PREFACE

Six years after the first edition, the target readership for *Management of Pituitary Tumors: A Clinician's Practical Guide, Second Edition* remains the trainee in the specialties that treat pituitary disorders. That trainee, possibly more than before, still needs a "user-friendly" guide to the many aspects of these complex conditions, and such a guide must be up to the minute in this rapidly changing field. We hope too that the specialist already treating one aspect of pituitary disease will find the book a helpful guide to keep abreast of advances in the associated specialties.

The book remains the combined view of a group of specialists in pituitary disease. Rather than the predominantly European views provided in the first edition, we have now taken a trans-Atlantic view and included the most up-to-date North American and European approaches to pituitary adenomas.

We still believe that centralized treatment improves the quality of care. In the UK and the US pituitary clinics/groups now regularly work together. It still holds true that this sort of interaction should hasten accurate diagnosis of such diseases as pituitary Cushing's and ensure the most appropriate treatment with the minimum of morbidity and delay.

Cost implications are of importance. Specialist groups may have greater "short-term" patient costs, but overall should be cheaper, with more appropriate investigational protocols and shorter stay, fewer complications, and better cure rate. Since fewer patients will require long-term replacement hormones, the overall cost is almost certainly lower. In the UK, it now seems easier to cross-refer patients out of health regions than it was five years ago, when the political quirks of the so-called "competitive market" were at their worst. In the US, however, managed health care systems often make this form of transfer to specialist groups outside their system financially unacceptable.

Endocrine management has undergone considerable change in the last decade. It would be almost unthinkable now to suggest surgery as primary treatment for prolactinomas, the argument for dopamine agonists having been won on grounds of both their effectiveness and their lack of side effects. The new territory for debate is the medical management of acromegaly. Nowadays some endocrinologists would favor the long-acting somatostatin analogs as first-line treatment. In the summer of 2000 at the European Workshop in Pituitary Adenomas, the debate on treatment was won by surgery, but only on a 70/30% vote. Interestingly, the same debate a few months later by the British Endocrine

Society was comfortably won by surgery—but will we be so comfortable in another six years? Similarly, the diagnosis and definition of cure in pituitary Cushing's disease continues to attract vigorous debate.

Pituitary surgery is still a highly specialized art. Ciric's audit from 1997 showed what can go wrong, even for those who consider themselves experienced, with between 200 and 500 cases *(1)*. Even these surgeons have a higher complication rate than those with 500 or more. It would theoretically be preferable if microadenoma surgery were carried out in centers that perform a minimum of 50 cases per year, but in practice very few units annually carry out even 50 transsphenoidal cases overall. With the incidence of endocrine-active tumors, this would mean that in the UK only six units would need to be considered as "endocrine pituitary surgery specialists." Yet there are still units with tiny experience declaring an interest. One UK neurosurgeon declares a special interest in pituitary surgery on eight operative procedures per year! Similar situations exist in the US, where some neurosurgery units with limited experience readily accept patients for transsphenoidal surgery.

Medical politics and patient groups will probably play an important part in the foreseeable future. Shalet *(2)* reported the experience in Manchester, UK, over a defined period when no single surgeon specialized in pituitary surgery; an average of eight cases were operated on per surgeon in the ten-year study period yielding a 17% cure rate. At the same time a dedicated group from New York, audited by their endocrinologist, was reporting long-term cure rates of 62%. Comparison audits like this make a very strong argument for specialist groups. The Internet and pressure from patient groups will do the rest.

Another major challenge is the aggressive marketing of endoscopic "minimally invasive" pituitary surgery. Responsible surgeons such as Cappabianca are well aware that the argument favoring this form of surgery over traditional transsphenoidal methods has yet to be made. The studies necessary to show improvement in outcome and shortened inpatient stay have yet to be started. For most of us, the event that prolongs inpatient stay is postoperative endocrine testing and, to a certain extent in the UK, tradition. However, it cannot be denied that minimally invasive surgery is less painful, and less likely to produce facial marking.

In 1995, the regular use of growth hormone replacement was hardly considered. Now in the UK it is a contentious issue, currently before the UK government's National Institute for Clinical Excellence (NICE), who will decide on "evidence-based" grounds whether we can prescribe this modestly priced medication to our patients. However, in the US, patients who have been shown to be GH deficient on dynamic testing are usually approved for therapy.

We hope that by broadening our author base we have been able to make *Management of Pituitary Tumors: A Clinician's Practical Guide, Second Edition*, less parochial. Clearly there are significant trans-Atlantic differences—in units of measurement (both of which are used in this edition) and in surgical procedure (in the US a neurosurgeon will often carry out the surgery after an otolaryngologist has made the approach). The trans-Atlantic editorial collaboration has the virtue of bringing out the similarities and differences in our respective approaches.

A number of developments in the use of radiotherapy in the last few years have not yet been shown to be genuine advances. Clearly, fewer patients are being referred for conventional radiotherapy and there is a significant increase in the use of the Gamma Knife. Sadly, despite theoretical advantages in this technique, which has been available for 20 years, there is surprisingly little good data available to assess its advantages and disadvantages. This issue is addressed in the relevant chapters.

A much neglected area in practice is consideration of the patient's experience during investigation, treatment, and followup. With the recent recognition and expansion of patient support groups, we believed it important to provide a patient's viewpoint. Although there may be trans-Atlantic differences in management, the fears and experiences of the patient will be essentially identical wherever they are treated.

***Michael P. Powell**, MB, BS, FRCS*
***Stafford L. Lightman**, MB, BChir, PhD, FRCP, FMedSci*
***Edward R. Laws, Jr.**, MD, FACS*

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2 Prolactinoma

Prakash Abraham, MB, BS, MD, MRCP, and John S. Bevan, MD, FRCP (Edin)

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INTRODUCTION

Prolactin (PRL) was characterized as a hormone distinct from growth hormone, which also has lactogenic activity, as recently as 1971. In humans, the predominant PRL species is a 23 kDa, 199-amino-acid, polypeptide synthesized and secreted by lactotroph cells in the anterior pituitary gland. Pituitary PRL production is under tonic inhibitory control by hypothalamic dopamine, such that pituitary stalk interruption produces hyperprolactinemia. The neuropeptides thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP) exert less important stimulatory effects on pituitary PRL release *(1)*. Prolactin is essential for postpartum milk production and lactation. During pregnancy, increasing estrogen production stimulates the pituitary lactotrophs and causes increased PRL secretion. However, high estrogen levels inhibit PRL stimulation of the breasts, and, as a result, lactation does not occur until the estrogen levels decline postpartum.

