Hyperprolactinemia

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INTRODUCTION

Prolactin secreting pituitary tumors are the most common type of hormone secreting pituitary tumors. They are also the only pituitary tumors which can be effectively primarily managed by medical means. Thus their identification and diagnosis is imperative to avoid unnecessary pituitary surgery.

PROLACTIN SECRETION

Prolactin is secreted by the lactotrophs in the anterior pituitary gland. Prolactin secretion is regulated by the hypothalamus. Unlike the other anterior pituitary hormones, however, the hypothalamic influence is predominantly of tonic inhibition.

The hypothalamus secretes a prolactin-release-inhibiting factor (PIF) and a prolactin-releasing factor (PRF). PIF is dopamine, although the possibility of the existence of non-catecholamine PIFs cannot be excluded. Additionally, gamma-aminobutyric acid (GABA) as well as other unidentified PIFs may play a role as an inhibitor. The nature of the physiological PRF is unclear. Thyrotropin-releasing hormone (TRH) can act as a PRF. Other candidates include vasoactive intestinal peptide (VIP), oxytocin, galanin and PHM-27.

CAUSES OF HYPERPROLACTINEMIA

The causes of hyperprolactinemia may be considered, in a simplified fashion, as resulting from four basic abnormalities of prolactin secretion. In some patients, however, it is not possible to elucidate the cause of hyperprolactinemia.

Hypothalamic Dopamine Deficiency

Diseases of the hypothalamusv(link to Von Werder chapter), such as tumors, arterio-venous malformations, and inflammatory processes such as sarcoidosis result in either diminished synthesis or release of dopamine. Furthermore, certain drugs (e.g. alpha-methyldopa and

reserpine) are capable of depleting the central dopamine stores.

Defective Transport Mechanisms

Section of the pituitary stalk results in impaired transport of dopamine from the hypothalamus to the lactotrophs. Pituitary or stalk tumors with abnormal blood supplies, or their pressure effects, may interfere with the circulatory pathway from the hypothalamus down the pituitary stalk to the normal lactotrophs or a tumor, producing effective dopamine deficiency due to a functional stalk section.

Lactotroph Insensitivity to Dopamine

Dopamine receptors have been found on human pituitary lactotroph adenoma cells. Receptor sensitivity to dopamine may be diminished, which would explain the lack of response to increased endogenous dopamine stimulation; however, an obvious response of the receptors to pharmacologic dopamine agonists makes this possibility less likely. Certain drugs act as dopamine-receptor-blocking agents, including phenothiazines (e.g. chlorpromazine), butyrophenones (haloperidol), and benzamides (metoclopramide, sulpiride, and domperidone). These drugs block the effects of endogenous dopamine and thus release lactotrophs from their hypothalamic inhibition. This sequence of events results in hyperprolactinemia.

Stimulation of Lactotrophs

Hypothyroidism may be associated with hyperprolactinemia. If hypothyroidism results in increased TRH production, then TRH (which can act as a PRF) could lead to hyperprolactinemia. Estrogens act directly at the pituitary level, causing stimulation of lactotrophs, and thus enhance prolactin secretion. Furthermore, estrogens increase the mitotic activity of lactotrophs, increasing cell numbers. Injury to the chest wall can also lead to hyperprolactinemia; this results from abnormal stimulation of the reflex associated with the rise in prolactin that is seen normally in lactating women during suckling.

CLINICAL MANIFESTATIONS OF HYPERPROLACTINEMIA

The symptoms associated with hyperprolactinemia may be due to several factors: the direct effects of excess prolactin, such as the induction of galactorrhea or hypogonadism; the effects of the structural lesion causing the disorder (i.e. the pituitary tumor), leading to, for example, headaches, visual field defects, or external ophthalmoplegia; or associated dysfunction of secretion of other anterior pituitary hormones.

The incidence of galactorrhea in hyperprolactinemic patients is between 30% and 80%, depending on the skill of the examiner and the degree of estrogen deficiency. Approximately 50% of women with galactorrhea, however, have normal prolactin and, as mentioned below, it is particularly those patients with very high prolactin levels, i.e. greater than 100ng/mL

(2000mU/L), who often have no galactorrhea – thus, it is a poor marker of hyperprolactinemia. Normal prolactin levels are below 18ng/mL (360mU/L).

Women with hyperprolactinemia usually present with menstrual abnormalities – amenorrhea or oligomenorrhea – or regular cycles with infertility. Occasionally, patients may present with menorrhagia. Menstrual disorders are often not seen with mild hyperprolactinemia but it is unusual for there to be no menstrual problems if the prolactin is greater than 180 ng/l (3,600 mU/L).

In contrast, men often present late in the course of the disease with symptoms of expansion of their pituitary tumor (i.e. headaches, visual defects, and external ophthalmoplegia) or symptoms from secondary adrenal or thyroid failure. These men, however, have usually been impotent for many years before their presentation. Because the disease is occult for many years men present late in the course of their disease and thus in contrast to women where microprolactinomas are most commonly seen, macroprolactinomas in men are usually found and the serum prolactin levels are usually much higher than those in women.

Occasionally, the syndrome may occur in prepubertal or peripubertal children, when it may present with delayed or arrested puberty or with headache and/or visual field defects or with growth arrest. Children and adolescents often present with aggressive prolactinomas, perhaps reflecting a different mechanism(s) of tumorigenesis rather than disease duration; it should not be forgotten that the rate of cell proliferation at this stage of the life cycle is greater.

DIFFERENTIAL DIAGNOSIS

It is important to exclude two causes of hyperprolactinemia: hypothyroidism and the ingestion of drugs that either deplete central dopamine or block dopamine receptors. Having excluded these two important causes, and any hypothalamic lesion, three common diagnostic possibilities remain: the patient may have a microadenoma, a macroadenoma or no tumor at all. If patients do not harbor an identifiable tumor, they are described as having idiopathic hyperprolactinemia. It is likely, however, that patients with this condition may harbor small microprolactinomas, which were undetected with less sensitive imaging tools used in the past, and even with MRI

A microadenoma is described as having a maximum diameter of up to 10mm (the maximal diameter of the normal pituitary gland), and a macroadenoma as having a diameter in excess of this. A microadenoma is often visualized using magnetic resonance imaging (MRI). Usually, the serum prolactin level is below 200ng/mL (4000mU/L) in patients with microadenomas. A macroadenoma that secretes prolactin is usually associated with a serum prolactin level of more than 200ng/mL (4000mU/L). If the patient has a macroadenoma and a serum prolactin level of less than 200ng/mL (4000mU/L), consideration should be given to the possibility that a nonfunctioning pituitary adenoma (pseudo-prolactinoma) is present, the hyperprolactinemia resulting from deprivation of some lactotrophs of dopaminergic inhibition. However, a laboratory artifact may lead to a wrong differential diagnosis between macroprolactinomas and pseudoprolactinomas. When serum prolactin is evaluated by two-site immunometric assays, large amounts of prolactin saturate both the capture and the signal antibodies, impairing their

binding, causing serum prolactin to be underestimated (the so-called “high-dose hook effect”). Therefore, patients bearing macroprolactinomas with extremely high serum prolactin levels (generally >1,000 ng/ml [>180,000 mU/L]) may present falsely low levels, e.g. 30-120 ng/ml (600-2,400 mU/L) range, causing the patient to be misdiagnosed as harboring a nonfunctioning pituitary adenoma. In order to avoid unnecessary surgery (treatment of choice for nonfunctioning tumors), prolactin assays with serum dilution are recommended in patients with macroadenomas who may harbor a prolactinoma.

