THE MANAGEMENT OF HYPERPROLACTINAEMIA

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SYNOPSIS

The almost simultaneous development of a radioimmunoassay for prolactin and of a dopamine agonist, bromocriptine, that specifically lowers prolactin levels, has focussed attention on the importance of hyperprolactinaemia in clinical practice. Hyperprolactinaemia is responsible for 20% of cases of amenorrhoea, and is an important cause of anovulatory infertility and male hypogonadism. On the other hand, hyperprolactinaemia may be the first manifestation of a pituitary prolactinoma in 40% of cases. Treatment is usually required because of infertility or galactorrhoea and in a minority of patients because of an expanding pituitary tumour. There is recent evidence that suggests that hyperprolactinaemia, by causing chronic estrogen deficiency, may lead to an increased risk of osteoporosis and it, therefore, appears that almost all patients with increased prolactin secretion should be treated.

INTRODUCTION

The development of a radioimmunoassay for prolactin (1) has allowed the pathophysiology of this hormone to be studied in detail and it is now realised that hyperprolactinaemia is the most common pituitary disorder encountered in clinical practice. It may present in a variety of ways, including amenorrhoea with or without galactorrhoea, oligomenorrhoea, luteal phase deficiency or anovulatory infertility. In men it is an important cause of hypogonadism. Proper management of hyperprolactinaemia is required because, even if it is clinically asymptomatic, the associated estrogen deficiency may lead insidiously to osteoporosis. (2) On the other hand, in 40% of the cases, hyperprolactinaemia may be the first manifestation of a pituitary prolactinoma. (3)

Diagnosis of hyperprolactinaemia

While hyperprolactinaemia may be suspected in a woman with reproductive dysfunction or galactorrhoea, or in a man who presents with impotence and lack of libido, the diagnosis is essentially based on measurements of serum prolactin. All patients with amenorrhoea should have serum prolactin measured because pathological hyperprolactinaemia is found in 13-23% of woman with amenorrhoea. (4) The absence of galactorrhoea does not reliably exclude hyperprolactinaemia as galactorrhoea is only found in one third of hyperprolactinaemic patients. While a wide range of dynamic tests of prolactin reserve have been described, measurement of the basal serum prolactin concentration is still the most valuable test. Interpretation of the serum prolactin values depend on the laboratory ranges which differ, and on the patient's estrogen status. Thus a borderline elevation of the serum prolactin concentration in a patient with amenorrhoea, and a negative progestogen challenge, is likely to be the cause of the patient's problems, while in a patient with anovulatory menstrual cycles, the same serum prolactin concentration is probably the result of the patient's menstrual disturbance. Once hyperprolactinaemia is established its cause should be found. There are only a few common causes of hyperprolactinaemia in clinical practice and essentially drug induced hyperprolactinaemia is excluded in the history while primary hypothyroidism should be excluded by measurement of serum thyroxine and TSH levels. Radiological evaluation is necessary in all cases of hyperprolactinaemia. Since a pituitary tumour can grow laerally as well as upwards, both plain AP and lateral films, in addition to a coned lateral view of the sella turcica, should be assessed. It must not, however, be concluded that all abnormal Xrays are indicative of pituitary tumour because an expanded fossa may well be caused by the empty sella syndrome (Diagram I and Figure I). This condition may arise either because of a defect in the dura allowing herniation of the subarachnoid space through the opening leading to expansion of the fossa, or because of regression of an existing pituitary tumour through tumour infarction or following therapy. Since empty fossas are the commonest cause of an abnormal pituitary fossa, CT scanning should be performed before surgical intervention or drug therapy are considered.

Place of CT scan

Plain X-rays only provide indirect assessment of the pituitary gland by imaging the bony surroundings. Diagnosis of superasellar extension of pituitary tumours previously depended on air-encephalography. The introduction of CT scanning with high resolution reconstructive techniques has allowed assessment of the tumour volume to be made much more safety. (5) This method also allows examination of the hypothalmic-pituitary anatomy for the presence of other pathologies, such as craniopharyngiomas and granulomata. Since CT scanning is expensive its use should be restricted to 2 indications:

(1) Moderate elevation of the serum prolactin concentrations in the presence of abnormal plain skull X-rays

(2) Significantly raised serum prolactin concentrations >100ng/ml because almost all such cases result from prolactin secreting adenomas.

