Symptomatic pituitary tumor enlargement after induced pregnancy

Case report

PAUL B. NELSON, M.D., ALAN G. ROBINSON, M.D., DAVID F. ARCHER, M.D., AND JOSEPH C. MAROON, M.D.

Departments of Neurological Surgery, Medicine, and Obstetrics and Gynecology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

A case is presented and 11 others are reviewed in which symptomatic pituitary tumor enlargement occurred during pregnancies that resulted from induced ovulation. The syndrome is usually characterized by headache and visual disturbances with bitemporal visual field abnormalities, but may present with ocular muscle palsies. The cases are divided into two groups. The patients in one group had a shorter duration of amenorrhea (3.8 years), developed symptoms before the 14th week of pregnancy, and were usually treated by tumor removal. Patients in the second group had a longer period of amenorrhea (10.2 years), developed symptoms after the 24th week of pregnancy, and their symptoms regressed with delivery of the infant. Tumor removal or termination of the pregnancy both resulted in resolution of symptoms. All pregnancies resulted in normal infants. This series provides guidelines for management of future cases.

KEY WORDS • pituitary tumor • pregnancy • amenorrhea

Pituitary tumors are found in 2% to 12% of patients with amenorrhea. Treatment of amenorrhea with gonadotropins and more recently bromocriptine (CB 154) now enables these infertile patients to become pregnant. The major risk of pregnancy in patients with pituitary tumors is further enlargement of the tumor with impairment of vision. Induced pregnancies are generally limited to patients without demonstrable pituitary tumors. However, patients with unrecognized or small pituitary tumors may undergo induced pregnancy and may develop evidence of tumor enlargement. A recent case is described and a review of 11 additional cases given.

Case Report

This 32-year-old woman had menarche at the age of 12 years, and regular menses until 18 years. Oligomenorrhea began at that time with primary infertility beginning at 22 years of age. Secondary amenorrhea with expressible galactorrhea began at 29 years of age. Peak prolactin level 3 years before admission was 235 ng/ml. Serum gonadotropin levels were normal. Eighteen months before admission she was treated with bromocriptine and became pregnant after 8 weeks of therapy. Frontal headache developed in the sixth week of this pregnancy, but subsided within 3 days. The pregnancy terminated in a spontaneous abortion at 3 months of gestation. Two
TABLE 1

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>headache &amp; visual field abnormalities</td>
<td>8</td>
</tr>
<tr>
<td>ocular muscle palsies</td>
<td>2</td>
</tr>
<tr>
<td>headache only</td>
<td>1</td>
</tr>
<tr>
<td>visual field abnormalities only</td>
<td>1</td>
</tr>
</tbody>
</table>

months before admission she was placed on a second trial of bromocriptine and established her second pregnancy within 8 weeks of starting therapy. She developed a right frontal headache and diplopia during the eighth week of her pregnancy. General physical examination was normal, but she had a right sixth cranial nerve palsy. Within 1 week, the right eyelid began to droop and she was hospitalized.

Examination. Right third and sixth cranial nerve palsies were present. The right pupil measured 4 mm and reacted poorly to light. Visual acuity, funduscopic examination, and formal visual fields were normal. Facial sensation and the corneal reflexes were normal. Polytomography of the sella turcica showed sloping of the sellar floor to the right. Computerized tomography was normal, but carotid angiography revealed lateral and superior displacement of the intracavernous and supraclinoid segments of the internal carotid artery on the right.

Operation. The patient underwent transsphenoidal removal of a pituitary adenoma on the third hospital day. The floor of the sella turcica was thinned and a necrotic tumor under pressure was found bulging into the area of the right cavernous sinus. The tumor was excised and the histological examination was compatible with a chromophobe adenoma.

Postoperative Course. Postoperative endocrine evaluation of pituitary function was normal. Serial prolactin levels during pregnancy were lower than normal but showed a rise parallel to the expected curve of pregnancy. A normal infant was delivered by cesarean section at 42 weeks gestation.

Review of the Literature

Eleven other cases of symptomatic enlargement of pituitary tumors in pregnancy after induced ovulation in amenorrheic women have been reported.1,4,8,9,11,12,14,15 Seven of the 11 were reported since 1975.8,9,11,14 Including the present case, the patients' mean age was 27 years, range 21 to 36 years, and the average period of amenorrhea was 6.5 years, range 1 to 16 years. Galactorrhea was present in six of 12 patients.1,8,9,14 Prolactin levels were determined in only two cases,14 and were elevated in both with peak values of 203 ng/ml and 235 ng/ml. Pre-induction skull films were interpreted as showing a normal sella turcica in seven of 10 patients.1,4,8,11,13 Three patients had asymmetry of the sellar floor without significant sellar enlargement.8,12 Induction was carried out with exogenous gonadotropins in 10 patients.1,4,5,8,9,12,13 and with bromocriptine in two patients.14