Another laboratory pitfall concerns the presence of high serum prolactin levels in subjects with few or no symptoms related to prolactin excess. Human prolactin circulates as monomeric prolactin and as larger forms which are indistinguishable by routine assays. Monomeric prolactin is the most common form, but serum prolactin can be elevated due to the presence of aggregates with low biological activity, such as big-big prolactin, leading to the so-called macroprolactinemia. The presence of molecular aggregates with low biological activity, such macroprolactin should be suspected when high serum prolactin levels are detected in patients without or with few signs and symptoms related to hyperprolactinemia. Precipitation with polyethylene glycol (PEG) is an excellent screening method. Chromatography confirms the presence of macroprolactin but is an expensive and time-consuming method; it is performed only when PEG precipitation results are inconclusive. Macroprolactinemia is a common finding, some reporting it as frequently as 8 to 42% of all cases; other centers find that it is extremely rare. Big-big prolactin biological activity is still controversial in the literature. Studies in vitro with rat Nb2 cells bioassays show either the presence or the absence of biological activity. A recent study using an human prolactin receptor-mediated assay compared with rat Nb2 cells assay showed that the activity displayed by macroprolactin toward the rat receptor may be inappropriate because it is not observed in the human prolactin receptor-mediated assay, consistent with the apparent absence of bioactivity in vivo. Most patients with macroprolactinemia do not manifest clinical features related to hyperprolactinemia, and do not need any treatment. Therefore, in order to avoid unnecessary medical or even surgical procedures, macroprolactin screening is important to consider when clinical features and serum prolactin assay results are not consonant with one another.

Enlargement of the pituitary fossa on a skull X-ray may represent the expansion of the fossa by the macroadenoma, but care should be exercised to exclude the possibility of cisternal herniation (a partially empty fossa) as a cause for the enlargement. CT and MRI scans are useful and will also demonstrate any hypothalamic pathology (link to Haughton chapter).

CHANGES IN THE BREAST DUE TO PROLACTIN

A woman with amenorrhea due to hyperprolactinemia does not develop the breast atrophy seen in postmenopausal women or in amenorrheic women who are gonadotropin-deficient or have primary ovarian failure. On examination, the breast and areola are well developed and the Montgomery tubercles are hyperplastic. If the breast is correctly examined, first by expressing it from the periphery towards the areola to empty milk ducts, followed by squeezing and lifting the areola (rather than the nipple itself) to empty the milk sinuses, galactorrhea can usually be found.

In patients with extremely high prolactin levels, galactorrhea may not be found. In male patients with hyperprolactinemia, there is usually no gynecomastia, but milk may be expressed from an entirely normal-sized male breast. The incidence of galactorrhea in men with hyperprolactinemia is low, however, being less than 30% (i.e. it is much less common than in women). Nevertheless, the presence of galactorrhea in man with a pituitary mass is an important clinical clue to the presence of hyperprolactinemia and possible prolactinoma

IMAGING OF THE PITUITARY (See Also Chapter 4)

The anatomy of the pituitary is optimally assessed by MRI. MRI allows imaging of the optic chiasm, the cavernous sinuses, the pituitary (both the normal gland and tumors), and its stalk. In addition, aneurysms of the carotid are immediately obvious. Thus MRI allows accurate measurement of the size of the pituitary and of any tumor and its relationship to the optic chiasm and cavernous sinuses. Cisternal herniation is also readily seen. If MRI is not available, CT scanning is also helpful but the resolution is less good and it is less satisfactory for delineating the relationship of the diaphragma sellae with the optic chiasm. There is little place for routine skull X-ray other than for delineating bony structures.

TREATMENT OF HYPERPROLACTINEMIA

Therapeutic strategy must consider several aspects, such as the patient's clinical presentation, the differences between microadenomas and macroadenomas concerning their natural history, the desire for pregnancy, and the patient's treatment preference, if applicable. Medical treatment with dopamine agonist drugs is currently the gold standard approach both for microprolactinomas and macroprolactinomas. Pituitary surgery, usually by the transsphenoidal approach(link to Laws chapter) is generally reserved for prolactinomas resistant to dopamine agonist drugs. For microadenomas, the results in the hands of most experienced surgeons are similar, with about 80% of serum prolactin normalization; however ~25% develop recurrence of hyperprolactinemia at five years after surgery even with the most experienced transsphenoidal surgeons. However, surgical results in macroprolactinomas are much poorer, mainly in big and/or invasive tumors Radiotherapy for prolactinomas generally bring poor results, and is currently reserved only for macroadenomas refractory both to medical and surgical treatment.

Dopamine Agonist Drug Therapy

The first dopamine agonist ergot compound to be used in clinical practice was bromocriptine, a peptide ergot. It was introduced in the early 1970s in Europe and thus there is more than 30 years of experience of the use of such compounds in the treatment of hyperprolactinemia. Bromocriptine has the advantage of having a long duration of action compared to dopamine itself or oral compounds such a levo-dopa.

Bromocriptine has a similar mode of action to dopamine in stimulating dopamine receptors on the prolactin-secreting pituitary cells – D2 receptors. Stimulation of these receptors leads to inhibition of both prolactin secretion and synthesis. After a single 2.5mg dose of bromocriptine

administered at 09.00h to women with hyperprolactinemia, prolactin secretion was inhibited within 2 hours and reached a nadir at 7 hours. When patients are treated chronically using 2.5mg three times per day, prolactin levels are maintained within the normal range, i.e. less than 20ng/mL (400mU/L), throughout a 24-hour period. Subsequently a variety of other compounds have been developed which are useful additions. These include pergolide mesylate, which only needs to be administered once per day, quinagolide, and cabergoline.