Prolactinomas are the most common hormonally active pituitary tumors. There is a marked female preponderance, and prolactinoma is relatively rare in men. Several studies have revealed small prolactinomas in approx 5% of autopsy pituitaries, most of which are undiagnosed during life. From a clinical stand-

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point, prolactinomas may be divided arbitrarily into *micro*prolactinomas (<10-mm diameter) and *macro*prolactinomas (>10-mm diameter). This is a useful distinction that predicts tumor behavior and indicates appropriate management strategies. Generally, microprolactinomas run a benign course. Some regress spontaneously, most stay unchanged for many years, and few expand to cause local pressure effects. Pooled data from seven studies, including 139 patients with untreated microprolactinomas, show documented tumor expansion in only 9 patients (7%) *(2)*. In contrast, macroprolactinomas may present with pressure symptoms, often increase in size if untreated, and rarely disappear.

Prolactinomas are usually sporadic tumors. Molecular genetics have shown nearly all to be monoclonal, suggesting that an intrinsic pituitary defect is likely to be responsible for pituitary tumorigenesis. Occasionally, prolactinoma may be part of a multiple endocrine neoplasia syndrome (MEN-1), but this occurs too infrequently to justify MEN-1 screening in every patient with a prolactinoma. Mixed growth hormone (GH)- and PRL-secreting tumors are well recognized and give rise to acromegaly in association with hyperprolactinemia. Malignant prolactinomas are rare. A few cases have been described that have proved resistant to aggressive treatment with surgery, radiotherapy, dopamine agonists, and, occasionally, chemotherapy. In a small proportion, extracranial metastases in liver, lungs, bone, and lymph nodes have been documented.

CLINICAL FEATURES OF PROLACTINOMA

The clinical features of prolactinoma are attributable to three main factors: hyperprolactinemia, space occupation by the tumor, and varying degrees of hypopituitarism (Table 1). The individual clinical picture will be determined by the gender and age of the patient and the tumor size. In brief, hyperprolactinemia stimulates milk production, particularly from the estrogen-primed breast, and inhibits hypothalamic gonadotropin-releasing hormone (GnRH) release, which leads to hypogonadotropic hypogonadism.

Premenopausal women, most of whom have microprolactinomas, usually have oligomenorrhea or amenorrhea (90%) and/or galactorrhea (up to 80%). Anovulatory infertility is common. Excluding pregnancy, hyperprolactinemia accounts for 10–20% of cases of secondary amenorrhea. In passing, it is worth remembering that most women with galactorrhea do not have menstrual disturbance, hyperprolactinemia, or a pituitary tumor.

Postmenopausal women are, by definition, already hypogonadal and markedly hypoestrogenemic. Hyperprolactinemia in this age group does not, therefore, present with classic symptoms and may be recognized only when a large pituitary adenoma produces headache and/or visual disturbance.

The men with hyperprolactinemia experience reduced libido, impotence (75%), and infertility associated with a reduced sperm count. Such symptoms

Table 1
Clinical Features of Prolactinoma

A. Caused by prolactin excess
- Women
  - Oligomenorrhea/amenorrhea
  - Galactorrhea
  - Infertility
  - Hirsutism/acne[a]
- Men
  - Reduced libido
  - Impotence
  - Infertility
  - Galactorrhea[a]

B. Caused by tumor size (usually in men)
  - Headache
  - Visual failure, classically bitemporal hemianopia
  - Cranial nerve palsies

C. Caused by other pituitary hormone deficiency
  - *Microprolactinoma*—other pituitary function usually normal
  - *Macroprolactinoma*—varying degrees of hypopituitarism may be present

[a]Less common features.

are often concealed or ignored, particularly by older men, so men tend to present later with larger tumors causing pressure symptoms (Table 1). Galactorrhea is uncommon in men but does occur occasionally. Weight gain is noted frequently by men with hyperprolactinemia. Prolactinoma is an unusual cause of delayed puberty in both sexes, and some advocate the routine measurement of serum PRL in this situation.

Reduced bone mineral density (BMD) is a well-recognized long-term effect of untreated hyperprolactinemia. Studies of women with hyperprolactinemia and amenorrheia women have shown reductions in trabecular BMD of approx 20% (range 10%–26%) and cortical BMD of 6% (range 2.5%–11%) *(3)*. Reduced estrogen levels, as well as the direct effect of hyperprolactinemia, play a role in osteopenia. A longitudinal follow-up study of untreated women with amenorrheia suggested that BMD loss is progressive in some but not all cases, patients who are overweight and those with higher androgen levels being afforded some protection *(4)*. Restoration of menses after therapy results in an increase in bone density, although it may not return to normal *(4,5)*. Men with hypogonadism secondary to hyperprolactinemia also have significant BMD reductions. In one study of 20 men, 16 had osteopenia at the spine and 6 at the hip *(6)*. Adolescents had lower bone densities at the time of diagnosis, and less improvement was observed after two yr of dopamine agonist therapy, compared with adults with prolactinomas *(7)*.

Table 2
Causes of Hyperprolactinemia

A. Physiologic
- Stress (venipuncture?)
- Pregnancy
- Lactation

B. Pharmacologic
- Anti-emetics (e.g., metoclopramide, domperidone, prochlorperazine)
- Phenothiazines (e.g., chlorpromazine, thioridazine)
- Many others[1]

C. Pathologic
- Primary hypothyroidism
- Pituitary tumors
  - Prolactinoma
  - GH secreting (30% of people with acromegaly)
  - Nonfunctioning (stalk pressure or disconnection hyperprolactinemia)
- Polycystic ovarian syndrome (10% of people with polycystic ovary syndrome)
- Hypothalamic lesions (rare)
  - Sarcoidosis
  - Langerhan's cell histiocytosis
  - Hypothalamic tumors
- Chest wall stimulation
  - Repeated breast self-examination
  - Post-herpes zoster
- Liver or renal failure

GH, growth hormone.

