

Relative resistance of a macroprolactinoma to bromocriptine therapy during pregnancy

B. S. Shanis and J. H. Check

Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Camden, New Jersey, USA

Key words: MACROPROLACTINOMA, PREGNANCY, PARLODEL

ABSTRACT

A woman presented with a pituitary macroadenoma with extensive suprasellar extension. Her initial response to bromocriptine therapy was good, allowing subsequent trans-sphenoidal surgical treatment. The tumor grew during pregnancy despite continued bromocriptine therapy, but it returned to prepregnancy size postdelivery.

There have been conflicting reports regarding the growth of pituitary tumors in pregnancy. Most recognize that some growth may occur, but only a small percentage of patients are reported to become symptomatic from the growth. Resistance to bromocriptine has been reported in non-pregnant patients. Patients who have had surgery or radiation therapy and did not receive bromocriptine treatment during pregnancy have been reported to have symptomatic growth of their residual tumor. This case demonstrates an unusual tumor that became resistant to bromocriptine during pregnancy, but whose sensitivity to the drug returned postdelivery.

CASE REPORT

We report herein a case of a patient with a macroadenoma which was under good control with bromocriptine therapy until she became pregnant.

The tumor grew during pregnancy, despite the continuance of bromocriptine.

The patient presented at the age of 38 years for infertility evaluation. She had been amenorrheic since the age of 18 years, with a diagnosis of premature ovarian failure, documented by elevated urine gonadotropins, that was confirmed at the age of 26 years by elevated serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Her LH and FSH at the age of 38 years were < 1.0 mIU/ml and the serum prolactin level was 1845 ng/ml. Serum prolactin was not obtained at the age of 18 or 26 years. Computerized axial tomography (CAT) scan showed a large macroadenoma of the pituitary with suprasellar extension to 27.5 mm above the sellar floor. The patient had significant visual loss. Because of the size and extent of suprasellar extension she was not initially considered a surgical candidate. She was treated with bromocriptine 12.5 mg/day and her visual symptoms improved. CAT scanning revealed a 50% reduction in size of the tumor within a few months (extension to 12.3 mm above sellar floor), although the serum prolactin level remained elevated at

1240 ng/ml. Serum thyroxine, thyroid-stimulating hormone (TSH) levels and 8:00 a.m. cortisol levels were normal.

A trans-sphenoidal hypophysectomy was performed 1 year after bromocriptine therapy was initiated since no further reduction in tumor size occurred and the serum prolactin was still increased at 437 ng/ml. The highest dosage of bromocriptine tolerated (light-headedness) was 12.5 mg. The drug had been administered initially at 1.25 mg/day with food and was increased by 1.25 mg intervals every 3–5 days. However, even after 2 weeks at 12.5 mg, raising the dosage to 13.75 mg again caused severe light-headedness. Because the tumor extended into the suprasellar space, along the sphenoid wing and in the cavernous sinus, a portion of the tumor was not resected. Histological evaluation showed pure antiprolactin immunostaining. Radiation therapy was not considered to be necessary. The patient was started on maintenance thyroid (0.2 mg/day L-thyroxine) and hydrocortisone therapy (30 mg/day). Bromocriptine therapy at 12.5 mg was maintained after surgery and her serum prolactin levels ranged from 90 to 155 ng/ml. The patient responded to human menopausal gonadotropin (hMG) therapy and did conceive twice, but had a blighted ovum and a fetal demise. Her third pregnancy was successful following hMG therapy again.

Visual field examination at 7 months' gestation revealed a bitemporal hemianopsia. Magnetic resonance imaging (MRI) examination found increased growth of the tumor to 50% of its previous size (13.5 mm above sellar floor). Nevertheless, the patient was treated expectantly and merely continued bromocriptine 12.5 mg/day, hydrocortisone 35 mg/day and L-thyroxine 0.2 mg/day. A boy was delivered, born 7 weeks premature, and follow-up MRI showed subsequent return of the tumor to prepregnancy size (i.e. microadenoma size).

The patient has continued on bromocriptine 12.5 mg/day and hydrocortisone 25 mg/day since. Thyroid studies have remained normal. An MRI 2 years later showed no change in size of the tumor.