Cabergoline has an extremely long biological half life and thus only needs to be administered either once or twice per week at a dose of 0.5 mg/dose. In refractory cases the dose can be increased gradually to 1 mg up to a daily dose. In addition to its long biological half-life, cabergoline is generally better tolerated than bromocriptine, so increasing the patient's adherence. Therefore, cabergoline is currently considered the first choice drug for the treatment of prolactinomas, except for patients wishing pregnancy in the short-term (see below). A recent study showing that patients with Parkinson's disease on cabergoline or pergolide presented high prevalence of valvular hearth disease brought some concern about the drug safety. It must be pointed out, however, that the doses of dopamine agonists for Parkinson's disease are much higher than for prolactinomas. Nevertheless, there are few reports of mild to moderate tricuspid regurgitation in patients with prolactinomas on cabergoline, although without clinical impact. Therefore, even if most of the studies do not show an association between use of cabergoline and cardiac valve disease in hyperprolactinemic patients, vigilance should be done, mainly in those on long-term, high dose of the dopamine agonist drug. The issue of echocardiographic assessment should be weighted individually, at the physician´s judgment.

Effects of Dopamine Agonist Drugs in Hyperprolactinemic Men

The first male patient commenced bromocriptine treatment at St Bartholomew's Hospital, London, in 1971, and his case illustrates a number of important points. Initially, the prolactin levels of the patient were extremely elevated, but the administration of bromocriptine lowered them into the normal range (undetectable by bioassay); this was associated with cessation of galactorrhea. Bromocriptine therapy normalized the patient's prolactin levels and gonadal function, restoring potency. Also cabergoline showed to be very effective in treating prolactinoma in men, even those bearing giant adenomas. Interestingly enough, testostesterone administration to men without correction of hyperprolactinemia generally do not improve libido and potency.

Dopamine Agonist Drugs in Amenorrhea

From experience of treating a large number of amenorrheic hyperprolactinemia women, the results of treating the first 58 appear to be representative of the success that can be achieved with bromocriptine (and other dopamine agonists) therapy (Fig. 1). Within 1 month of starting therapy, a regular menstrual cycle is restored in approximately 25% of patients. Within 2 months, regular menstrual cycling can be restored in over 60% and, within 10 months, in some 80%. Those patients who did not experience restoration of regular menstrual cycles (with only one or two exceptions) had previously undergone surgery or radiotherapy for their pituitary tumor – this rendered them gonadotropin-deficient. Thus, if hyperprolactinemia is the cause of

amenorrhea, the chances of restoring normal gonadal function by medical therapy alone are extremely good, around 85%.

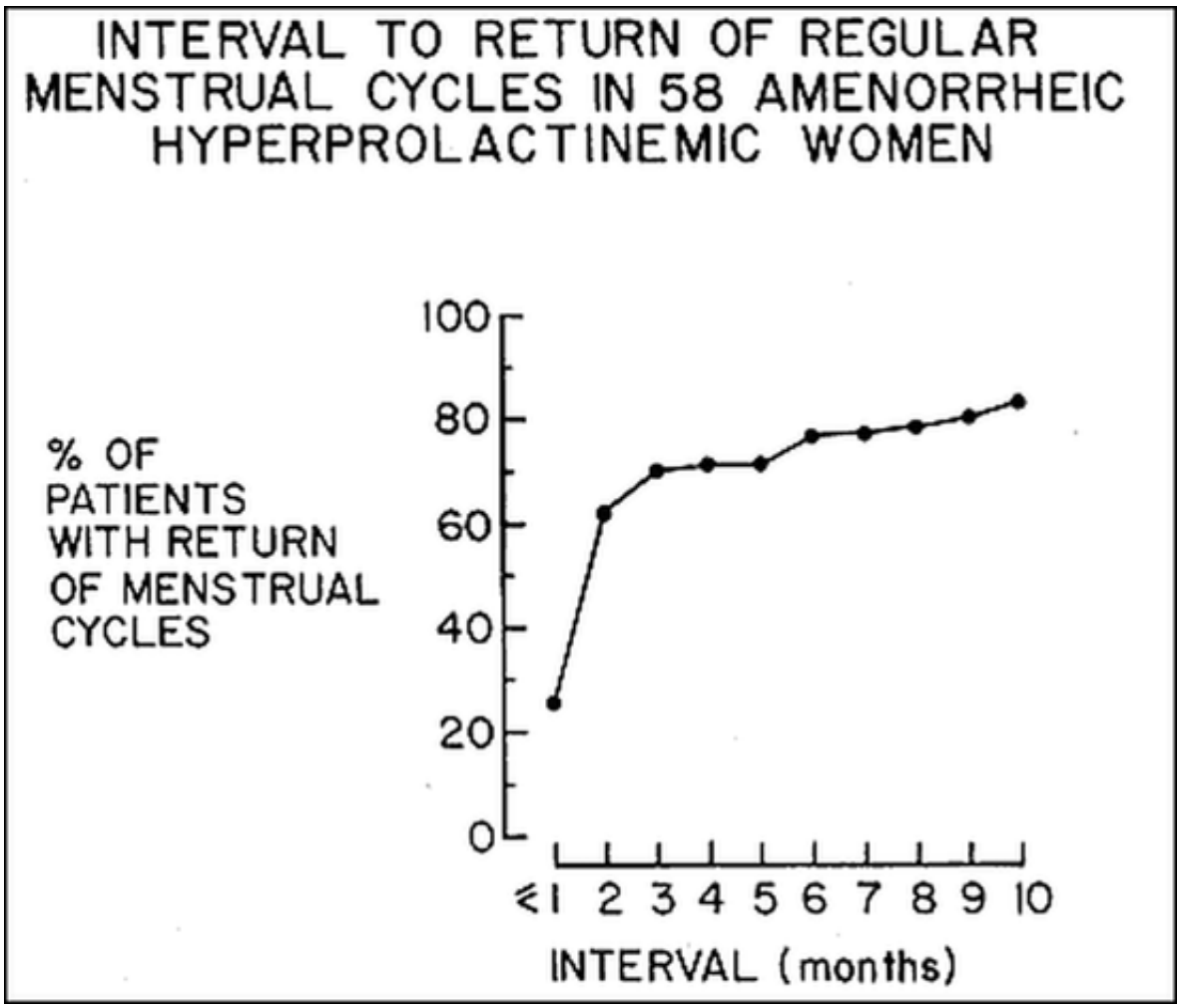

Figure 1. Success rate of bromocriptine in amenorrhea. If hyperprolactinemia is the cause of amenorrhea, the chances of restoring normal gonadal function with bromocriptine are very good. After 1 month of treatment, one woman in four will return to normal menstrual cycling; within 2 months, this number will increase to six out of 10; and after 10 months, eight out of 10 women will be menstruating normally. (Most of the remaining 20% have had pituitary surgery and irradiation therapy and are gonadotropin-deficient.)

