Dopamine Agonist Therapy

After the prolactin level has remained normalized for at least 2 years and the size of the tumor has significantly decreased by at least 50% without evidence of compression of the optic chiasm, the dopamine agonist can be tapered to lower doses that continue to control hyperprolactinemia and tumor growth. If there is no evidence of cavernous sinus invasion, a trial of drug cessation may be instituted, as long as the patient receives close monitoring for tumor enlargement with serial MR imaging. Normoprolactinemia was sustained after cessation of bromocriptine in approximately 25% of women who were treated for at least 2 years,^{64,105} although cessation of bromocriptine therapy in patients with macroprolactinomas usually leads to tumor expansion and recurrence of hyperprolactinemia.^{86,102} Cessation of dopamine agonist therapy may be considered in postmenopausal women harboring microprolactinomas.

The success of sustained normoprolactinemia after cessation of bromocriptine therapy has been variable (range 7–38%).^{66,86,105,110,143,148,150,160} Tumor enlargement has been noted in approximately 10% of cases and probably relates to the duration of treatment before withdrawal of medication.^{66,143} Cessation of bromocriptine within 1 year after initiation of treatment appears to have a higher risk of tumor enlargement than cessation in those patients who have undergone longer treatments.^{95,102,134} Patients who have recurrent hyperprolactinemia after cessation of bromocriptine therapy may anticipate tumor recurrence, although the increase in the size of the lesion may be very slow.⁶⁶

There is some evidence that cabergoline may have the potential for definitive control of hyperprolactinemia and tumor growth. Colao, et al.,²¹ reported sustained normalization of serum prolactin levels after withdrawal of cabergoline in 69% of patients with microprolactinomas and 64% of those with macroprolactinomas without evidence of new tumor growth. The rate of recurrence at 5 years was higher among patients with macroprolactinomas and those with microprolactinomas in whom there was neuroimaging evidence of residual tumor than in those in whom there was no neuroimaging evidence of residual tumor. Although there was no evidence of tumor recurrence in the face of recurrent hyperprolactinemia, the follow-up period was relatively short and probably insufficient to determine the true rate of tumor control.

Pituitary Apoplexy in Patients With Prolactinomas: Medical or Surgical Therapy?

Although most surgeons recommend emergency transsphenoidal decompression and administration of glucocorticoids for patients who present with pituitary apoplexy,^{4,11,44,78,80,83} some have reported excellent results with dopamine agonist therapy in patients with prolactinomas who display pituitary apoplexy.^{13,80} Brisman, et al.,¹³ reported on a patient with a macroprolactinoma who presented with pituitary apoplexy and a third nerve palsy and was treated with bromocriptine and glucocorticoids. The third nerve palsy completely resolved within 48 hours. We have also used bromocriptine in the successful treatment of a patient with a macroprolactinoma who presented with

severe headache and right ophthalmoplegia due to non-hemorrhagic pituitary apoplexy (Fig. 3).⁸⁰ Although the optimal treatment for patients with prolactinomas who experience pituitary apoplexy remains controversial, we recommend an initial trial of dopamine agonist therapy in conjunction with glucocorticoids for patients who have no or minimal visual loss. If patients present with visual loss or if their visual loss progresses despite dopamine agonist therapy, emergency transsphenoidal decompression is indicated.

SURGICAL TREATMENT

Indications for Treatment

The efficacy of pharmacological therapy has limited the indications of resection of prolactinomas. Surgery is rarely curative in patients with macroprolactinomas and is usually reserved for patients who cannot tolerate medical therapy or for whom medical therapy is ineffective.^{1,123,139,157} Sustained normoprolactinemia following cessation of medical therapy has not been demonstrated in all cases and, therefore, there may be a role for curative surgery of microprolactinomas in patients who do not wish to receive long-term medical therapy.^{31,87,149,158} Surgery may also be indicated in patients who are dependent on antipsychotic medications, because dopamine agonists can precipitate psychotic episodes.¹⁰⁷ In patients who have persistent hyperprolactinemia, progressive tumor enlargement, or persistent tumor mass effect despite maximal medical therapy, surgery may be indicated. Resection should be considered if impaired visual function or cranial nerve palsies are not immediately responsive to medical treatment, especially in patients with pituitary apoplexy as mentioned earlier. Even if surgery is not curative, as is the case with most macroprolactinomas (< 50% cure rate),^{1,139} tumor cytoreduction frequently increases the responsiveness of dopamine ago-

Fig. 3. Coronal T₂-weighted (left) and axial Gd-enhanced T₁-weighted (right) images obtained in a patient who presented with severe headache and right ophthalmoplegia caused by nonhemorrhagic pituitary apoplexy in a macroprolactinoma. The patient's symptoms resolved after bromocriptine therapy. There is also thickening of the sphenoid sinus mucosa (left), which is usually present in cases of pituitary apoplexy.

nists and thereby lowers the required dosage.^{133,145} Multimodal therapy with surgical debulking and subsequent adjuvant therapy (stereotactic radiosurgery or medical therapy) may be an effective strategy, especially if there is evidence of cavernous sinus invasion. Although some surgeons have reported that prior long-term treatment with dopamine agonists alters the consistency of the tumor and hinders its resection,⁷⁶ we have not found this to be the case. With giant and invasive prolactinomas, pretreatment with a dopamine agonist may improve the safety and success of subsequent surgery.¹⁵⁶