DISCUSSION

Hyperprolactinemic patients are at increased risk for tumor enlargement in pregnancy¹. The high levels of estrogen are believed to stimulate pituitary

DNA synthesis, prolactin mRNA, prolactin secretion and meiotic activity². Normally the pituitary enlarges in pregnancy and the number and size of lactotrophs increases^{3,4}. However, the risk of a clinically significant increase in tumor size for microprolactinomas has been found to be only 1–5%⁵.

There is disagreement on the effect of estrogen on prolactin levels: Abu-Fadil and colleagues⁶ showed a 1.5–2-fold increase in circulating prolactin levels, while Corenblum⁷ showed a decrease. Fourteen pregnant patients studied by Woodhouse and co-workers⁸ (including two with extrasellar disease) were withdrawn from bromocriptine therapy and none of these demonstrated signs or symptoms of tumor growth. Other studies^{9–11} showed symptomatic growth of pituitary tumors with cessation of bromocriptine therapy, which resolved after parturition.

Only one of 21 patients with macroprolactinomas in pregnancy developed visual symptoms when bromocriptine was continued during gestation¹². There was, however, regrowth of tumor without symptoms in three-quarters of patients in their first pregnancy after stopping bromocriptine therapy¹³. Crosignani and associates¹⁴ showed it was possible to quickly suppress symptomatic suprasellar growth in pregnancy with bromocriptine. Molitch^{5,15} showed all prolactinomas decreased in size on bromocriptine therapy, but some shrank only minimally.

There are reports of patients with prior surgical or radiation treatment of their pituitary who developed symptoms in pregnancy. One study reported 76 pregnancies in 73 women showing 4% with headaches and 5% with visual disturbance; only one patient was treated¹⁶. A case report of a patient with prior irradiation of her pituitary tumor who stopped her bromocriptine treatment when she conceived, found increasing visual symptoms during the pregnancy, but no treatment was given¹⁷.

Numerous studies report resistance of pituitary adenomas to bromocriptine. Maraschini and colleagues¹⁸ observed three of 16 patients with macroprolactinomas did not respond to bromocriptine therapy with normalization of prolactin levels. Tumor shrinkage was observed in only eight of 15 patients¹⁸. In a study by Brue and co-workers¹⁹, 27 of 288 patients did not normalize prolactin levels on bromocriptine. Twenty-four had no reduction

in size or growth of their tumors¹⁹. Both size and growth of tumor subsequently shrank, without bromocriptine therapy, possibly related to intratumoral hemorrhage²⁰.

None of these studies described any cases similar to the case presented herein where the resistance only occurred during pregnancy. However, in the case presented, the resistance to bromocriptine during pregnancy may have been only relative rather than absolute since the possibility exists that had the patient tolerated a higher dose of bromocriptine, the resistance would not have been demonstrated. Nevertheless, to our knowledge, there has been no other case reported to date where a dose of bromocriptine sufficient to inhibit tumor growth in the non-pregnant state became ineffective when the woman became pregnant but restored efficacy postpartum. This circumstance might possibly be more common despite a paucity of case descriptions since many clinicians may merely raise the dosage during pregnancy and the tumor shrinks and the physician never reports the case. However, this probably occurs less often following previous external beam radiotherapy.

It would have been interesting to see if the tumor, although becoming resistant to bromocriptine therapy during pregnancy, would have responded to quinagolide (CV 205-502), a new non-ergot dopamine agonist^{21,22}. In one study of 21 patients with prolactinomas (15 of whom had a macroadenoma) who were resistant to bromocriptine, 50% responded to quinagolide²³. Unfortunately, quinagolide was not available in the United States except for clinical trials when the patient was presented.

The mechanism of resistance of prolactinomas to bromocriptine is unclear. There may be several sites in the dopamine-D2 receptor-second messenger pathways that may be involved in such a resistance phenomenon. One study suggested that there may be a decrease in D2 dopamine receptor sites in some of the adenomatous lactotrophs from bromocriptine-resistant prolactinoma patients²⁴. Possibly the demonstration of this case, where the rise in pregnancy hormones caused at least a relative resistance to bromocriptine which disappeared once these hormone levels were normalized postpartum, might help to further evaluate the mechanism of resistance to dopamine agonists in some prolactinomas.

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