Long-Term Effects of Bromocriptine

To study the long-term effects of bromocriptine on prolactin secretion, a group of patients was carefully evaluated (Fig. 2). Ten blood samples were taken from each patient before treatment; at 3, and 6 months on therapy. All patients were treated with the same dose of bromocriptine (2.5mg three times per day). In all cases, bromocriptine lowered prolactin levels.

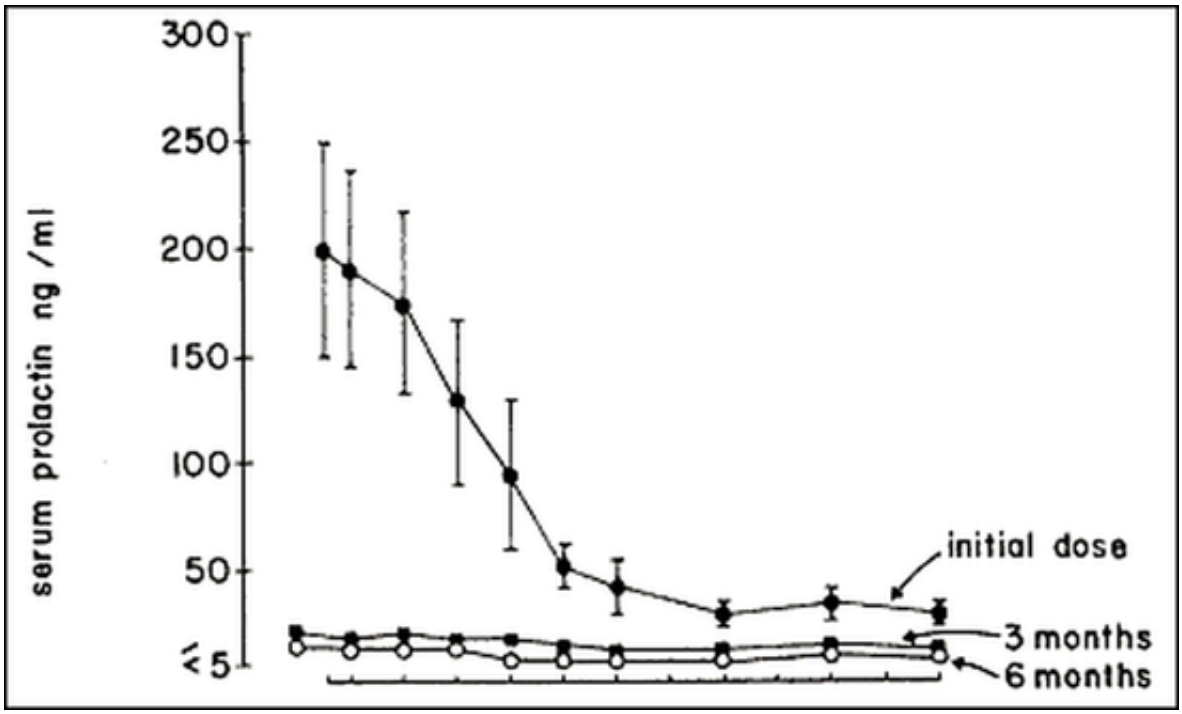

Figure 2. Long-term effects of bromocriptine therapy. Prolactin levels in a group of patients on long-term bromocriptine therapy were tested before therapy; after 3 months, 6 months (during which time all patients received bromocriptine 2.5mg three times per day) In all cases, prolactin remained suppressed throughout the year and, in most cases, prolactin levels were held within the normal range. Gonadal function was restored, even in patients whose prolactin levels did not return to normal. Reproduced with permission from J Clin Endocrinol Metab 50:1026 1033.

Hyperprolactinemia and Ovulation

Ovulation is normally associated with a dip in basal body temperature, and normal luteal function with a temperature rise. Basal body temperature is therefore a useful means of documenting ovulation. When hyperprolactinemic patients have had their prolactin levels and periods restored to normal by bromocriptine therapy, they usually demonstrate a biphasic temperature pattern. One patient had suffered from polymenorrhea for many years and was found to be hyperprolactinemic. Bromocriptine normalized her periods, and therapy was withdrawn after 1 year. During therapy, the basal body temperature chart showed a normal biphasic pattern but, following withdrawal of bromocriptine, prolactin levels rose to more than 100ng/mL (2000mU/L), galactorrhea returned, and the temperature pattern immediately became monophasic. Although the patient did not become amenorrheic, she developed irregular (presumably anovulatory) periods. Two weeks following reinstitution of therapy, the patient ovulated, demonstrating a postovulatory temperature rise. She has subsequently had a regular cycle and three successful pregnancies, each with the help of bromocriptine.

Hyperprolactinemic Hypogonadism

The pathogenesis of the hypogonadal state in hyperprolactinemia is poorly understood. In men, testosterone levels are usually low but can occasionally be normal, while in women, a hypoestrogenic state may occur, with loss of ovulation. The clinical features in hyperprolactinemic women, however, differ from those in the postmenopausal state since breast atrophy is absent and gonadotropin levels are not elevated.

Suppression of Gonadal Function in Hyperprolactinemia

The mechanisms which may account for the suppression of gonadal function in hyperprolactinema include suppression of gonadotropin secretion; inhibition of positive estrogen feedback on luteinizing hormone (LH) secretion in women; an increase in adrenal androgen secretion; and blockade of the effects of gonadotropins at the gonadal level. It is probable that an important mechanism is prolactin feedback at the hypothalamus, which alters secretion of gonadotropin-releasing hormone (GnRH), thus causing LH and follicle-stimulating hormone (FSH) secretion to become inappropriately low relative to gonadal steroid levels. Reduction in the normal LH pulsatility, essential for normal gonadal function, also occurs. Prolactin may interfere with LH and FSH action at the gonad, blocking progesterone synthesis, and may stimulate adrenal androgen secretion.

Reduction in Size of Prolactinomas

Surgical therapy of large prolactin-secreting pituitary tumors is unsatisfactory since it is only capable of normalizing serum prolactin levels or gonadal function in fewer than 20% of patients, particularly those with high prolactin levels, so there is a need for another approach to the problem. Three major lines of evidence suggest that medical therapy may help in the treatment of these large tumors.