The transsphenoidal approach is the initial preferred surgical route and is associated with low rates of morbidity and mortality.^{19,82} The extended transsphenoidal approach may be used in some cases in which the tumor is located beyond the confines of the sella turcica.^{62,67,81,85} Even in cases of giant prolactinoma, a transsphenoidal approach should be considered first; however, a pterional approach should be considered if there is a great deal of lateral tumor extension into the sylvian fissure.^{85,123}

Surgery for Microprolactinomas

In patients with hyperprolactinemia due to a microprolactinoma, transsphenoidal surgery by an experienced pituitary surgeon should be considered a potentially curative procedure (Fig. 4).^{1,31,149,158} The realization that medical therapy may require long-term treatment in some cases (a particularly significant factor in young patients) and consideration of the very low morbidity and mortality rates associated with contemporary transsphenoidal resection in experienced hands should factor into the decision-making process. Sustained normoprolactinemia following cessation of medical therapy occurs in some cases but not in others. The costs and burden of potentially long-term medical treatment in a young patient with a long life expectancy must be considered, especially in a young woman desiring restoration of fertility. In patients who harbor microprolactinomas and have serum prolactin levels lower than 200 ng/ml, transsphenoidal surgery performed by experienced pituitary surgeons at high-volume centers offers more than a 90% chance of biochemical and oncological cure^{1,31,61,108} with minimal risks of morbidity and mortality of less than 1%.^{19,81} Furthermore, the continued

evolution of endoscopic approaches for tumor resection, which are somewhat less invasive, may reduce the morbidity rate of the surgical approach even further.⁶⁵ The financial cost of treatment over a 10-year period in cases in which surgery is uncomplicated is similar to that of long-term dopamine agonist therapy.¹³⁸

In a recent study by Amar, et al.,¹ a cure rate of 91% was achieved in patients with microprolactinomas. There was a higher correlation with a biochemical cure if the preoperative serum prolactin level was less than 200 ng/ml. Similarly, in a study by Tyrrell, et al.,¹³⁹ women with preoperative prolactin levels higher than 200 ng/ml and those harboring larger and more invasive prolactinomas had poorer outcomes (37–41% cure rate). In their series, long-term remission was achieved in patients with microadenomas and noninvasive macroadenomas (that is, those with a moderate suprasellar extension and focal sphenoid sinus invasion). Lower postoperative serum prolactin levels are the best predictors of a long-term cure. Amar, et al.,¹ demonstrated that fasting morning serum prolactin levels obtained on the 1st postoperative day that were lower than 10 ng/ml predicted a 100% cure rate in microprolactinomas and a 93% cure rate in macroprolactinomas. A hormone level between 10 and 20 ng/ml still could be used to predict a 100% cure in patients harboring microprolactinomas, but not in those with macroprolactinomas (0% cure rate).

The choice of transsphenoidal surgery for microprolactinomas should take into account the size and location of the tumor, the preoperative serum prolactin level, the age of the patient, the desire for restoration of fertility, the efficacy and tolerability of dopamine agonists, and the experience of the surgeon. Surgery should not be considered unless a complete removal of the microprolactinoma with biochemical cure is an expected outcome. The presence of a symptomatic microprolactinoma, especially in a young patient, should remain an indication for microsurgical or endoscopic transsphenoidal resection.

STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery is becoming increasingly popular in the treatment of both functioning and nonfunction-

Fig. 4. Coronal T₁-weighted MR images obtained before (left) and after (right) Gd administration in a 25-year-old woman who presented with amenorrhea and galactorrhea caused by a microprolactinoma. The patient's initial serum prolactin level was 47.7 ng/ml. She underwent a complete transsphenoidal resection of the tumor. The morning fasting serum prolactin level obtained on postoperative Day 1 was 1 ng/ml, which was suggestive of a biochemical cure.

ing pituitary adenomas.^{53,54,69,70,77,103,104,121} Current MR imaging methods enable high-resolution images and dose planning with excellent accuracy. The preliminary data regarding tumor control and normalization of hypersecretory syndromes after radiosurgery appear favorable. Stereotactic radiosurgery can offer a therapeutic option to patients with prolactinomas as a secondary treatment after failed transsphenoidal surgery or failed medical therapy.⁷⁷ Other authors have proposed stereotactic radiosurgery as a primary treatment for prolactinomas in patients who are reluctant to undergo long-term medical therapy or resection.¹⁰⁴ The proximity of the pituitary gland to the region of radiosurgical treatment, however, may carry the risk of developing hypopituitarism. Longer follow-up periods are necessary to assess the likelihood of this complication.

Landolt and Lomax⁷⁷ reported the cases of 20 patients who underwent gamma knife surgery for residual prolactinomas after unsuccessful transsphenoidal surgery or failed medical therapy. Five patients regained normoprolactinemia and medical therapy was discontinued. Eleven patients experienced improvement, which was defined by normalized prolactin levels or by levels that had decreased by 20% with the continued requirement of medical therapy at lower doses. Treatment failed in four patients who were receiving dopamine agonist therapy at the time of radiosurgery, indicating some radioprotective effect of the dopamine agonist therapy. The authors have suggested that this therapeutic regimen be stopped temporarily during radiosurgical treatment.