The combination of radiological findings and serum prolactin estimations help to diagnose the underlying pathology. Since, in general, serum prolactin concentrations correlate directly with the size of a prolactinoma, we expect markedly raised serum prolactin concentrations if a large pituitary tumour is found

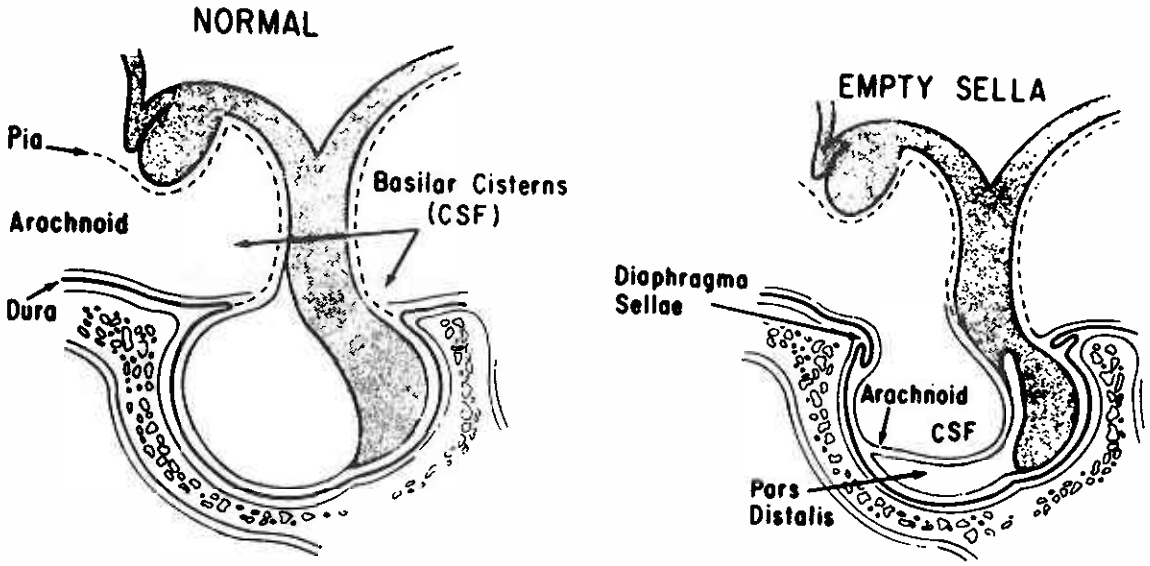

Diagram I — The diagram on the left shows the normal relationship of the meninges to the pituitary gland in which the arachnoid surrounds the aperture through which the pituitary stalk passes. The pituitary gland is bounded superiorly by the diaphragma sella formed by reflections of dura. The pia extends down the pituitary stalk to just above the pituitary gland where it is reflected and blends with the diaphragma sellae. In the empty sella syndrome there is an incompetent diaphragma sellae so that the arachnoid membrane herniates through it.