1. Visual field defects due to prolactinomas pressing on the optic chiasm improve rapidly with dopamine agonist therapy alone.
2. Dopamine agonist therapy has been shown, by neuroradiologic evaluation, to reduce the size of prolactinomas.
3. Bromocriptine Reduces Dna Turnover and the Mitotic Index in the in Situ Pituitary of the Rat.

Bromocriptine reduces pituitary tumor size in 75-80% of patients with large prolactin-secreting tumors, even with gross extrasellar extension. The type of result that can be expected is illustrated by a patient with a large prolactin-secreting tumor, who was treated with bromocriptine alone. The patient had a suprasellar extension and visual field defects. Visual field plots from this patient before and during treatment, as well as after withdrawal and reinstitution of bromocriptine therapy, are illustrated in Figure 3. Before therapy (baseline), the patient had a bitemporal hemianopia, complete in the left eye and incomplete in the right eye. The visual fields were greatly improved after 10 days, and only an equivocal superior bitemporal quadrantic defect to the low intensity object was present after nearly 1 year. By 13 days after withdrawal of medical treatment, the tumor had enlarged again and the field defects recurred as an almost complete temporal hemianopia in the left eye and a partial temporal hemianopia in

the right. Progressive improvement in visual fields was again observed over the subsequent 6 months after reintroduction of therapy.

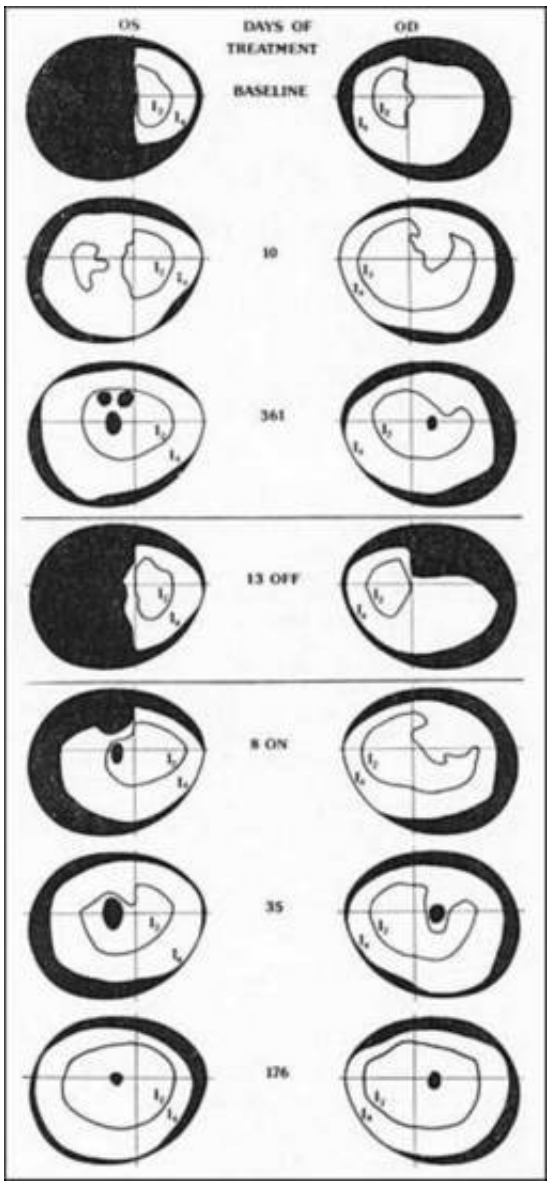

Figure 3. Visual field plots in hyperprolactinemia. The visual fields shown here were plotted using a Goldmann perimeter, under identical conditions, with a 0.25mm2 object at two different light intensities: 1000 apostilb (I4) and 100 apostilb (I2). The black periphery indicates a normal visual field for comparison. An almost complete bitemporal hemianopia (pretherapy), which had almost disappeared after 1 year of treatment with bromocriptine, returned on cessation of therapy and began to subside after reinstitution of bromocriptine. Reproduced with permission from J Clin Endocrinol Metab 53:480 483

Changes in Pituitary Volume During Bromocriptine Therapy

Figure 4 illustrates coronal CT head scans (postenhancement) from the patient whose visual fields are shown in Figure 4(a), performed on a Delta 25 scanner, illustrates the situation before therapy; Figure 4(b) shows a scan performed on a GE 8800 scanner 2 weeks after starting bromocriptine therapy, 2.5mg three times per day. Before therapy, Figure 4(a) shows an enlargement of the pituitary fossa and an enhancing mass extending inferiorly into the sphenoid sinus, superiorly into the chiasmatic cistern, and abutting on the third ventricle. Two weeks post-treatment, Fig. 4(b) shows a marked reduction in tumor size, with regression of the suprasellar extension. The chiasmatic cistern is now largely free of tumor, apart from a finger-like process to the left of the midline. The intrasellar high density is present in the pre-enhancement scan and represents calcification within the tumor. Within the short space of 2 weeks, therefore, there was marked reduction in the size of the pituitary and a consequent decompression of the optic chiasm, which explains the rapid improvement in visual fields observed in this patient.