DIAGNOSTIC INVESTIGATIONS

Causes of Hyperprolactinemia

The causes of hyperprolactinemia can be divided simply into physiologic, pharmacologic, and pathologic (Table 2). The normal PRL range for nonpregnant women is <500 mU/L (20 μg/L) and for men <300 mU/L (12 μg/L). Pregnancy is the most common cause of hyperprolactinemic amenorrhea, and serum PRL concentrations may rise as high as 8000 mU/L (320 μg/L) during the third trimester. Normal lactation is also associated with quite marked elevation of serum PRL. As predicted from the physiologic dopaminergic inhibition of PRL secretion, treatment with dopamine receptor antagonist drugs commonly induces hyperprolactinemia. Serum PRL levels may rise as high as 5000 mU/L (200 μg/L). This is a particular problem with the major tranquilizers (e.g., chlorpromazine) and anti-emetics (e.g., metoclopramide). A source of potential confusion may arise if a patient does not reveal that he or she is taking an over-the-counter preparation, such as a combined medication for the treatment

of migraine, which contains both an analgesic and an anti-emetic. Similarly, some nonprescribed herbal or alternative remedies contain constituents that cause PRL elevation. Thus, a comprehensive drug history is essential. With regard to pathologic causes of hyperprolactinemia, it is important to exclude primary hypothyroidism. Modest hyperprolactinemia is present in 40% of patients, although only 10% have levels > 600 mU/L (24 μg/L). Nevertheless, some young women with hypothyroidism may present with menstrual disturbance and galactorrhea, together with few typical hypothyroid symptoms. Once venipuncture stress, pregnancy, interfering drugs, and primary hypothyroidism are excluded, significant hyperprolactinemia is usually associated with a pituitary adenoma (Table 2).

Interpretation of Prolactin Immunoassay Results

Macroprolactin

PRL in human serum exists in multiple molecular forms, with three dominant species identified by gel filtration chromatography: monomeric PRL (23 kDa), big PRL (50–60 kDa), and big-big PRL (macroprolactin, 150–170 kDa). Macroprolactin is a complex of PRL, with an IgG antibody that is detected by most, but not all, PRL immunoassays. The clinical significance and biologic activity of macroprolactin remain contentious. Recent studies have indicated that this PRL species is present in significant amounts in up to 20% of hyperprolactinemic sera. However, many patients with macroprolactinemia do not exhibit typical hyperprolactinemic symptoms, and preliminary data suggest that this prolactin variant is virtually never associated with macroprolactinoma. The presence of macroprolactin can be confirmed by a simple polyethylene glycol precipitation method *(8)*. Presently, there is little justification for detailed pituitary investigation after the finding of macroprolactinemia in an essentially asymptomatic individual.

Prolactin Hook Effect

If serum PRL concentrations are extremely high (as in some men with giant prolactinomas), the amount of PRL antigen may cause antibody saturation in PRL immunoradiometric assays (IRMAs), leading to artifactually low PRL results. This is known as the high-dose hook effect and has been occasionally recognized in other immunoassays (e.g., β-human chorionic gonadotropin [hCG]). This artifact may lead to misdiagnosis and inappropriate surgery for some patients with macroprolactinoma. If an IRMA is employed, serum PRL should always be assayed *in dilution* in any patient with a large pituitary lesion that might be a prolactinoma *(9)*.

Dynamic Prolactin Function Tests

Several dynamic tests have been proposed for the evaluation of hyperprolactinemia. However, a recent survey showed that only 15% of UK

clinical endocrinologists routinely use dynamic PRL function tests, with most using thyrotropin-releasing hormone (TRH) rather than a dopamine antagonist. In our experience, the intravenous (iv) administration of a dopamine antagonist (such as 10 mg metoclopramide) is a simple well-tolerated procedure that provides clinically useful information, particularly for patients with modest serum PRL elevations. Dopamine antagonist administration to normal individuals results in a marked rise in serum PRL concentration (to at least three times basal) together with little or no change in serum thyroid-stimulating hormone (TSH) (<2 mU/L rise). In contrast, patients with pituitary microlesions and macrolesions have blunted PRL responses. Patients with microprolactinomas may, in addition, show exaggerated TSH responses owing to enhanced dopaminergic tone on the anterior pituitary thyrotrophs (via short-loop hypothalamic feedback).

Sawers and coworkers reviewed 84 patients with hyperprolactinemia whose screening had included a domperidone test and high-resolution magnetic resonance imaging (MRI) *(10)*. They found that 18 of 20 patients with normal PRL responses to domperidone had normal MRI scans, and the other 2 had only microadenomas. In contrast, 18 of the remaining 64 patients with abnormal PRL responses had lesions greater than 10 mm in diameter. Of the rest, 63% had microadenomas. Dopamine antagonist testing can therefore identify a subset of hyperprolactinemic patients for whom detailed pituitary imaging is mandatory. Conversely, a normal PRL response to domperidone obviates the need for pituitary imaging and can reduce usage of this limited resource.

Dopamine antagonist testing can also be useful before and after surgery for microprolactinoma. Webster and colleagues described a series of 82 patients with hyperprolactinemia submitted to surgery for suspected prolactinoma *(11)*. No tumor was found in three cases, including the only two patients with normal PRL and TSH responses to domperidone. Overall, 79% of patients had early postoperative normalization of serum PRL, but there were three relapses during long-term follow-up. Two of these had persistently abnormal PRL and TSH responses to domperidone, even when basal PRL levels remained normal.

Thus, although few patients with microprolactinoma are now treated surgically, these data are important because they indicate that dopamine antagonist testing can confirm (or refute) the presence of a microprolactinoma with reasonable certainty. Clinicians may regard this confirmatory biochemical evidence to be helpful in the medical management of such patients when histologic proof of the diagnosis will not be forthcoming.

TRH testing is less discriminatory and generally not helpful in hyperprolactinemia investigation. However, the test may have limited use in the evaluation of patients with GH- or gonadotrophin-secreting tumors, a proportion of whom will show paradoxical stimulation of hormone release.

Diagnostic Value of the Basal Serum Prolactin Concentration

Most patients with microprolactinomas have basal serum PRL concentrations less than 5000 mU/L (200 μg/L). In patients with pituitary macrolesions, the basal serum PRL is of considerable diagnostic value. A value greater than 5000 mU/L is virtually diagnostic of a macroprolactinoma and with a level greater than 10,000 mU/L (400 μg/L), there is no other possible diagnosis. A serum PRL concentration lower than 2000 mU/L (18 μg/L) in a patient with a pituitary macrolesion usually indicates disconnection hyperprolactinemia rather than tumoral secretion of the hormone. This is due most commonly to a nonfunctioning pituitary macroadenoma, although intrasellar craniopharyngioma and numerous other neoplastic and inflammatory pathologies may masquerade as pseudopituitary adenomas *(12)*. An intermediate serum PRL level (2000–5000 mU/L or 80–200 μg/L) in a patient with a large pituitary lesion produces an area of diagnostic uncertainty that dynamic PRL function tests cannot resolve; approx 50% of such patients will have true prolactinomas and the remainder disconnection hyperprolactinemia *(12,13)*.