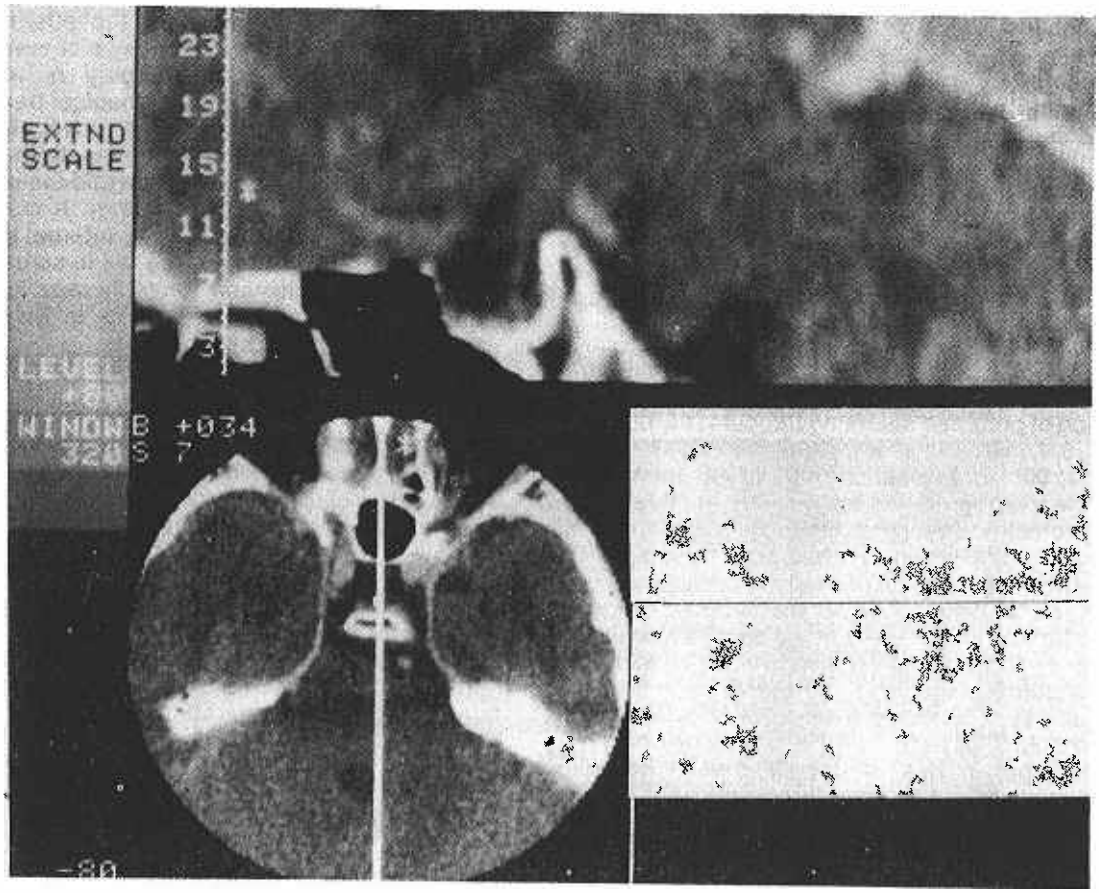

Figure I — Sagittal and coronal reconstruction of a CT scan showing the empty sella syndrome.

radiologically and the tumour is a prolactinoma. Hence, if the serum prolactin concentration is only mildly raised in the presence of a large pituitary tumour, it suggests that the tumour does not secrete prolactin but has suprasellar extension and is causing secondary hyperprolactinaemia by interfering with the production or transport of prolactin inhibiting factor (PIF). Calcification above, or within, the fossa in the presence of mild hyperprolactinaemia would indicate a craniopharyngioma.

Other Endocrine evaluation

Pituitary function should be fully assessed in all patients with superasellar pathology.

Indications for treatment

Treatment is usually dequired because of infertility. It may sometimes be needed because of galactorrhoea, symptoms of estrogen deficiency or simply because the patient desires to resume regular menstruation. A minority of patients need treatment because of an expanding pitutary tumour. Finally, there are recent data to suggest that hyperprolactinaemia, by causing chronic estrogen deficiency, may lead to an increased risk of osteoporosis. (2, 6) It, therefore, appears that almost all patients with increased prolactin secretion should be treated.

Medical treatment of hyperprolactinaemia

Bromocriptine is effective and is the treatment of choice in patients with hyperprolactinaemia, unless primary hypothyroidism is the cause of the increased prolactin levels, in which case replacement therapy with thyroxine is appropriate. Bromocriptine is a long acting dopamine agonist and has now been used for more than a decade. Both its safety and efficacy are well established. The overwhelming majority of hyperprolactinaemic patients treated with bromocriptine show a rapid decline in serum prolactin concentrations and resume ovulation. (7) It has been shown that the cumulative conception rate (CCR) in treated patients is no different from that of normal fertile women (8). Bromocriptine does, however, produce side effects, including nausea and postural hypotension and, therefore, it is important to begin treatment with a small dose given together with food at night. We start treatment with a dose of 1.25 mg at night for 2-3 days, increasing to 1.25 mg twice a day for 2-3 days and then 2.5mg twice a day for a week. We maintain the dose at 5mg. for 2-3 weeks and then recheck the serum prolactin concentration. If the serum prolactin level is still high, then the dose of bromocriptine is increased to 2.5 mg three times a day. Once the serum prolactin concentration is suppressed into the normal range and ovulatory cycles have resumed no further biochemical monitoring is needed and it is often possible to lower the dose to 50%-75% of the initial therapeutic dose. For patients on long term treatment the patient is asked to stop treatment once a year for 3 weeks and both the serum prolactin and mid-luteal progesterone levels are measured. A decision can then be made whether to continue treatment. If, at the initiation of treatment, the serum prolactin concentration falls into the normal range but the patient remains anovulatory, then an alternative cause of anovulation must be sought. We have found that such patients often have polycystic ovaries.