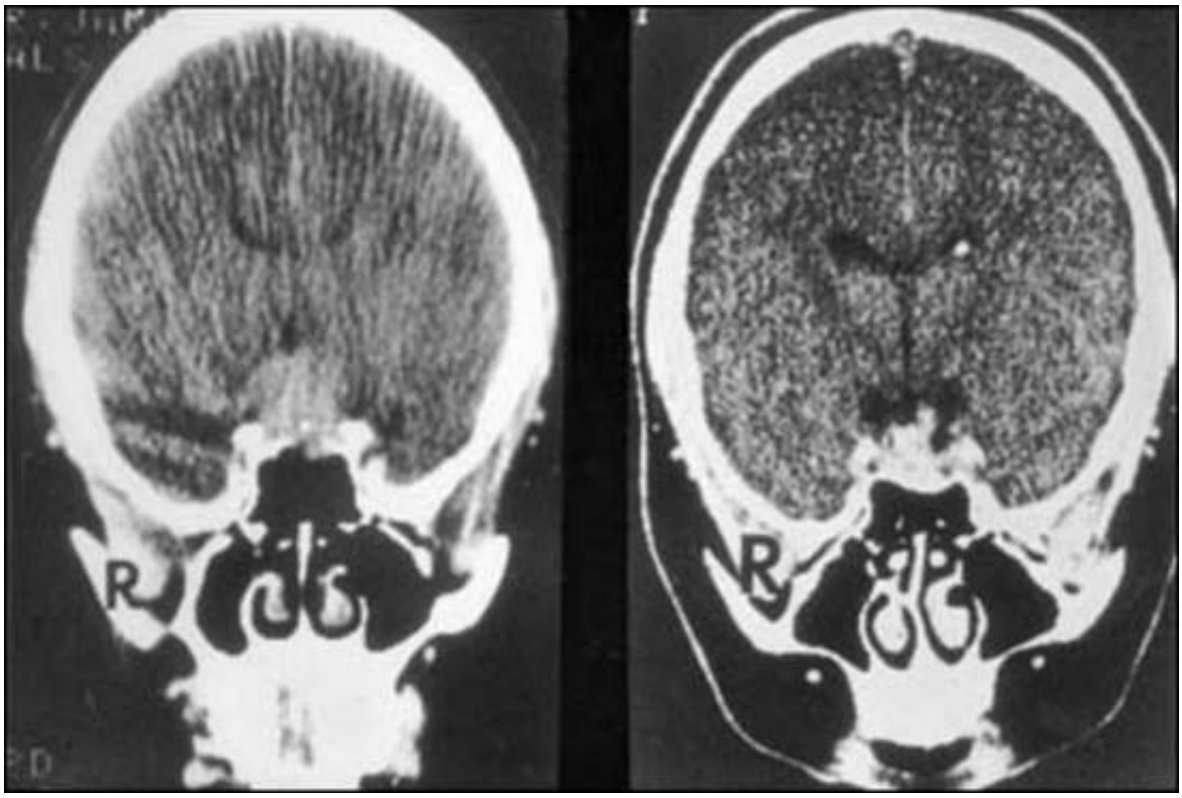

Figure 4. Coronal CT head scans before and during treatment with bromocriptine. Magnetic resonance imaging (T1 weighted with gadolinium enhancement) of a man harboring a large macroprolactinoma. A1(coronal view) A2 (sagittal view) before treatment and B1 (coronal view) and B2 (sagittal view), after one month of cabergoline (0,5mg thrice a week) treatment. The significant tumor shrinkage was paralleled by serum prolactin decrease from 6,600 ng/mL to 540 ng/mL and by visual improvement

Of 16 patients with large prolactin-secreting tumors, 13 showed similar changes. The three patients in whom these changes were not observed were:

1. a patient with a pituitary cyst that was associated with a small prolactinoma, but in whom the majority of the pituitary mass was the cyst;
2. a patient with an extremely large tumor that was reduced in size but still remained large. The patient's serum prolactin level fell by 90% but still remained elevated at 328ng/mL (6560mU/L) at the end of 9 months of therapy, indicating relative resistance to dopamine agonists, probably because of dysfunctional or reduced numbers of dopamine receptors;
3. a patient who had only been treated for 6 weeks and in whom there was as yet only equivocal evidence of reduction in the size of the tumor.

Other groups have had similar results with other dopamine agonist drugs. It seems that at least 65% of macroadenomas with large extrasellar extensions (or even more with cabergoline) may be treated with dopamine agonists alone to shrink the tumors and to relieve the mass effects and the hormonal excess.

Changes in Serum Prolactin Levels

In patients with macroadenomas, the serum prolactin levels can be readily suppressed with bromocriptine therapy. Figure 5 shows serum prolactin levels throughout the day after an initial 2.5mg oral dose of bromocriptine administered at 09.00h to the patient whose visual field plots and CT scans are shown in Figures 3 and 4, as well as those from a patient with a similar problem. After a single dose of bromocriptine, the prolactin levels fell by approximately 90%. The mean and absolute range of prolactin levels in samples taken at the same time intervals before therapy (baseline) and during bromocriptine therapy, 7.5mg/day, are also shown in Figure 6. In the first patient, the prolactin levels were suppressed into the normal range (less than 18ng/mL, 360mU/L) and in the second patient, prolactin levels, although lowered, did not return to normal. With treatment over 1 year, however, the levels continued to fall to 78ng/mL (1560mU/L). In these patients, as with the patients with microadenomas, gonadal function is usually restored to normal. As previously noted, when therapy was withdrawn at 1 year, visual field defects recurred in the first patient and this was associated with prolactin levels rising again to 2580ng/mL (51.6u/L) at 13 days in comparison to the pretreatment level (3940ng/mL, 78.8 u/L). However, it should be noted that, in male patients on bromocriptine, prolactin levels usually fall rapidly and easily into the normal range. If this does not occur, gonadal function may not return to normal.