Pan, et al.,¹⁰⁴ described 164 patients with prolactinomas who underwent primary treatment with gamma knife surgery. A mean follow-up period of 33.2 months was available in 128 patients. Tumor growth was controlled in all but two patients who eventually underwent transsphenoidal surgery. A biochemical cure was attained in 52% of patients and an improvement in 28% of patients. Among this group, nine infertile women became pregnant 2 to 13 months after treatment and all gave birth to healthy children. One infertile woman who was unresponsive to bromocriptine became sensitive to the medication after radiosurgery. In 31 (29%) of 108 patients who were observed for longer than 2 years, persistent hyperprolactinemia could be normalized by bromocriptine after radiosurgery.

Pituitary Transposition

In cases of macroprolactinomas with cavernous sinus invasion that are refractory to medical therapy, we recommend surgical debulking and postoperative stereotactic radiosurgery to treat any residual tumor in the cavernous sinus. After the primary tumor is adequately debulked using a transsphenoidal approach, we perform a technique for pituitary gland transposition (sometimes referred to as "hypophyseopexy").^{30,84} This technique involves transposing the normal pituitary gland away from the cavernous sinus tumor and interposing a fat graft between the normal gland and the tumor in the cavernous sinus. This increases the distance between the normal pituitary gland and the residual tumor to facilitate radiosurgical treatment of the tumor, thereby reducing the effective biological dose to the normal pituitary gland. This reduction decreases the

likelihood that hypopituitarism may develop. The details of this technique have been described elsewhere in the literature.^{30,84}

CONCLUSIONS

Prolactinomas left untreated cause persistent endocrinopathy with the sequelae of gonadal dysfunction, osteoporosis, and, possibly, tumor mass effect. First-line therapy with dopamine agonists is effective in normalizing hyperprolactinemia and shrinking tumor size. Resection is indicated in patients who cannot tolerate medical therapy or in whom it fails. Surgery should also be considered in patients with microprolactinomas when complete tumor removal with a biochemical cure is an expected outcome. Stereotactic radiosurgery is an option for those patients in whom medical and surgical treatments have failed and may be considered as a primary treatment in those who do not wish to undergo medical or surgical treatment.

References

1. Amar AP, Couldwell WT, Chen JC, et al: Predictive value of serum prolactin levels measured immediately after transsphenoidal surgery. *J Neurosurg* **97**:307–314, 2002
2. Anonymous: Pituitary adenomas and oral contraceptives: a multicenter case-control study. *Fertil Steril* **39**:753–760, 1983
3. Arafah BM, Neikl KE, Gold RS, et al: Dynamics of prolactin secretion in patients with hypopituitarism and pituitary macroadenomas. *J Clin Endocrinol Metab* **80**:3507–3512, 1995
4. Arnesen M, Scheithauer BW: Aggressive small cell tumor of the skull base. *Ultrastruct Pathol* **18**:191–197, 1994
5. Artese R, D'Osvaldo DH, Moloczniak I, et al: Pituitary tumors in adolescent patients. *Neurol Res* **20**:415–417, 1998
6. Barkan AL, Chandler WF: Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the "high-dose hook effect": case report. *Neurosurgery* **42**:913–916, 1998
7. Bergh T, Nilius SJ, Enoksson P, et al: Bromocriptine-induced regression of a suprasellar extending prolactinoma during pregnancy. *J Endocrinol Invest* **7**:133–136, 1984
8. Bevan JS, Webster J, Burke CW, et al: Dopamine agonists and pituitary tumor shrinkage. *Endocr Rev* **13**:220–240, 1992
9. Biller BM: Diagnostic evaluation of hyperprolactinemia. *J Reprod Med* **44**:1095–1099, 1999
10. Biller BM, Baum HB, Rosenthal DI, et al: Progressive trabecular osteopenia in women with hyperprolactinemic amenorrhea. *J Clin Endocrinol Metab* **75**:692–697, 1992
11. Bills DC, Meyer FB, Laws ER Jr, et al: A retrospective analysis of pituitary apoplexy. *Neurosurgery* **33**:602–609, 1993
12. Blackwell RE: Hyperprolactinemia. Evaluation and management. *Endocrinol Metab Clin North Am* **21**:105–124, 1992
13. Brisman MH, Katz G, Post KD: Symptoms of pituitary apoplexy rapidly reversed with bromocriptine. Case report. *J Neurosurg* **85**:1153–1155, 1996
14. Brue T, Pellegrini I, Priou A, et al: Prolactinomas and resistance to dopamine agonists. *Horm Res* **38**:84–89, 1992
15. Caccavelli L, Feron F, Morange I, et al: Decreased expression of the two D2 dopamine receptor isoforms in bromocriptine-resistant prolactinomas. *Neuroendocrinology* **60**:314–322, 1994
16. Canales ES, Garcia IC, Ruiz JE, et al: Bromocriptine as prophylactic therapy in prolactinoma during pregnancy. *Fertil Steril* **36**:524–526, 1981
17. Carter JN, Tyson JE, Tolis G, et al: Prolactin-screening tumors and hypogonadism in 22 men. *N Engl J Med* **299**:847–852, 1978
18. Ciccarelli E, Camanni F: Diagnosis and drug therapy of prolactinoma. *Drugs* **51**:954–965, 1996
19. Ciric I, Ragin A, Baumgartner C, et al: Complications of trans-