In those patients in whom bromocriptine has been

used to achieve pregnancy it has been found to be safe for mother and baby (9). Since bromocriptine can cross the placenta (10) on empirical grounds we stop the bromocriptine once pregnancy is diagnosed, unless there is some specific indication to continue treatment. On the other hand, if fertility is not immediately desired, effective contraception should be provided. There is no contraindication to using the combined oral contraceptive pill in hyperprolactinaemic patients so long as they are on bromocriptine.

Medical treatment of prolactinomas

It is now well established that bromocriptine will not only lower serum prolactin levels but can also cause regression of prolactin secreting tumours (11, 12, 13) — Figure 2, 3, 4. In an analyses of 10 series, (12) it has been found that 90% of prolactinomas will regress on bromocriptine treatment and even very large tumours with serum prolactin concentrations of 2000-3000ng/ml (80000-120000IU/l) will show remarkable shrinkage. (14) In our experience the dose needed to shrink tumours is often as low as 5mg a day. In the minority of cases where no tumour shrinkage is noted despite a fall in the prolactin concentrations, a non prolactin secreting tumour should be suspected. In comparison, surgery will produce cyclic menses in only 40% of patients with macro- and 80% of patients with microadenomas (15, 16) and carries a risk of complications, including panhypopituitarism. Moreover, bromocriptine is often needed postoperatively to normalise the prolactin levels and induce ovulation, especially for the large tumours. Finally, even in an excellent neurological centre a 40% recurrence rate of hyperprolactinaemia with 6 years of surgery for microadenomas (17) has been reported. As a result of the effectiveness of bromocriptine in decreasing the size of even large prolactinomas, the place of surgery is increasingly limited to those patients where medical treatment has failed. Radiotherapy has been advocated in the management of large prolactinomas, both as primary treatment and as prophylaxis to avoid tumour enlargement during subsequent pregnancy. It may be given either as external beam (18) or as internal (interstititil) (19) radiotherapy. However, the fall in serum prolactin concentrations following X-ray therapy is slow and panhypopituitarism remains a risk in the long term. We do not, therefore, favour its use.

Prolactinomas in pregnancy

This is the major area of controversy. Since the pituitary enlarges in normal pregnancy, there has been a fear that if ablative surgery or radiotherapy is not used prior to conception the tumour may regrow during pregnancy especially if bromocriptine is stopped once pregnancy is diagnosed. In the case of microadenomas the risk of tumour growth during pregnancy is <5% (20) and bromocriptine alone is generally accepted as the treatment of choice because it produces superior conception rates and avoids the hazards of surgery. Where large prolactinomas are concerned, it was previously believed that the risk of serious complications in pregnancy may occur in up to 35% of cases. (20) However, the essential point is that the majoirty of cases in this report did not receive bromocriptine for induction of ovulation. In 1982 Bergh et al (21) reported their experience in 18 patients with large prolactinomas which produced 23 pregnancies. In 22 out of 23 cases pregnancy proceeded uneventfully. In 1 case the