Pituitary Imaging and Ophthalmological Assessment

This is similar to the assessment of patients with other pituitary and parapituitary lesions and is described in Chapters 5 and 6.

General Pituitary Function

Larger pituitary masses may cause hypopituitarism by either direct pituitary compression or disruption of hypothalamic control mechanisms. Patients with microprolactinomas usually have normal GH, adenocorticotropic hormone (ACTH), and TSH function. However, with macroprolactinomas, the degree of hypopituitarism is likely to be proportional to the size of the tumor. With the largest tumors, ACTH and TSH deficits may be present at diagnosis in approx 20% of patients, and GH deficiency is almost invariable. All patients with macroprolactinomas should have full pituitary function testing, using the methods described in Chapter 12.

TREATMENT OF PROLACTINOMA

An algorithm for the management of prolactinoma is given in Fig. 1.

Treatment Indications

Most patients with prolactinoma require active treatment. Infertility, menstrual disturbance with long-standing hypogonadism (risk of secondary osteoporosis), troublesome galactorrhea, an enlarging pituitary tumor and tumor

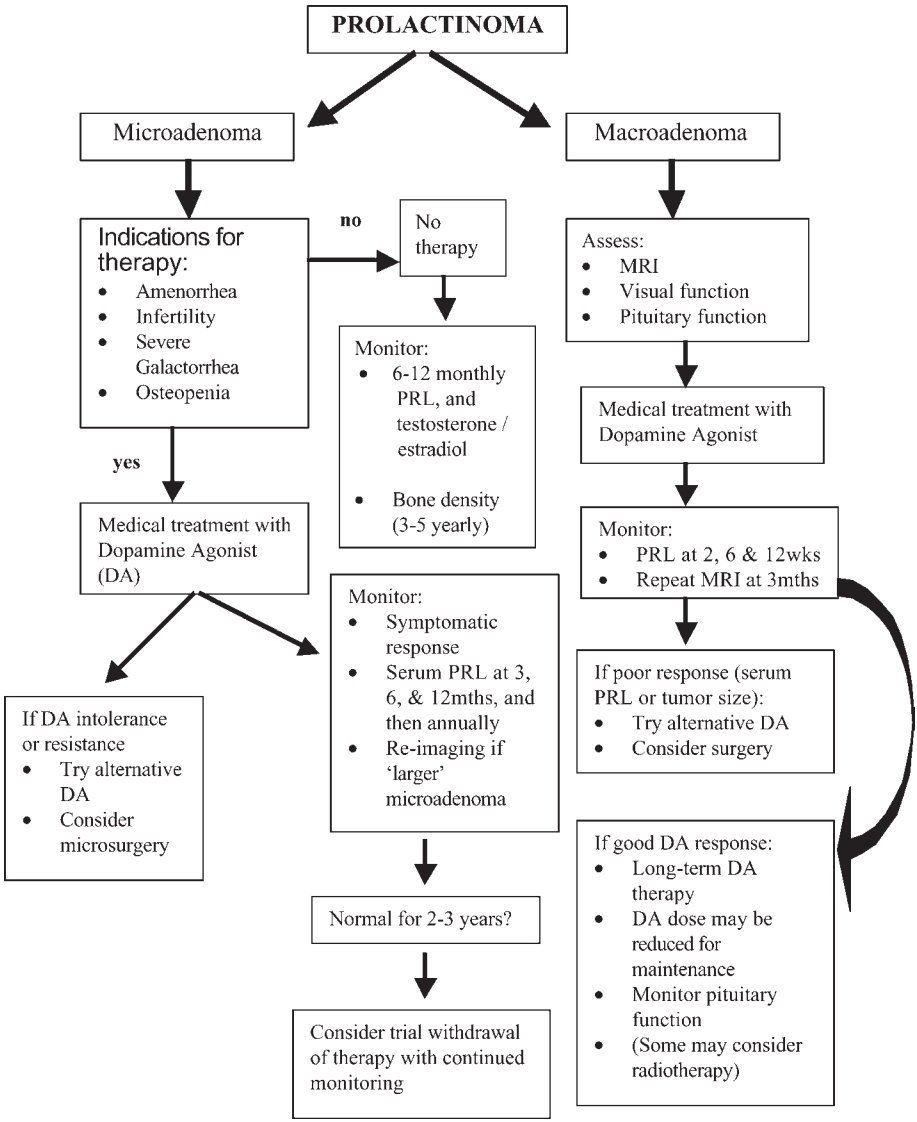

Fig. 1. Management algorithm for prolactinoma.

pressure effects (particularly visual failure) are all indications for treatment. As will be seen, dopamine agonist drugs are now indicated as primary medical therapy for patients with prolactinomas of *all* sizes. However, an important exception is the patient with a pituitary macrolesion and minor PRL elevation, who is most likely to have a nonfunctioning pituitary adenoma requiring surgery

for decompression and histologic diagnosis. It may be reasonable to simply observe some patients with microprolactinomas, particularly if circulating sex steroid concentrations are judged to be adequate and BMD is normal.

Dopamine Agonists

The introduction of medical therapy with dopamine agonists revolutionized the treatment of patients with prolactinoma. The first such drug was bromocriptine, a semisynthetic ergopeptine derivative, introduced in 1971. On a global basis, this probably remains the most widely used dopamine agonist, but the introduction of other longer acting and better tolerated drugs, such as cabergoline and quinagolide, is altering this pattern, at least in the Western world. Many UK endocrine units now use cabergoline as first-choice dopamine agonist after a large comparative study with bromocriptine, which convincingly demonstrated its superiority in terms of tolerability, patient convenience, and possibly also efficacy *(14)*. All dopamine agonists may produce unwanted side effects, including, in decreasing order of importance, upper gastrointestinal disturbance (especially nausea), postural hypotension, constipation, nasal stuffiness, and Raynaud's phenomenon. These can be minimized by using an incremental dosage schedule and taking tablets during meals.