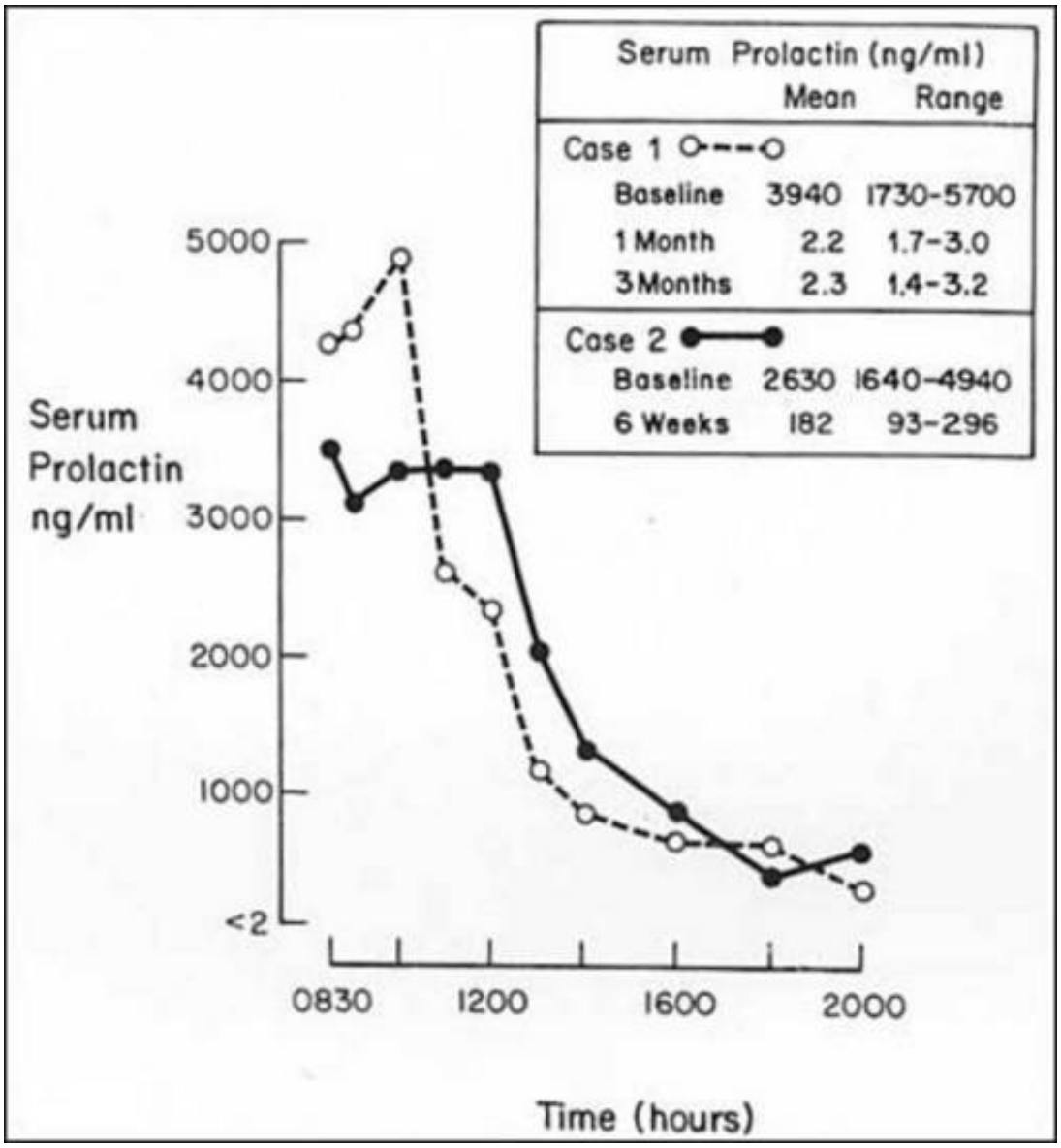

Figure 5. Changes in serum prolactin levels after bromocriptine administration. The effect on serum prolactin levels throughout the day of a single 2.5mg oral dose of bromocriptine at 09.00h is shown. Case 1 is the patient whose visual field chart and CT scans are shown in Figures 3 & 4. Case 2 is a patient with a similar problem. In patients such as these, even when prolactin levels do not come down to the normal range, gonadal function is usually restored.Reproduced with permission from J Clin Endocrinol Metab 51:438 445.

Side Effects

Side effects of bromocriptine therapy occur only at the start of treatment and disappear with continued therapy. There are no long-term problems associated with chronic treatment at the doses used for hyperprolactinemia – usually 7.5mg/day and rarely more than 15mg/day.

If treatment is started with full doses or increased too quickly, dizziness, nausea, and postural hypotension may occur. To avoid such effects, bromocriptine must always be taken during a meal. Administration should be started at night, with a sandwich and glass of milk, when the patient retires to bed. After taking half a tablet (1.25mg) for three nights, half a tablet is added with breakfast. After a further three days an additional half a tablet is added with lunch. At intervals of three days, additional half tablets (1.25mg increments) may be progressively added until achievement of the usual dose of one tablet (2.5mg) taken three times daily, in the middle of breakfast, lunch, and the evening meal. If side effects still occur, longer intervals and smaller increments should be used. Once established on an effective dose it is now established that the whole dose can be given once daily, again during the main course of a main meal. In a small proportion of patients psychosis or anxiety can be precipitated by the administration of dopamine-agonist drugs. These are usually adequately managed either by stopping the dopamine-agonist medication or lessening the dose. These symptoms are more common in parkinsonian patients, but in this group the brain is diseased and the doses used are much greater than for the indication of prolactinoma.

The only group of patients who do not suffer from such side effects if given the full dose immediately is puerperal women. They may be given bromocriptine 2.5mg two or three times daily to suppress puerperal lactation, without side effects, if treatment is started within 24 hours of delivery. The reasons for this difference are unknown.

There are several other dopamine agonists that lower serum prolactin levels and reduce tumor size to a similar extent to bromocriptine. These drugs include pergolide, lisuride, qinagolide, and cabergoline. These compounds are associated with a similar side effect profile to that observed with bromocriptine. Cabergoline has the advantage that it only needs to be taken once or twice per week and may have a reduced incidence of side effects. With the exception of bromocriptine, safety during pregnancy has not been demonstrated. As experience with cabergoline has accumulated it appears that some patients who could not be controlled with other dopamine agonists, e.g. bromocriptine or pergolide, could be controlled by cabergoline. On occasion, the dosing may need to be increased as frequently as daily. Because of its long duration of action, the side effect profile and efficacy appear to be better than with any other dopamine agonist drug.

Can dopamine agonist drug be withdrawal without recurrence of hyperprolactinemia?

One of the drawbacks of medical treatment of prolactinomas is the need for long-term therapy. As a matter of fact, treatment with bromocriptine and other dopamine agonist drugs generally is considered as “symptomatic”, since bromocriptine discontinuation leads to recurrence of hyperprolactinemia in most patients and to tumor regrowth, at least after short-term use. Concerning long-term therapy with bromocriptine, a recent retrospective study showed that 25.8% of 62 patients with microprolactinomas and 15.9% of 69 patients with macroprolactinomas treated with bromocriptine for a median time of 47 months persisted normoprolactinemic after a median time of 44 months of drug withdrawal. There were no statistically significant differences regarding age, gender, bromocriptine initial dose and length of use, tumor size, pregnancy during treatment, and previous pituitary surgery or radiotherapy among patients who persisted with normoprolactinemia and those who did not. Another study

encompassed a large cohort of hyperprolactinemic patients on cabergoline. The drug was discontinued in patients who attained normoprolactinemia, at least 50% of tumor reduction or disappearance on image, and at least 2 years of follow-up after cabergoline withdrawal. It was demonstrated that serum prolactin remained normal in 76%, 70% and 64% of patients with “idiopathic” hyperprolactinemia, microprolactinomas and macroprolactinomas, respectively. This great discrepancy between results with bromocriptine and cabergoline was not confirmed by a recent study dealing just with microprolactinomas. The question regarding why long-term findings differ from short-term ones may be answered by the formerly described microscopic alterations of the lactotroph during bromocriptine administration, suggesting a cytostatic effect related to short-term therapy and a cytocidal one to long-term treatment, which could explain the maintenance of normoprolactinemia after drug withdrawal. Another factor that may influence remission of prolactinomas is their natural history. Nevertheless, the influence of the natural history of non treated prolactinomas, many of them reaching “spontaneous normoprolactinemia, cannot be rulled-out.