The most common presenting symptoms were headache followed by visual disturbances with bitemporal visual field abnormalities (Table 1).1,4,8,9,11,12 Occasionally patients developed ocular muscle palsies,4 headache only,8 or visual field abnormalities only.14 X-ray films of the sella turcica obtained at the time of onset of the symptoms were interpreted as abnormal in all of the 11 patients.1,4,5,8,9,11-13

The time of gestation at which symptoms of tumor enlargement were noted was in a bimodal distribution, occurring before the 14th week,1,3,8,12 and after the 24th week1,3,8,11,13,14 (Fig. 1). The mean duration of amenorrhea differed in the two groups. In patients with symptoms before the 14th week of pregnancy, the duration of amenorrhea was 3.8 years ± 0.94 SEM, while in patients with symptoms developing after the 24th week of gestation, the duration was 10.2 years ± 2.31 SEM, p < 0.025. The overall correlation between length of amenorrhea and duration of pregnancy prior to onset of symptoms was highly significant, p < 0.01 (Fig. 2). Four of seven patients in the group with early onset and four of five patients in the group with late onset were primipara.
Pituitary tumor enlargement after induced pregnancy

Treatment of patients also differed in the early and late groups. Five of seven patients in the early group had definitive tumor treatment during pregnancy; four by surgical removal of the tumor and one by yttrium-90 implant. Two patients in the early group were treated conservatively: one developed mild symptoms that improved without treatment, and the second patient developed headache alone early in pregnancy and mild visual symptoms later in pregnancy. Only one of the five patients in the group with late onset had hemorrhage into the tumor which caused abrupt onset of headache and a complete bitemporal visual field loss. Three patients had induced labor or caesarian section, and one patient was followed to term on steroids. The overall results were excellent. In all women the symptoms subsided with removal of tumor or by termination of the pregnancy, and in every case the improvement was rapid. All pregnancies resulted in normal children; nine single infants, two sets of twins, and one set of triplets.

Discussion

While enlargement of the pituitary gland is a normal physiological concomitant of pregnancy, symptomatic enlargement is probably limited to patients with pre-existing pituitary tumors.Gemzell reported pituitary enlargement in four of 250 amenorrheic women with pregnancy induced with gonadotropins. If the incidence of pituitary tumors in women with amenorrhea is approximately 7%, 11% of patients with pituitary tumors may develop symptoms after induced pregnancy.
Evaluation of infertility in women now usually includes prolactin levels, plasma gonadotropins, and polytomography of the sella turcica, followed by visual field examination and anterior pituitary hormone testing if these values are abnormal. If a pituitary tumor is demonstrated and an infertile woman desires pregnancy, primary treatment of the tumor by surgical removal or irradiation or a combination of these therapies should be completed before ovulation is induced.\textsuperscript{3,8,11} However, some pituitary tumors may cause amenorrhea before the tumor is large enough to be detected by x-ray changes in the sella turcica or by visual field abnormalities. Thus, unsuspected tumors may exist in women where ovulation is induced and may enlarge during pregnancy. Headache followed by visual disturbances are the most common symptoms of tumor enlargement and the appearance of these symptoms in any pregnancy should alert the physician to the possibility of a pituitary tumor.

The earlier appearance of symptoms during pregnancy in patients with a short duration of pre-existing amenorrhea suggests a possible difference in growth potential of the tumors in these women. Although repeat pregnancies may cause further stimulation of tumor growth, parity did not appear to be the factor that divided the patients into the early and late groups. Patients with more rapidly growing tumors may present early in the course of tumor development and if pregnancy is induced these tumors may enlarge rapidly. Patients with amenorrhea for many years and normal-sized sellas may have slower growing tumors, and even with the stimulus of pregnancy several months may be required to induce symptomatic tumor growth.

A biological difference in the tumors in these two groups may explain the good results obtained with strikingly different treatments. The patients with earlier appearance of symptoms were usually treated definitively and if these tumors have greater growth potential such treatment was indicated. Transsphenoidal tumor removal was accomplished at this stage of pregnancy without adverse effects on the fetus and with the relief of symptoms in the mother. On the other hand, patients who reached the latter stage of pregnancy before symptoms developed were safely followed until delivery. Symptoms in the mother regressed rapidly when the pregnancy ended. Occasionally, mild or transient symptoms early in pregnancy have been followed without treatment, and severe or progressive symptoms occurring late in pregnancy have required definitive tumor treatment before delivery. All women did well and had normal infants. It is possible that reported cases are biased in favor of cases with a favorable outcome, but the data indicate that pregnant women can safely undergo pituitary surgery early in gestation and that even symptomatic pituitary tumors can be followed when discovered near the end of gestation. The therapy reported in this series would seem to provide guidelines for management of future cases.

Addendum


References

Pituitary tumor enlargement after induced pregnancy


This work was supported by Health and Research Services Foundation of Pittsburgh Grant T-62; National Institutes of Health Grant AM16166; and the Clinical Research Unit of the University of Pittsburgh Grant RR-00056.

Address reprint requests to: Joseph C. Maroon, M.D., Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261.