- sphenoidal surgery: results of a national survey, review of the literature, and personal experience. **Neurosurgery** **40**: 225–237, 1997
20. Colao A, Annunziato L, Lombardi G: Treatment of prolactinomas. **Ann Med** **30**:452–459, 1998
21. Colao A, Di Sarno A, Cappabianca P, et al: Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. **N Engl J Med** **349**:2023–2033, 2003
22. Colao A, Di Sarno A, Landi ML, et al: Long-term and low-dose treatment with cabergoline induces macroprolactinoma shrinkage. **J Clin Endocrinol Metab** **82**:3574–3579, 1997
23. Colao A, Di Sarno A, Landi ML, et al: Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. **J Clin Endocrinol Metab** **85**:2247–2252, 2000
24. Colao A, di Sarno A, Pivonello R, et al: Dopamine receptor agonists for treating prolactinomas. **Expert Opin Investig Drugs** **11**:787–800, 2002
25. Colao A, Di Sarno A, Sarnacchiaro F, et al: Prolactinomas resistant to standard dopamine agonists respond to chronic cabergoline treatment. **J Clin Endocrinol Metab** **82**:876–883, 1997
26. Colao A, Loche S, Cappa M, et al: Prolactinomas in children and adolescents. Clinical presentation and long-term follow-up. **J Clin Endocrinol Metab** **83**:2777–2780, 1998
27. Colao A, Merola B, Sarnacchiaro F, et al: Comparison among different dopamine-agonists of new formulation in the clinical management of macroprolactinomas. **Horm Res** **44**:222–228, 1995
28. Comtois R, Robert F, Hardy J: Immunoradiometric assays may miss high prolactin levels. **Ann Intern Med** **119**:173, 1993
29. Corsello SM, Ubertini G, Altomare M, et al: Giant prolactinomas in men: efficacy of cabergoline treatment. **Clin Endocrinol** **58**:662–670, 2003
30. Couldwell WT, Rosenow JM, Rovit RL, et al: Hypophysectomy technique for radiosurgical treatment of cavernous sinus pituitary adenoma. **Pituitary** **5**:169–173, 2002
31. Couldwell WT, Rovit RL, Weiss MH: Role of surgery in the treatment of microprolactinomas. **Neurosurg Clin N Am** **14**: 89–92, 2003
32. Cunnah D, Besser M: Management of prolactinomas. **Clin Endocrinol** **34**:231–235, 1991
33. David SR, Taylor CC, Kinon BJ, et al: The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. **Clin Ther** **22**:1085–1096, 2000
34. De Luis DA, Becerra A, Lahera M, et al: A randomized cross-over study comparing cabergoline and quinagolide in the treatment of hyperprolactinemic patients. **J Endocrinol Invest** **23**: 428–434, 2000
35. De Rosa M, Colao A, Di Sarno A, et al: Cabergoline treatment rapidly improves gonadal function in hyperprolactinemic males: a comparison with bromocriptine. **Eur J Endocrinol** **138**:286–293, 1998
36. Delgrange E, Donckier J: Prolactinomas apparently resistant to quinagolide respond to cabergoline therapy. **J Clin Endocrinol Metab** **82**:2755–2756, 1997
37. Delgrange E, Maiter D, Donckier J: Effects of the dopamine agonist cabergoline in patients with prolactinoma intolerant or resistant to bromocriptine. **Eur J Endocrinol** **134**: 454–456, 1996
38. Di Sarno A, Landi ML, Cappabianca P, et al: Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. **J Clin Endocrinol Metab** **86**:5256–5261, 2001
39. Di Sarno A, Landi ML, Marzullo P, et al: The effect of quinagolide and cabergoline, two selective dopamine receptor type 2 agonists, in the treatment of prolactinomas. **Clin Endocrinol** **53**:53–60, 2000
40. Di Somma C, Colao A, Di Sarno A, et al: Bone marker and bone density responses to dopamine agonist therapy in hyperprolactinemic males. **J Clin Endocrinol Metab** **83**:807–813, 1998
41. Duntas LH: Prolactinomas in children and adolescents—consequences in adult life. **J Pediatr Endocrinol Metab** **14** Suppl 5:1227–1232; 1261–1262, 2001
42. Duvoisin RC: Digital vasospasm with bromocriptine. **Lancet** **2**:204, 1976
43. Dyer EH, Civit T, Visot A, et al: Transsphenoidal surgery for pituitary adenomas in children. **Neurosurgery** **34**:207–212, 1994
44. Ebersold MJ, Laws ER Jr, Scheithauer BW, et al: Pituitary apoplexy treated by transsphenoidal surgery. A clinicopathological and immunocytochemical study. **J Neurosurg** **58**: 315–320, 1983
45. Edwards CR, Forsyth IA, Besser GM: Amenorrhoea, galactorrhoea, and primary hypothyroidism with high circulating levels of prolactin. **Br Med J** **3**:462–464, 1971
46. Fearington EL, Rand CH Jr, Rose JD: Hyperprolactinemia-galactorrhea induced by verapamil. **Am J Cardiol** **51**: 1466–1467, 1983
47. Ferrari C, Crosignani PG: Medical treatment of hyperprolactinaemic disorders. **Hum Reprod** **1**:507–514, 1986
48. Ferrari C, Paracchi A, Mattei AM, et al: Cabergoline in the long-term therapy of hyperprolactinemic disorders. **Acta Endocrinol (Copenh)** **126**:489–494, 1992
49. Ferrari CI, Abs R, Bevan JS, et al: Treatment of macroprolactinoma with cabergoline: a study of 85 patients. **Clin Endocrinol** **46**:409–413, 1997
50. Franks S, Jacobs HS, Nabarro JD: Prolactin concentrations in patients with acromegaly: clinical significance and response to surgery. **Clin Endocrinol** **5**:63–69, 1976
51. Franks S, Murray MA, Jequier AM, et al: Incidence and significance of hyperprolactinaemia in women with amenorrhea. **Clin Endocrinol** **4**:597–607, 1975
52. Frieze TW, Mong DP, Koops MK: “Hook effect” in prolactinomas: case report and review of literature. **Endocr Pract** **8**: 296–303, 2002
53. Ganz JC: Gamma Knife treatment of pituitary adenomas. **Stereotact Funct Neurosurg** **64** (Suppl 1):3–10, 1995
54. Ganz JC, Backlund EO, Thorsen FA: The effects of Gamma Knife surgery of pituitary adenomas on tumor growth and endocrinopathies. **Stereotact Funct Neurosurg** **61** (Suppl 1): 30–37, 1993
55. Gehlbach DL, Bayliss P, Rosa C: Prolactin and thyrotropin responses to nursing during the early puerperium. **J Reprod Med** **34**:295–298, 1989
56. Gemzell C, Wang CF: Outcome of pregnancy in women with pituitary adenoma. **Fertil Steril** **31**:363–372, 1979
57. Greenspan SL, Oppenheim DS, Klibanski A: Importance of gonadal steroids to bone mass in men with hyperprolactinemic hypogonadism. **Ann Intern Med** **110**:526–531, 1989
58. Honbo KS, van Herle AJ, Kellett KA: Serum prolactin levels in untreated primary hypothyroidism. **Am J Med** **64**:782–787, 1978
59. Iffy L, TenHove W, Frisoli G: Acute myocardial infarction in the puerperium in patients receiving bromocriptine. **Am J Obstet Gynecol** **155**:371–372, 1986
60. Jacobs HS, Franks S, Murray MA, et al: Clinical and endocrine features of hyperprolactinaemic amenorrhoea. **Clin Endocrinol** **5**:439–454, 1976
61. Jane JA Jr, Laws ER Jr: The surgical management of pituitary adenomas in a series of 3,093 patients. **J Am Coll Surg** **193**: 651–659, 2001
62. Jane JA Jr, Thapar K, Kaptain GJ, et al: Pituitary surgery: transsphenoidal approach. **Neurosurgery** **51**:435–444, 2002
63. Jasonni VM, Raffelli R, de March A, et al: Vaginal bromocriptine in hyperprolactinemic patients and puerperal women. **Acta Obstet Gynecol Scand** **70**:493–495, 1991
64. Jeffcoat WJ, Pound N, Sturrock ND, et al: Long-term follow-up of patients with hyperprolactinaemia. **Clin Endocrinol** **45**: 299–303, 1996