Cabergoline and quinagolide are newer dopamine agonists, which have been licensed in the UK during the last decade. Table 3 summarizes the recent prospective comparative studies of these agents, both with each other and with bromocriptine. Bromocriptine normalized PRL in 57% of patients, compared with 85% taking cabergoline and 78% taking quinagolide. Cabergoline was better tolerated, with mild adverse effects reported in only 37% and fewer than 3% of patients withdrawing from therapy. Bromocriptine caused mild adverse effects in 67%, with 13% of patients needing to cease therapy. Table 4 provides an overview of recent publications addressing cabergoline efficacy and tolerability. In pooled data from 1485 patients (972 with microadenomas and 513 with macroadenomas), PRL was normalized in 87% of patients. Adverse effects were noted in 26% of patients, but only 1.7% of patients had to discontinue therapy. It is notable that cabergoline was effective (approx 80%) and well tolerated (>90%) in the majority of patients with bromocriptine resistance (164 patients) and bromocriptine intolerance (267 patients). Colao and colleagues reported that 17 of 20 patients resistant to quinagolide achieved normoprolactinemia during cabergoline therapy, although a proportion may have been poorly compliant with quinagolide *(29)*.

Bromocriptine is used in a dose of 2.5 mg two or three times daily. It is now clear that the doses of 20–40 mg/d used in early studies are no more efficacious and produce more side-effects. Cabergoline is usually effective in a dose of 0.5–1.0 mg once or twice *weekly* and quinagolide in a *once-daily* dose of 75–150 μg. To minimize side effects, patients should be advised to take these two newer

Table 3
Prospective Comparative Studies of Bromocriptine, Cabergoline, and Quinagolide

Study author (year) (ref)	*Drugs*[a]	*Total patients*	*Study design and duration*	*Prolactin normalization (PRL n)*	*Return of menses or normal gonadal function (G) (%)*	*Mild adverse effects (AD) (%)*	*Drug withdrawal (WD)*
Webster	BCR	236	MC,R	138 (58%)	84	78	27 (12%)
(1994) *(14)*	CBG	223	DB (8 wk)	186 (83%)	93	68	7 (3%)
Van der Heijden	BCR	24	R, DB,	14 (70%)	79	66	4 (16%)
(1991) *(15)*	QUI	23	24 wk	17 (81%)	80	78	1 (14%)
Verhelst	BCR	5	R, DB,	2 (40%)	70	60	0
(1991) *(16)*	QUI	7	24 wk	3 (43%)	82	57	1 (14%)
Homburgh	BCR	11	R, DB,	3 (27%)	82	64	4 (36%)
(1990) *(17)*	QUI	11	24 wk	10 (91%)	91	82	0
Giusti	CBG	12	R, NB	10 (83%)	82	50	1 (8%)
(1994) *(18)*	QUI		CO, 12 wk	6 (50%)	80	90	2 (16%)
Di Sarno	CBG	39[b] (23	NB, CO	22 (95%) mic	100% (mic)	0	0
(2000) *(19)*		mic and 16 mac)	52 wk	14 (87%) mac			
	QUI			23 (100%) mic	100% mic	30	0
				14 (87%) mac	62% mac		
De Luis DA	CBG	20	R, NB,	18 (90%)	95	30	0
(2000) *(20)*	QUI		CO, 12 wk	15 (75%)	90	55	0

[a]Bromocriptine: Total 276, PRL n: 157 (57%), G: 79%, AD: 67%, WD: 35 (13%); Cabergoline: Total 294, PRL n: 256 (85%), G: 91%, AD: 37%, WD: 8 (2.5%); Quinagolide: Total 112, PRL n: 88 (78%), G: 84%, AD: 65%, WD: 4 (3.5%)
[b]All other studies had few macroadenomas (only 6 out of 643 patients).

BCR, bromocriptine; CBG, cabergoline; QUI, quinagolide; R, Randomized; MC, multicenter; DB, double blind; NB, nonblinded; CO, crossover; PRL n, PRL normalization; G, gonadal function; AD, adverse effects; WD, drug withdrawal; mic, microadenoma; mac, macroadenoma.

Table 4
Overview of Cabergoline Efficacy and Tolerability in Patients With Hyperprolactinemic Disorders

Year	Author (reference)	Micro[a]/ macro adenoma	% Patients with PRL normalization	% Side effects	% Dropouts	% Patients with tumor reduction[b]	BCR-resistant/ intolerant
1989	Ciccarelli *(21)*	27/3	81	48	11	71	0/7
1989	Ferrari *(22)*	38/8	85	15	0	83	
1992	Ferrari *(23)*	108/19	90	23	0	79	10/1
1993	Webster *(24)*	161/1	92	40	3		0/27
1994	Webster *(14)*	223/0	83	68	3		
1995	Pascal-Vigneron *(25)*	60/0	93	52	3.3		
1996	Biller *(26)*	0/15	73	Minimal	0	73	5/5
1997	Ferrari *(27)*	0/85	61	25	4.7	66	16/32
1997	Muratori *(28)*	26/0	96	24	0	68	
1997	Colao *(29)*	8/19	85	22	0	48	27/0
1997	Colao *(30)*	0/23	83	4	0	61	6/2
1999	Verhelst *(31)*	249/181	86	13	3.9	67	58/140
1999	Cannavo *(32)*	26/11	92	12	0	96	
2000	Pontikides *(33)*	0/12	100	15	0	100	
2000	Pinzone *(34)*	3/10	92				
2000	Di Sarno *(19)*	23/16	92	0	0	30	23/16
2000	De Luis *(20)*	20/0	90	30	0		
2000	Colao *(35)*	0/110	99[c]	5	0	47[d]	19/37
Totals or means		972/513	87	26	1.7	66	164/267

[a]Includes idiopathic hyperprolactinemia and empty sella.
[b]Criteria differ between studies and imaging was performed on only subgroups of patients.
[c]74% after 6 mo, the remainder after higher doses (up to 3.5 mg/wk) *for 18 to 24 mo.*
[d]92% in patients who had no previous exposure to dopamine agonists, with complete disappearance in 61%.

drugs, together with a snack, just before retiring to bed. It is worth noting that acute psychotic reactions have been described with quinagolide, albeit rarely. It is unclear whether this important side effect is drug specific because acute psychosis was encountered occasionally in previous patients treated with large bromocriptine doses.