Prolactinomas resistant to dopamine agonists

About 10% of patients with prolactinomas are resistant to dopamine agonist therapy. If a patient has been responsive and then becomes unresponsive this is a potentially dangerous situation. Thus if a patient develops progressive hyperprolactinemia and tumor growth while continuing on dopamine agonist therapy then an alternative strategy needs to be considered. Initially pituitary surgery should be considered although if the tumor is unresectable due to its invasiveness or location (e.g. cavernous sinus) then gammaknife or cyberknife radiation or even conventional external pituitary radiation should be considered after surgical debulking. In tumors which are unresponsive to this approach a limited experience and success has been achieved using temozolomide. This treatment should be carried out by an experienced neuro-oncologist. (Neff LM, Weil M, Cole A, Hedges TR, Shucart W, Lawrence D, Zhu JJ, Tischler AS, Lechan RM 2007 Temozolomide in the treatment of an invasive prolactinoma resistant to dopamine agonists. Pituitary 10:81–86, Bush ZM, Longtine IA, Cunningham T, Schiff D, Jane JA Jr., Vance ML, Thorner MO, Laws, ER Jr., Lopes MBS 2010 Temozolomide Treatment for Aggressive Pituitary Tumors: Correlation of Clinical Outcome with O6-Methylguanine Methyltransferase (MGMT) Promoter Methylation and Expression JCEM 95: E280-E290)

Pregnancy and Bromocriptine

Many hyperprolactinemic women would like to become pregnant and, since the administration of dopamine agonist drugs lowers the prolactin levels and restores gonadal function, conception resents little difficulty. There are, however, several important considerations that must be recognized by both physician and patient, including the possible teratogenic sequelae of fetal exposure to bromocriptine and other drugs.

There is no evidence for teratogenicity in animal studies and, in 1400 women who were taking bromocriptine when they conceived, there is no evidence of increased incidence of abortion, multiple pregnancy, or fetal abnormalities. Until these babies have lived their own complete life cycles, however, the possibility of unexpected late effects cannot be excluded. In order to

minimize fetal exposure to bromocriptine, it is suggested that patients should initially use mechanical contraception. Once regular menstrual cycles have occurred, preferably at least three, contraceptive precautions are discontinued. In this way, pregnancy can be suspected as soon as a menstrual period is 48 hours overdue. At that time, a serum human chorionic gonadotropin assay should be performed to confirm the pregnancy, and the patient should discontinue bromocriptine therapy. In this way, the fetus is exposed to bromocriptine for a theoretical maximum of 16 days.

There is little doubt that patients with pituitary tumors run a small, but significant, risk of expansion of the tumor during pregnancy. It is very difficult, however, to assess the absolute risk. With microadenomas which did not undergone prevous surgery or radiotherapy, the incidence seems to be between 1,6% and 5,5%.In patients with macroadenomas also not operated on or irradiated , the incidence is higher, between 15.5% and 41%. However, the risk of complications may be lower in women previously operated or irradiated. This risk is unrelated to bromocriptine therapy prior to pregnancy but may occur when fertility is induced with other drugs, including exogenous gonadotropins and clomiphene, and even when no drug therapy has been employed in patients with pre-existing pituitary adenomas.

In practice, the problem of pregnancy is not great, since the vast majority of women who present with hyperprolactinemia only have microadenomas. To avoid major problems, it is extremely important that patients undergo careful endocrine, neuroradiologic, and neuro-ophthalmologic evaluation prior to treatment. If there is no suprasellar extension, and if the patient harbors only a microadenoma, then the risk of clinically significant swelling of the pituitary is extremely small; it is therefore suggested that the patient is evaluated clinically at bimonthly intervals throughout the pregnancy. If the patient has a macroadenoma and suprasellar extension, a strong case can be made for transsphenoidal decompression of the tumor prior to pregnancy. However, in those patients with a good response to dopamine agonists in terms of prolactin normalization and tumor shrinkage within sellar boundaries, at least one year before pregnancy, the drug can be withdrawal and reintroduced if tumor re-growth is observed If such approach fails, pituitary surgery or premature delivery, if feasible, would be indicated. Additionally, in case of tumor apoplexy high-dose dexamethasone may improve clinical symptoms and also may reduce the chances of fetal respiratory distress if premature delivery is needed.

In recent years, pregnancies have been described in patients using other DA such as quinagolide, and cabergoline. Although there is no evidence of increased frequency of abortions or malformations in cabergoline-induced pregnancies, the drug’s long action, which persists up to three weeks after its withdrawal, associated with fewer (albeit increasing) data when compared to bromocriptine (around 800 versus over 6,000 pregnancies), limit the confidence that can be used in prescribing it for patients who wish to conceive or its use during pregnancy. In the Uniited States bromocriptine is the only FDA approved drug for inducing pregnancy in hyperprolactinemic women.

It is, however, possible even for these patients to go through pregnancy without developing visual disturbances and, furthermore, even if visual disturbances occur in one pregnancy, the problem may not recur in subsequent ones.

Thus, the approach to the patient with a prolactin-secreting macroadenoma who desires pregnancy can be either expectant or prophylactic. The authors believe that, as the risk of swelling of the adenoma is less than 20%, it is reasonable to adopt an expectant policy. Others suggest that pituitary decompression should be performed surgically, and still others recommend that external pituitary irradiation is given. It is not clear whether external pituitary irradiation or decompression of the pituitary by surgery, or both, completely prevent symptom-generating pituitary enlargement. It should be stressed that, so far, no patient has become permanently blind following expansion of the tumor during pregnancy.

If visual field defects or headaches from tumor expansion do occur during pregnancy, a number of therapeutic options are available. Following termination of the pregnancy, either by abortion or delivery of the baby, tumors have become smaller and such symptoms and headaches have resolved in all cases. Thus, if such symptoms occur early in pregnancy, therapeutic termination may be indicated. If they occur in the eighth month of pregnancy, premature delivery of the baby may be decided upon, although, if field defects and symptoms are minor, careful observation may be all that is required. The most problematic situation arises when symptoms occur in the middle trimester. At that time, it is suggested that bromocriptine therapy is restarted and in the great majority of patients there is rapid reduction in the tumor size and further swelling is prevented. If this is unsuccessful, high-dose dexamethasone can be used to achieve the same ends. Dexamethasone also reduces the chances of fetal respiratory distress occurring should premature delivery be needed. As a last resort, transsphenoidal surgery during pregnancy can be, and has been, used to decompress the tumor. Since such complications are extremely rare, however, little data have to date been accumulated.

CONCLUSION

Dopamine-agonist therapy for hyperprolactinemia leads to a reversal of the hyperprolactinemic hypogonadal state without risk of the development of pituitary insufficiency. Dopamine-agonist therapy is effective not only in patients with microadenomas but also in the majority of patients with large prolactin-secreting tumors in reducing tumor size; however, the tumor size may increase (as may prolactin levels) after withdrawal of therapy. This may give rise to problems because of compression of vital structures by the tumor.

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