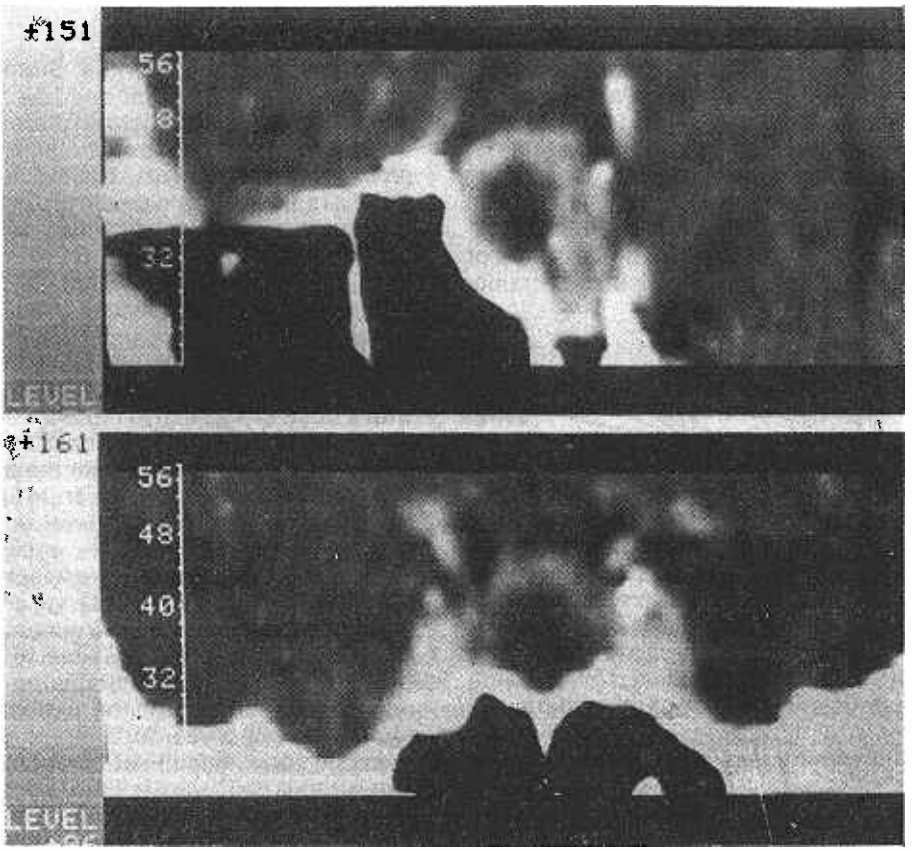

Figure 2 — Sagittal (top) and coronal (bottom) reconstructions of a CT scan in a young woman who presented with amenorrhoea and a high prolactin level. There is a large macroprolactinoma with suprasellar extension.

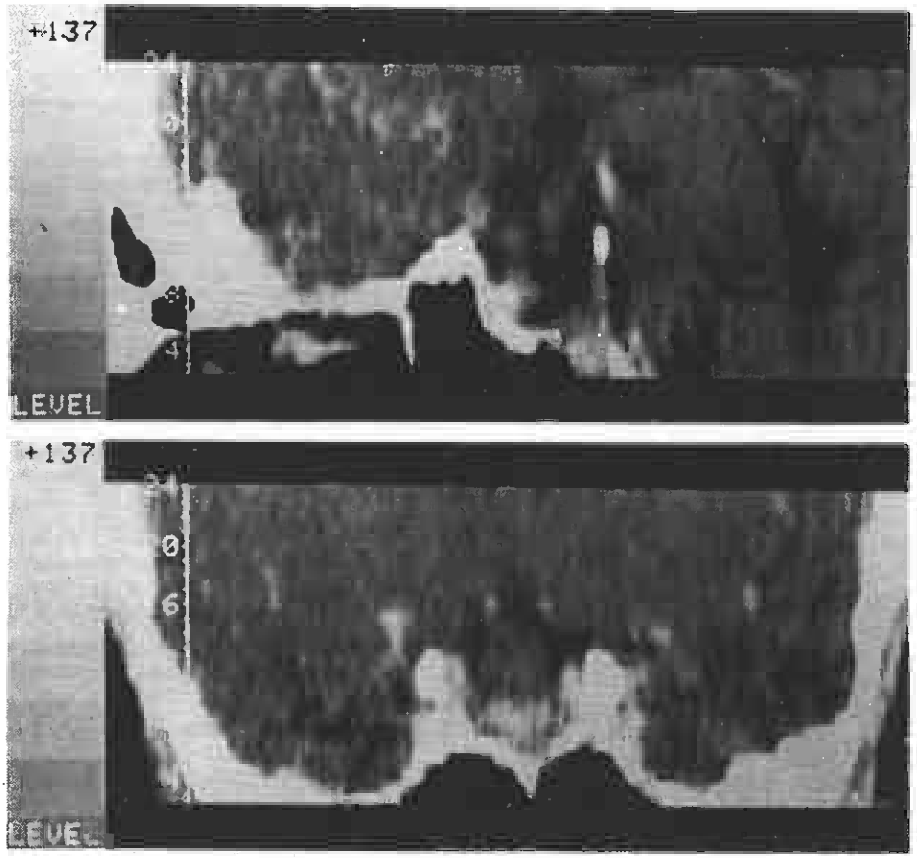

Figure 3 — Sagittal (top) and coronal (bottom) reconstructions of CT scans in the same patient as shown in figure 2 after 5 months of treatment with bromocriptine. The prolactinoma has shrunk considerably.