Microprolactinomas

Dopamine Agonists

Medical therapy is remarkably effective in the treatment of microprolactinoma. In the early studies of patients treated with bromocriptine, normoprolactinemia or ovulatory cycles were restored in 80%–90% of patients. Fertility returned within 2 mo in 70% of women. Galactorrhea disappeared or was greatly reduced in the majority of patients, usually within a few days or weeks. In the more recent comparative study of cabergoline and bromocriptine, resumption of ovulatory cycles or occurrence of pregnancy was documented in 72% of cabergoline patients (up to 1.0 mg twice weekly) compared with 52% in the bromocriptine group (up to 5.0 mg twice daily) *(14)*. The number of women with stable normoprolactinemia was also higher in the cabergoline group (83% vs 58%).

Tumor shrinkage occurs during long-term treatment, although this is less critical than for patients with macroprolactinomas. Importantly, a minority of patients may be cured after a period of dopamine agonist treatment. The mechanism is unknown. The probability of cure remains unclear but perhaps between 10% and 20% of microprolactinomas remit with time. It has been suggested that a dopamine agonist-induced pregnancy increases the chances of remission *(36)*. For these reasons, most endocrinologists interrupt dopamine agonist treatment every 2–3 yr, for further clinical assessment and PRL testing. In doing so, one should remember that women may continue to have ovulatory cycles for 3–6 mo after withdrawal of the long-acting drug cabergoline *(23)*.

Transsphenoidal Surgery

In some centers, transsphenoidal surgery may be offered as an alternative to medical therapy. Indeed, surgery may be essential if the patient is intolerant of or resistant to dopamine receptor agonists. Surgical success is critically dependent on surgical experience and tumor size. In most large centers, normoprolactinemia is achieved postoperatively in 60% to 90% of patients, with results for larger microprolactinomas (4–9 mm diameter) being significantly better than for smaller ones *(11)*. Previous dopamine agonist therapy may hamper surgery but this is less troublesome for microprolactinomas than it is for macroprolactinomas. Recurrence of hyperprolactinemia, usually without radiologically evident tumor, is well recognized. Early reports suggested this might occur in up to 50% of microprolactinoma patients, but a recent meta-analysis of 1224 surgically treated microprolactinomas gave a recurrence figure of 17% *(2)*. However,

it should be stressed that long-term follow-up is still quite short. Using normoprolactinemia as the main criterion of cure, it is probably reasonable to speak of a *long-term surgical cure rate* of between 50% and 70% when counseling patients with respect to choice of therapy. It is, of course, important also to mention the small but measurable morbidity of transsphenoidal surgery (*see* Chapter 8), together with the small risk of loss of normal pituitary function. The latter would be particularly important if the patient wished fertility.

Owing to the excellent therapeutic responses to either dopamine agonists or transsphenoidal surgery, radiotherapy is no longer considered acceptable primary therapy for microprolactinoma.

Observation (Including Oral Contraception)

Longitudinal studies suggest that only 7% of microprolactinomas progress to larger lesions. Hence, in a woman with a microprolactinoma who has normal menses and libido and nontroublesome galactorrhoea and who does not wish to become pregnant, there may be no clear indication for antiprolactinoma therapy. Before recommending simple observation of a microprolactinoma, most endocrinologists would wish to confirm adequate circulating sex steroid concentrations (mean estradiol >200 pmol/L [55 pg/mL]) in a woman and testosterone >7 nmol/L (2 ng/mL) in a man), together with BMD within one standard deviation of age-related mean values. In this situation it would be reasonable to monitor the patient with 6–12 monthly serum PRL and estradiol/testosterone estimations, supplemented with bone densitometry every 3–5 yr, thus enabling individualized timing of any intervention. The question of oral contraceptive safety often arises. There are good data confirming the safety of oral contraceptive in combination with a dopamine agonist in women with microprolactinomas but no satisfactory prospective studies of treatment with an oral contraceptive alone. If the latter course of action is taken, serum PRL should be checked every 3–6 mo, with the addition of dopamine agonist therapy should the serum PRL level rise above an arbitrary target level (e.g., twice the basal level).

Macroprolactinomas

Dopamine Agonists

These drugs directly activate pituitary D2 dopamine receptors, mimicking the action of endogenous hypothalamic dopamine. In addition to reducing PRL secretion, D2 receptor stimulation results in rapid involution of the cellular protein synthetic machinery and thus marked reduction in lactotroph cell size. This effect, together with an antimitotic action, accounts for the rapid and sustained tumor shrinkage, which enables these drugs to be used as *primary therapy* for patients with larger prolactinomas, even those with pressure effects.

Dopamine agonist treatment is followed typically by a rapid fall in serum PRL (within hours) and tumor shrinkage (within days or weeks). Tumor regression is

often followed by an improvement in visual function over a (short) time course that rivals that seen after surgical decompression of the chiasm. Thus, patients with macroprolactinomas with visual failure are no longer the neurosurgical emergency they were previously regarded to be. Nevertheless, it is important that all patients with a pituitary macrolesion producing chiasmal compression should have serum PRL measured urgently (and checked in dilution—*see* "Interpretation of Prolactin Immunoassay Result," earlier). An illustrative patient is shown in Fig. 2.

Shrinkage rates. A meta-analysis of 271 well-characterized macroprolactinomas treated with dopamine agonists showed that 79% of tumors shrank by more than a quarter and 89% shrank to some degree *(37)*. The pretreatment PRL level is not a reliable predictor of tumor shrinkage, because 83% of tumors showed significant tumor shrinkage in both the >100,000 mU/L (4000 μg/L) and 5000–10,000 mU/L (200–400 μg/L) groups. Of the macroprolactinomas large enough to produce chiasmal compression, 85% showed significant tumor shrinkage.

Time course of shrinkage. Tumor shrinkage can be demonstrated with a week or two of starting dopamine agonist therapy, and most shrinkage takes place during the first 3 mo of treatment *(37,38)*. However, in many patients, shrinkage continues at a slower rate during many months. It is recommended to repeat MRI 2–3 mo after commencing dopamine agonist therapy and, if there has been an acceptable response, at longer intervals thereafter.