65. Jho HD, Carrau RL: Endoscopic endonasal transsphenoidal surgery: experience with 50 patients. **J Neurosurg** **87**:44–51, 1997
66. Johnston DG, Hall K, Kendall-Taylor P, et al: Effect of dopamine agonist withdrawal after long-term therapy in prolactinomas. Studies with high-definition computerised tomography. **Lancet** **2**:187–192, 1984
67. Kaptain GJ, Vincent DA, Sheehan JP, et al: Transsphenoidal approaches for the extracapsular resection of midline suprasellar and anterior cranial base lesions. **Neurosurgery** **49**:94–101, 2001
68. Katz E, Schran HF, Adashi EY: Successful treatment of a prolactin-producing pituitary macroadenoma with intravaginal bromocriptine mesylate: a novel approach to intolerance of oral therapy. **Obstet Gynecol** **73**:517–520, 1989
69. Kim MS, Lee SI, Sim JH: Gamma Knife radiosurgery for functioning pituitary microadenoma. **Stereotact Funct Neurosurg** **72** (Suppl 1):119–124, 1999
70. Kim SH, Huh R, Chang JW, et al: Gamma Knife radiosurgery for functioning pituitary adenomas. **Stereotact Funct Neurosurg** **72** (Suppl 1):101–110, 1999
71. Kletzky OA, Vermesh M: Effectiveness of vaginal bromocriptine in treating women with hyperprolactinemia. **Fertil Steril** **51**:269–272, 1989
72. Klibanski A, Biller BM, Rosenthal DI, et al: Effects of prolactin and estrogen deficiency in amenorrheic bone loss. **J Clin Endocrinol Metab** **67**:124–130, 1988
73. Klibanski A, Greenspan SL: Increase in bone mass after treatment of hyperprolactinemic amenorrhea. **N Engl J Med** **315**:542–546, 1986
74. Konopka P, Raymond JP, Merceron RE, et al: Continuous administration of bromocriptine in the prevention of neurological complications in pregnant women with prolactinomas. **Am J Obstet Gynecol** **146**:935–938, 1983
75. Lamberts SW, Zweens M, Klijn JG, et al: The sensitivity of growth hormone and prolactin secretion to the somatostatin analogue SMS 201–995 in patients with prolactinomas and acromegaly. **Clin Endocrinol** **25**:201–212, 1986
76. Landolt AM: Surgical treatment of pituitary prolactinomas: postoperative prolactin and fertility in seventy patients. **Fertil Steril** **35**:620–625, 1981
77. Landolt AM, Lomax N: Gamma knife radiosurgery for prolactinomas. **J Neurosurg** **93** (Suppl 3):14–18, 2000
78. Laws ER Jr, Ebersold MJ: Pituitary apoplexy—an endocrine emergency. **World J Surg** **6**:686–688, 1982
79. Lim VS, Ferreri E: Hyperprolactinemia in chronic renal failure. **Int J Artif Organs** **4**:152–153, 1981
80. Liu JK, Couldwell WT: Pituitary apoplexy: diagnosis and management. **Contemporary Neurosurgery** **25**:1–6, 2003
81. Liu JK, Das K, Weiss MH, et al: The history and evolution of transsphenoidal surgery. **J Neurosurg** **95**:1083–1096, 2001
82. Liu JK, Orlandi RR, Apfelbaum RI, et al: Novel closure technique for the endonasal transsphenoidal approach. Technical note. **J Neurosurg** **100**:161–164, 2004
83. Liu JK, Rovit RL, Couldwell WT: Pituitary apoplexy. **Seminars in Neurosurgery** **12**:315–320, 2001
84. Liu JK, Schmidt MH, MacDonald JD, et al: Hypophysial transposition (hypophysopexy) for radiosurgical treatment of pituitary tumors involving the cavernous sinus. Technical note. **Neurosurg Focus** **14** (5):Article 11, 2003
85. Liu JK, Weiss MH, Couldwell WT: Surgical approaches to pituitary tumors. **Neurosurg Clin N Am** **14**:93–107, 2003
86. Liuzzi A, Dallabonzana D, Oppizzi G, et al: Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. **N Engl J Med** **313**:656–659, 1985
87. Liuzzi A, Oppizzi G: Microprolactinomas: why requiem for surgery? **J Endocrinol Invest** **19**:196–198, 1996
88. Maira G, Anile C: Pituitary adenomas in childhood and adolescence. **Can J Neurol Sci** **17**:83–87, 1990