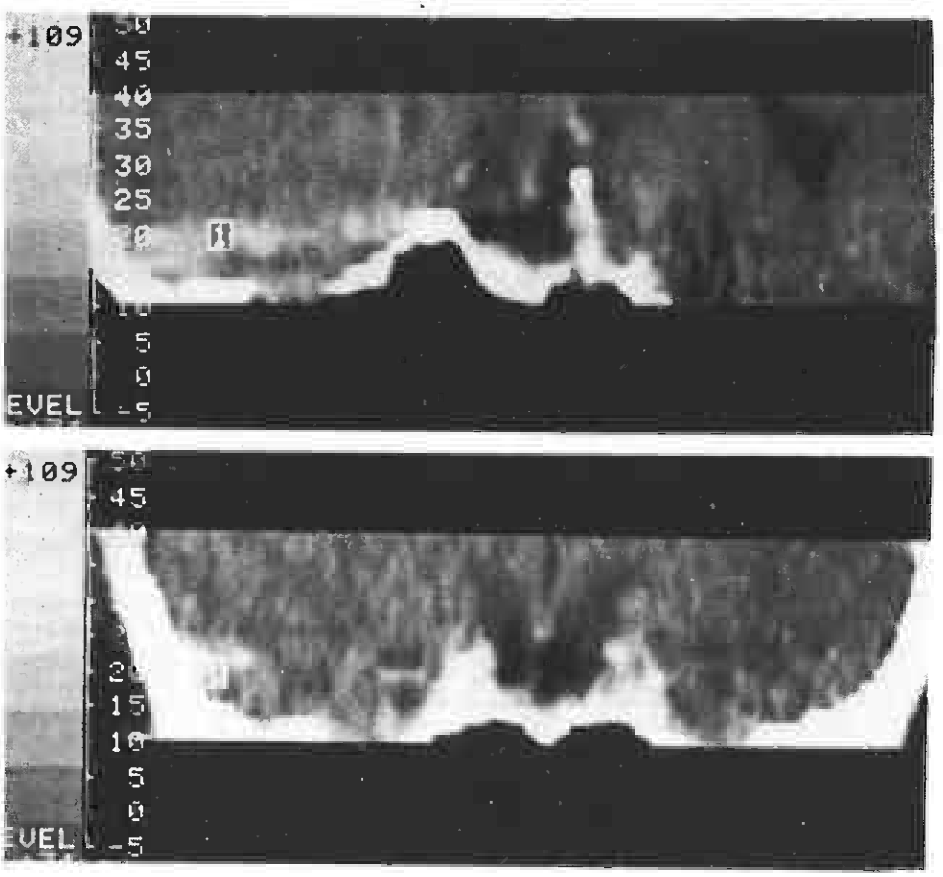

Figure 4 — Sagittal (top) and coronal (bottom) reconstructions of the CT scan of the same patient after 1 year of bromocriptine as sole therapy. The macroprolactinoma has largely disappeared and the sella is almost empty.

patient developed a visual defect at 30 weeks of pregnancy but when bromocriptine was reintroduced this quickly reversed. Our policy at the Middlesex is to use bromocriptine alone to treat macroprolactinomas requiring fertility. We advise that contraception be used, and pregnancy deferred, until a repeat CT scan has shown that the tumour has shrunk back into the fossa. Once pregnancy is diagnosed we stop bromocriptine and monitor the patient clinically with monthly visual field examination. If pituitary expansion occurs and results in clinical symptoms, we reinstitute treatment with bromocriptine after CT scanning. We have found that this will rapidly produce tumour regression and allows pregnancy to be safely continued. (22) In the event that there is insufficient tumour shrinkage seen on the prepregnancy CT scan surgery has to be considered. Conservative surgery is indicated to preserve anterior pituitary function even at the risk of incomplete removal of the tumour because the objective of surgery is decompression of the sella turcica. Remission and control of the tumour is provided by postoperative treatment with bromocriptine. This combined approach has been found sufficient to induce ovulation and allow pregnancy to proceed safely.

Long term follow up of medically treated hyperprolactinaemic patients

We have recently addressed this issue and for a more detailed account the reader is referred this review. (3) In summary, in the long term follow-up of hyperprolactinaemic women, including those with prolactinomas, treated with bromocriptine, the clinical response has been consistently favourable, there has been no cumulative side effects and there is no tumour progression or growth of proven prolactinomas. (23) We have found that in hyperprolactinaemic patients without tumours and serum prolactin levels <2000iU/l 60% of patients are cured in that basal prolactin levels remain normal and ovulatory cycles continue even after bromocriptine is stopped. (24) Finally, in series which report the effect of bromocriptine withdrawal after long term therapy in prolactinomas, although hyperprolactinaemia may recur in the majority of cases, there is no recurrence of tumours. (25)

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