Amount of shrinkage and visual recovery. Approx 40% of macroprolactinomas treated with dopamine agonists for between 1 and 3 mo show tumor-size reduction of at least one half. Of those treated for 1 yr or longer, almost 90% show such shrinkage *(37)*. Colao and colleagues in a recent prospective study of 110 patients with macroprolactinoma have suggested that tumor shrinkage is greater in previously untreated (*de novo*) patients *(35)*. Tumor shrinkage (>80% of pretreatment volume) was noted, with standard doses of cabergoline in 92% of *de novo* patients, compared with 42% of dopamine-agonist-intolerant and 30% of dopamine-agonist-resistant patients. Tumor shrinkage was only 38% in patients with previously responsive tumors switched to cabergoline because of poor compliance with or nonavailability of a previous dopamine agonist.

Visual field defects improve in approx 90% with these abnormalities. It is important to stress that although early visual improvement occurs frequently, it may be several months before maximum benefit accrues. Thus, persistence of a visual field defect is not an absolute indication to proceed to surgery.

Serum PRL responses. Suppression of serum PRL usually accompanies successful tumor shrinkage. Indeed, all of the responsive patients in the meta-analysis showed a fall in serum PRL of at least 50%, and in 58% of patients serum PRL became entirely normal *(37)*.

Effects on pituitary function. Several investigators have demonstrated recovery of impaired anterior pituitary function in association with tumor shrinkage. Importantly, these data have been extended recently to include recovery of GH

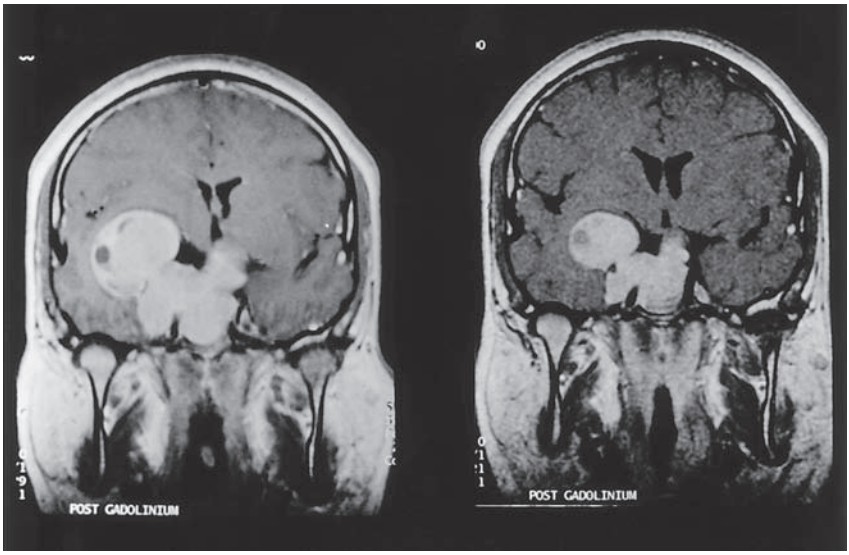

Fig. 2. This 26-yr-old-man presented via the ophthalmology clinic with a 6-mo history of headache and decreased color vision and a 1-mo history of bitemporal visual field loss. He also described episodes suggestive of temporal lobe epilepsy. Initial serum prolactin level was enormously raised at 821,000 mU/L (normal <300) and MRI showed a 7.4-cm invasive macroadenoma, extending into the right temporal lobe (left hand panel). Serum testosterone was reduced at 4 nmol/L and gonadotropin concentrations were low. Thyroid and adrenal functions were normal. He commenced cabergoline 0.5 mg twice weekly, and the dose was incremented to 1 mg twice weekly after 4 mo. His headaches subsided within 1 mo, visual fields were normal after 4 mo and the TLE episodes disappeared. Serum prolactin fell to 84,060 mU/L after 4 d and to 12,790 mU/L after 9 mo. MRI showed a considerable reduction in tumor size after 3 mo of medical therapy (right hand panel).

reserve, which may obviate the need for expensive GH replacement in a proportion of patients *(39,40)*. In contrast, it is worth noting that at least two thirds of men with successfully treated prolactinomas have persistently subnormal testosterone levels and require androgen supplementation *(37)*. Details of gonadal function in women with medically treated macroprolactinomas are difficult to glean from the literature. Cyclical menses return in more than 90% of premenopausal women. The effects on pregnancy are discussed in "Pregnancy and Prolactinomas," following.

Dopamine agonist resistance. Overall, the acquisition of dopamine agonist resistance during therapy is rare, even with treatment periods of 10 or more years. A handful of cases have been described, however *(37)*.

Dopamine agonist withdrawal. Although prolactinomas usually remain sensitive to dopamine agonists, the drugs do not appear to provide a definitive cure for macroprolactinoma and most patients have to remain on long-term therapy.

Immediate tumor re-expansion may occur after drug withdrawal following medium-term therapy (up to 1 yr). Such re-expansion is less common after long-term treatment (several years), but the return of hyperprolactinemia in most patients suggests that tumor regrowth would occur over time. In practice, the dose of dopamine agonist can often be reduced considerably once initial tumor regression has been achieved, with ongoing satisfactory control of tumor size.

Nonshrinking prolactinomas. Approx 10% of genuine macroprolactinomas fail to regress during dopamine agonist therapy. The mechanism of this primary resistance is obscure because most patients with nonshrinking tumors have marked suppression of serum PRL levels. Some resistant tumors have large cystic components, some have atypical histology, and some have a deficiency of membrane-bound D2 dopamine receptors *(37)*.

Management strategies. Macroprolactinoma is virtually certain if serum PRL is greater than 5000 mU/L (200 μg/L) in a patient with a pituitary macrolesion, and primary treatment with a dopamine agonist has an excellent chance of tumor volume reduction. As noted in"Diagnostic Value of the Basal Serum Prolactin Concentration," earlier, a serum PRL level between 2000 and 5000 mU/L (80–200 μg/L) presents some diagnostic uncertainty. The choice between dopamine agonists and surgery will depend on several factors, including local surgical expertise, the severity of any visual failure, patient preference, and clinical judgment. A closely supervised dopamine agonist therapy trial is perfectly reasonable, provided surgery is performed in the event of visual deterioration or failure of the lesion to shrink after, at most, 3 mo of therapy. Using dopamine agonists, visual failure will persist for longer if the lesion is not a prolactinoma, but up to 50% of patients will avoid surgery. It is important to note that dopamine agonists reduce PRL secretion from both normal and tumorous lactotrophs; therefore, serum PRL is likely to fall, irrespective of the cause of the hyperprolactinemia. Pituitary macrolesions associated with PRL levels less than 2000 mU/L (80 μg/L) are rarely prolactinoma, and surgery should be undertaken to decompress the lesion and provide a histologic diagnosis.