89. Miki N: Cabergoline, a hopeful medicine for prolactinomas and non-tumoral hyperprolactinemia. **Intern Med** **40**:845–846, 2001
90. Minniti G, Jaffrain-Rea ML, Ferretti E, et al: Macroprolactinomas as cause of delayed puberty. A report of two cases and effects of medical therapy. **Minerva Endocrinol** **21**:67–71, 1996
91. Molitch ME: Diagnosis and treatment of prolactinomas. **Adv Intern Med** **44**:117–153, 1999
92. Molitch ME: Management of prolactinomas. **Annu Rev Med** **40**:225–232, 1989
93. Molitch ME: Management of prolactinomas during pregnancy. **J Reprod Med** **44**:1121–1126, 1999
94. Molitch ME: Medical management of prolactin-secreting pituitary adenomas. **Pituitary** **5**:55–65, 2002
95. Molitch ME: Medical treatment of prolactinomas. **Endocrinol Metab Clin North Am** **28**:143–169, 1999
96. Molitch ME: Pathologic hyperprolactinemia. **Endocrinol Metab Clin North Am** **21**:877–901, 1992
97. Molitch ME: Pregnancy and the hyperprolactinemic woman. **N Engl J Med** **312**:1364–1370, 1985
98. Molitch ME, Thorne MO, Wilson C: Management of prolactinomas. **J Clin Endocrinol Metab** **82**:996–1000, 1997
99. Morange I, Barlier A, Pellegrini I, et al: Prolactinomas resistant to bromocriptine: long-term efficacy of quinagolide and outcome of pregnancy. **Eur J Endocrinol** **135**:413–420, 1996
100. Nickelsen T, Jungmann E, Althoff P, et al: Treatment of macroprolactinoma with the new potent non-ergot D2-dopamine agonist quinagolide and effects on prolactin levels, pituitary function, and the renin-aldosterone system. Results of a clinical long-term study. **Arzneimittelforschung** **43**:421–425, 1993
101. Orrego JJ, Chandler WF, Barkan AL: Pergolide as primary therapy for macroprolactinomas. **Pituitary** **3**:251–256, 2000
102. Orrego JJ, Chandler WF, Barkan AL: Rapid re-expansion of a macroprolactinoma after early discontinuation of bromocriptine. **Pituitary** **3**:189–192, 2000
103. Pan L, Zhang N, Wang E, et al: Pituitary adenomas: the effect of gamma knife radiosurgery on tumor growth and endocrinopathies. **Stereotact Funct Neurosurg** **70** (Suppl 1):119–126, 1998
104. Pan L, Zhang N, Wang EM, et al: Gamma knife radiosurgery as a primary treatment for prolactinomas. **J Neurosurg (Spine)** **3**:93:10–13, 2000
105. Passos VQ, Souza JJ, Musolino NR, et al: Long-term follow-up of prolactinomas: normoprolactinemia after bromocriptine withdrawal. **J Clin Endocrinol Metab** **87**:3578–3582, 2002
106. Pellegrini I, Rasolonjanahary R, Gunz G, et al: Resistance to bromocriptine in prolactinomas. **J Clin Endocrinol Metab** **69**:500–509, 1989
107. Peter SA, Autz A, Jean-Simon ML: Bromocriptine-induced schizophrenia. **J Natl Med Assoc** **85**:700–701, 1993
108. Randall RV, Laws ER Jr, Abboud CF, et al: Transsphenoidal microsurgical treatment of prolactin-producing pituitary adenomas. Results in 100 patients. **Mayo Clin Proc** **58**:108–121, 1983
109. Rasmussen C, Bergh T, Nillius SJ, et al: Return of menstruation and normalization of prolactin in hyperprolactinemic women with bromocriptine-induced pregnancy. **Fertil Steril** **44**:31–34, 1985
110. Rasmussen C, Bergh T, Wide L: Prolactin secretion and menstrual function after long-term bromocriptine treatment. **Fertil Steril** **48**:550–554, 1987
111. Ricci E, Parazzini F, Motta T, et al: Pregnancy outcome after cabergoline treatment in early weeks of gestation. **Reprod Toxicol** **16**:791–793, 2002
112. Rigg LA, Lein A, Yen SS: Pattern of increase in circulating prolactin levels during human gestation. **Am J Obstet Gynecol** **129**:454–456, 1977
113. Robert E, Musatti L, Piscitelli G, et al: Pregnancy outcome after treatment with the ergot derivative, cabergoline. **Reprod Toxicol** **10**:333–337, 1996
114. Sato S, Hanew K, Sasaki A, et al: Enhanced prolactin secretion

- in patients with primary hypothyroidism during thyroid replacement. **Tohoku J Exp Med** 144:425–431, 1984
115. Schlechte J, el-Khoury G, Kathol M, et al: Forearm and vertebral bone mineral in treated and untreated hyperprolactinemic amenorrhea. **J Clin Endocrinol Metab** 64:1021–1026, 1987
 116. Schlechte J, Sherman B, Halmi N, et al: Prolactin-secreting pituitary tumors in amenorrheic women: a comprehensive study. **Endocr Rev** 1:295–308, 1980
 117. Schlechte JA: Clinical practice. Prolactinoma. **N Engl J Med** 349:2035–2041, 2003
 118. Schlechte JA: Prolactinoma. **Curr Ther Endocrinol Metab** 6:45–47, 1997
 119. Schultz PN, Ginsberg L, McCutcheon IE, et al: Quinagolide in the management of prolactinoma. **Pituitary** 3:239–249, 2000
 120. Shimon I, Melmed S: Management of pituitary tumors. **Ann Intern Med** 129:472–483, 1998
 121. Shin M: Gamma knife radiosurgery for pituitary adenoma. **Biomed Pharmacother** 56 (Suppl 1):178S–181S, 2002
 122. Shringi MS, Vaidya RA, Gogate J: Prolactin producing pituitary tumors in postmenopausal patients—"infrequent or infrequently recognized". **Fertil Steril** 69:603–605, 1998
 123. Shrivastava RK, Arginteanu MS, King WA, et al: Giant prolactinomas: clinical management and long-term follow up. **J Neurosurg** 97:299–306, 2002
 124. Sievertsen GD, Lim VS, Nakawatase C, et al: Metabolic clearance and secretion rates of human prolactin in normal subjects and in patients with chronic renal failure. **J Clin Endocrinol Metab** 50:846–852, 1980
 125. Skrabanek P, McDonald D, Meagher D, et al: Clinical course and outcome of thirty-five pregnancies in infertile hyperprolactinemic women. **Fertil Steril** 33:391–395, 1980
 126. Smith CR, Butler J, Norman MR: Biological activity of serum prolactin in patients with primary hypothyroidism. **Ann Clin Biochem** 25 (Pt 5):540–545, 1988
 127. Smythe GA, Brandstater JF: Serum prolactin and brain and pituitary monoamine responses to chronic monoamine oxidase inhibition in the rat. **Aust J Biol Sci** 32:543–547, 1979
 128. Snieppen SB, Steensgaard-Hansen F, Feldt-Rasmussen U: Cardiac effects of low-dose growth hormone replacement therapy in growth hormone-deficient adults. An 18-month randomised, placebo-controlled, double-blind study. **Horm Res** 58:21–29, 2002
 129. Snyder PJ, Jacobs LS, Utiger RD, et al: Thyroid hormone inhibition of the prolactin response to thyrotropin-releasing hormone. **J Clin Invest** 52:2324–2329, 1973
 130. Steiner J, Cassar J, Mashiter K, et al: Effects of methyl dopa on prolactin and growth hormone. **Br Med J** 1:1186–1188, 1976
 131. St-Jean E, Blain F, Comtois R: High prolactin levels may be missed by immunoradiometric assay in patients with macroprolactinomas. **Clin Endocrinol** 44:305–309, 1996
 132. Stoffer SS, McKeel DW Jr, Randall RV, et al: Pituitary prolactin cell hyperplasia with autonomous prolactin secretion and primary hypothyroidism. **Fertil Steril** 36:682–685, 1981
 133. Thorner MO: Prolactinoma. **West J Med** 139:703–705, 1983
 134. Thorner MO, Perryman RL, Rogol AD, et al: Rapid changes of prolactinoma volume after withdrawal and reinstitution of bromocriptine. **J Clin Endocrinol Metab** 53:480–483, 1981
 135. Toffle RC, Webb SM, Tagatz GE, et al: Pregnancy-induced changes in prolactinomas as assessed with computed tomography. **J Reprod Med** 33:821–826, 1988
 136. Toft AD, Boyns AR, Cole EN, et al: The effect of thyrotrophin-releasing hormone on plasma prolactin and thyrotrophin levels in primary hypothyroidism. **Clin Endocrinol** 2: 289–295, 1973
 137. Touraine P, Plu-Bureau G, Beji C, et al: Long-term follow-up of 246 hyperprolactinemic patients. **Acta Obstet Gynecol Scand** 80:162–168, 2001