The Present Role of Radiotherapy and Surgery

Medical treatment alone is an acceptable option for most patients with macroprolactinoma, particularly those with fertility needs in whom adjunctive therapy might compromise gonadotropin function. Physicians should be aware of the infrequent complication of cerebrospinal fluid (CSF) rhinorrhea, which may occur after shrinkage of inferiorly invasive tumors and may be difficult to correct surgically.

Some endocrinologists consider that dopamine agonist therapy alone is unsuitable for long-term management of macroprolactinoma and recommend external beam radiotherapy. Although PRL levels fall during a several-year period after radiotherapy, enabling dopamine agonist withdrawal in a propor-

tion of patients, this treatment is likely to be followed by varying degrees of hypopituitarism.

A meta-analysis of 1256 macroprolactinomas treated with primary surgery showed PRL normalization in only 32% of patients *(2)*. Consequently, in view of the effectiveness of medical treatment, only a minority of patients with large tumors should now require surgical intervention. There are three situations in which some clinicians might consider surgery, and a cautionary note on the effect of dopamine agonists on prolactinoma fibrosis is necessary.

First, some macroprolactinomas have considerable suprasellar tissue, even after prolonged dopamine agonist therapy, and some clinicians may be inclined to debulk these tumors before radiotherapy. However, there is a direct relationship between tumor fibrosis and duration of medical treatment such that surgery is made much more difficult and may even be hazardous if dopamine agonists have been given for more than 3 mo *(38,41)*. Furthermore, it is now clear that external radiotherapy can be given safely to patients with persistent suprasellar disease, and anecdotal reports of tumor swelling and visual deterioration have assumed undeserved prominence. Second, up to 10% of macroprolactinomas may require surgery after failure of dopamine agonist shrinkage, most of which are likely to be treated surgically within a few months of presentation, particularly if vision is compromised. Third, it is possible that if short-term dopamine agonist therapy produces a compact intrasellar tumor, which will be uncommon with large adenomas, some may be curable by subsequent surgery. This remains unproven. Overall, it would seem prudent to limit pre-operative medical treatment to a maximum of 3 mo, if surgery is to be undertaken. Gamma Knife radiosurgery is offered in few specialized centers, especially in situations where PRL cannot be normalized with dopamine agonists or microsurgery *(42)*.

Pregnancy and Prolactinomas

Management Recommendations

Estrogens have a marked effect on PRL synthesis and secretion, and the hormonal changes of normal pregnancy cause marked lactotroph hyperplasia. MRI studies have confirmed a gradual doubling in pituitary volume during gestation. In view of these effects of pregnancy on normal lactotrophs, it is not surprising that prolactinomas may also increase in size.

The potential risk to the patient depends on the prepregnancy size of the prolactinoma. For women with microprolactinomas, the risk of clinically relevant tumor expansion is small indeed—less than 2%. Dopamine agonists can be safely stopped in such patients as soon as pregnancy is confirmed. Nevertheless, they should be advised to report for urgent assessment in the event of severe headache or any visual disturbance. Routine endocrine review may be arranged on two or three occasions during the pregnancy, but formal charting of visual fields is unnecessary and measurement of serum PRL provides no useful infor-

mation, given the considerable PRL rise during normal gestation. Patients can safely breast-feed their infants.

There has been some controversy concerning the risk of pregnancy for women with larger prolactinomas. In early reviews, macroprolactinoma expansion was reported to occur in nearly 40%, but many of these women received ovulation induction with gonadotrophins and not dopamine agonists. More recent reviews suggest that symptomatic macroprolactinoma expansion occurs in well under 20% of women. The figure is probably 5% or lower in women, given a several-month course of dopamine agonist before conception *(43)*.

Some clinicians continue to recommend conservative debulking surgery or even radiotherapy before pregnancy in women with macroprolactinomas to reduce the likelihood of major tumor expansion. However, dopamine agonists may be safely employed as sole therapy, using the following strategy. Medical treatment should be used for a minimum of 6 mo preferably 12 mo, together with follow-up MRI to assess residual suprasellar extension, *before* conception is attempted. If the tumor has shrunk to within the fossa, the dopamine agonist can be withdrawn once pregnancy is confirmed, with a less than 10% chance of re-expansion problems. If neurologic problems do occur, *bromocriptine* should be started during the pregnancy and this will restore tumor control in nearly all cases *(38)*. If there is significant suprasellar tumor before conception, the choice is between debulking surgery or continuing bromocriptine throughout the pregnancy. The latter is effective but present experience is limited to slightly more than 100 women.

Dopamine Agonist Safety

There is no evidence of teratogenicity in the offspring of women treated with simple bromocriptine-induced ovulation or those treated throughout pregnancy with the drug. Nevertheless, the oldest bromocriptine child is still only 25 years old, and it is prudent not to use the drug during pregnancy unless absolutely necessary.

Safety data for the newer dopamine agonists, cabergoline and quinagolide, are limited to a few hundred pregnancies, compared with several thousand for bromocriptine. Nevertheless, no new problems have yet emerged. As of May 1999, the manufacturer of cabergoline had data on 334 pregnancies in 301 women treated with the drug. The spontaneous abortion rate in 294 pregnancies with known outcome was 9.5%, well within the expected range. The fetal malformation rate also falls within reported ranges for the general population, and no malformation has occurred more than once. Because clinical experience is limited in relation to pregnancy and because the drug has a long half-life, it is still recommended that cabergoline be stopped 1 mo before intended conception. However, this is clinically inconvenient and requires repeated monitoring of prolactin and ovarian status. Ultimately, it is hoped that sufficient safety data will

be gathered to enable the drug to be used in the same way as bromocriptine. As of March 1999, the manufacturer of quinagolide had data on 178 pregnancies in 159 women treated with the drug, 14.6% of whom ended in spontaneous abortion. Nine fetal malformations were diagnosed, including two infants with Down syndrome. These figures also fall within the expected normal ranges. Quinagolide has an intermediate duration of action and, in acknowledgment of the limited pregnancy experience, the data sheet recommends that the drug be withdrawn as soon as pregnancy is confirmed.

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