 138. Turner HE, Adams CB, Wass JA: Trans-sphenoidal surgery for microprolactinoma: an acceptable alternative to dopamine agonists? **Eur J Endocrinol** 140:43–47, 1999
 139. Tyrrell JB, Lamborn KR, Hannegan LT, et al: Transsphenoidal microsurgical therapy of prolactinomas: initial outcomes and long-term results. **Neurosurgery** 44:254–263, 1999
 140. Urban RJ, Veldhuis JD: A selective serotonin reuptake inhibitor, fluoxetine hydrochloride, modulates the pulsatile release of prolactin in postmenopausal women. **Am J Obstet Gynecol** 164:147–152, 1991
 141. Van de Kar LD, Lorens SA, Urban JH, et al: Effect of selective serotonin (5-HT) agonists and 5-HT₂ antagonist on prolactin secretion. **Neuropharmacology** 28:299–305, 1989
 142. van Roon E, van der Vijver JC, Gerretsen G, et al: Rapid regression of a suprasellar extending prolactinoma after bromocriptine treatment during pregnancy. **Fertil Steril** 36:173–177, 1981
 143. van 't Verlaat JW, Croughs RJ: Withdrawal of bromocriptine after long-term therapy for macroprolactinomas; effect on plasma prolactin and tumour size. **Clin Endocrinol** 34:175–178, 1991
 144. Vance ML, Evans WS, Thorner MO: Drugs five years later. Bromocriptine. **Ann Intern Med** 100:78–91, 1984
 145. Vance ML, Thorner MO: Prolactinomas. **Endocrinol Metab Clin North Am** 16:731–753, 1987
 146. Vartej P, Poiana C, Vartej I: Effects of hyperprolactinemia on osteoporotic fracture risk in premenopausal women. **Gynecol Endocrinol** 15:43–47, 2001
 147. Vician L, Shupnik MA, Gorski J: Effects of estrogen on primary ovine pituitary cell cultures: stimulation of prolactin secretion, synthesis, and preprolactin messenger ribonucleic acid activity. **Endocrinology** 104:736–743, 1979
 148. Wang C, Lam KS, Ma JT, et al: Long-term treatment of hyperprolactinaemia with bromocriptine: effect of drug withdrawal. **Clin Endocrinol** 27:363–371, 1987
 149. Wang MY, Weiss MH: Is there a role for surgery for microprolactinomas? **Seminars in Neurosurgery** 12:289–294, 2001
 150. Warfield A, Finkel DM, Schatz NJ, et al: Bromocriptine treatment of prolactin-secreting pituitary adenomas may restore pituitary function. **Ann Intern Med** 101:783–785, 1984
 151. Webster J: Cabergoline and quinagolide therapy for prolactinomas. **Clin Endocrinol** 53:549–550, 2000
 152. Webster J: A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. **Drug Saf** 14:228–238, 1996
 153. Webster J, Piscitelli G, Polli A, et al: A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. **N Engl J Med** 331:904–909, 1994
 154. Weiss M: Pituitary tumors: an endocrinological and neurosurgical challenge. **Clin Neurosurg** 39:114–122, 1992
 155. Weiss MH: Medical and surgical management of functional pituitary tumors. **Clin Neurosurg** 28:374–383, 1981
 156. Weiss MH, Wyckoff RR, Yadley R, et al: Bromocriptine treatment of prolactin-secreting tumors: surgical implications. **Neurosurgery** 12:640–642, 1983
 157. Wilson CB: Role of surgery in the management of pituitary tumors. **Neurosurg Clin N Am** 1:139–159, 1990
 158. Wolfsberger S, Czech T, Vierhapper H, et al: Microprolactinomas in males treated by transsphenoidal surgery. **Acta Neurochir** 145:935–941, 2003
 159. Yen SS, Ehara Y, Siler TM: Augmentation of prolactin secretion by estrogen in hypogonadal women. **J Clin Invest** 53: 652–655, 1974
 160. Zarate A, Canales ES, Cano C, et al: Follow-up of patients with prolactinomas after discontinuation of long-term therapy with bromocriptine. **Acta Endocrinol** 104:139–142, 1983

Manuscript received February 16, 2004.

Accepted in final form March 2, 2004.

Address reprint requests to: William T. Couldwell, M.D., Ph.D., Department of Neurosurgery, University of Utah School of Medicine, 30 North 1900 East, Suite 3B409, Salt Lake City, Utah 84132. email: William.Couldwell@hsc.utah.edu.