Effects of bromocriptine-induced pregnancy on prolactin-secreting pituitary tumours


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Abstract. Twenty-eight women with hyperprolactinaemia and amenorrhoea received bromocriptine treatment which resulted in 31 term pregnancies. Bromocriptine treatment was stopped as soon as pregnancy was established. Nineteen of the women had radiological signs of a pituitary tumour. The pregnancies were clinically uneventful in all cases except one who developed headache. Post-partum sellar X-ray showed pregnancy-induced enlargement of the pituitary fossa in 4 of the 28 women. Regression of the radiological changes occurred in 3 of the 4 women within 2 years after the delivery. The women with abnormal sellar X-rays had no difference in the mean prolactin levels before treatment and after pregnancy and lactation while all the women with normal sellae had lower prolactin levels after pregnancy than before. Three women resumed regular spontaneous menstruations after pregnancy and lactation but only one conceived again.

Thus, serious pituitary tumour complications are rare in hyperprolactinaemic women with bromocriptine-induced pregnancies. The pregnancy does not worsen the condition. Resolution of hyperprolactinaemia after bromocriptine-induced pregnancy is an unfrequent finding.

Resolution of hyperprolactinaemia with return of regular spontaneous menstruations after bromocriptine-induced pregnancies has been described in single patients with hyperprolactinaemic amenorrhoea (Mornex et al. 1978; Cowden & Thomson 1979; Issacs 1979; Noble 1979). Recently Jacobs & Thobani (in press) reported that 10 of 23 hyperprolactinaemic women had remission of hyperprolactinaemia and resumption of normal ovulation after pregnancy induced by bromocriptine.

Here we report on the effect of bromocriptine-induced pregnancy on prolactin secretion and ovulatory function in 28 hyperprolactinaemic women, 19 of whom had radiological signs of a pituitary tumour.

Patients and Methods

Twenty-eight women, aged 24–37 years, with hyperprolactinaemia and long-lasting amenorrhoea were treated with bromocriptine, resulting in at least one term pregnancy. One of the women had primary amenorrhoea and the others secondary amenorrhoea of 6 months to 13 years duration (median 5 years).

Radiological examination of the sella turcica including hypocycloidal polytomography showed an asymmetrical and/or enlarged pituitary fossa in 19 of the 28 women. In 9 women the sella was symmetrical and of normal size. The pituitary fossa was classified from the skull X-rays according to Thorner et al. (1979) (Table I). Computerized axial tomography in 15 of the women with abnormal sellae showed no evidence of empty sella or suprasellar extension of a pituitary tumour. None of the women had received prior tumour therapy either by surgery or irradiation. The visual fields were normal in all the women.

Prolactin in serum was measured radioimmunologically by the use of 125I-labelled human prolactin and rabbit anti-human prolactin antibodies coupled to CNBr-activated ultrafine Sephadex particles (Bergh et al. 1978b). The prolactin (VLS 3) and antiprolactin (VLS 3) preparations were kindly supplied by National Institutes of Health, Bethesda. The prolactin concentrations in serum before treatment ranged between 30 and 565 μg/l (mean 71 μg/l). There was no significant difference in the mean serum prolactin levels between the groups with
normal and abnormal pituitary fossae. The normal range for healthy women was 2–15 μg/l (mean 6.5 μg/l). The routine clinical and endocrinological evaluation gave no evidence of any abnormality in the thyroid or adrenal function. None of the women were taking any drugs known to stimulate prolactin secretion.

Bromocriptine (Parlodel®, Pravidel®, Sandoz AG) was given in daily doses between 2.5 mg and 10 mg (mean 5.7 mg) for 1–22 months (median 4 months) before conception occurred. The bromocriptine therapy was stopped as soon as pregnancy was suspected, usually within one week after the expected day of menstruation. During pregnancy all the women were followed up with monthly visual field determinations in addition to the clinical examinations. All the patients had post-partum sellar X-ray examinations to check whether the pituitary fossa had changed. All the patients breastfed their babies. In 4 women the milk production ceased within one month post-partum.

### Results

Thirty-one term pregnancies occurred after bromocriptine treatment of the 28 hyperprolactinaemic women and resulted in 32 healthy children (Table 1). The clinical course of the pregnancies was uneventful in all but one of the women who developed headache from the second trimester. All the women had normal visual fields throughout the pregnancy. The prolactin levels before bromocriptine treatment and after the women had stopped breastfeeding are shown in Fig. 1. The women with normal sellar X-rays had a mean prolactin level which was lower after weaning than before treatment ($P < 0.01$) while the women with abnormal pituitary radiology showed no such difference (Table 2).

### Table 1.
Pituitary fossa classification according to Thorner et al. (1979) and outcome of pregnancy in 28 women treated with bromocriptine.

<table>
<thead>
<tr>
<th>Pituitary fossa before pregnancy</th>
<th>Patients</th>
<th>Prolactin range, μg/l</th>
<th>Outcome of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spontaneous abortion</td>
</tr>
<tr>
<td>B0</td>
<td>9</td>
<td>32–148</td>
<td>5</td>
</tr>
<tr>
<td>B1</td>
<td>2</td>
<td>34,95</td>
<td>–</td>
</tr>
<tr>
<td>B1E</td>
<td>1</td>
<td>68</td>
<td>–</td>
</tr>
<tr>
<td>B2</td>
<td>3</td>
<td>44,46,480</td>
<td>2</td>
</tr>
<tr>
<td>B2E</td>
<td>1</td>
<td>30</td>
<td>–</td>
</tr>
<tr>
<td>B3</td>
<td>2</td>
<td>40,65</td>
<td>–</td>
</tr>
<tr>
<td>B3E</td>
<td>2</td>
<td>40,90</td>
<td>–</td>
</tr>
<tr>
<td>B4</td>
<td>8</td>
<td>49–565</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>8</td>
<td>31</td>
</tr>
</tbody>
</table>

B0: normal, B1: asymmetry < 1 mm, B2: asymmetry 1–3 mm, B3: asymmetry > 3 mm, B4: double contour throughout, asymmetry > 3 mm. E: erosion.

### Table 2.
Mean prolactin levels before treatment and after pregnancy and lactation in the women with normal and abnormal sellae. In brackets geometric mean ± standard error of the mean.

<table>
<thead>
<tr>
<th></th>
<th>Prolactin μg/l</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After weaning</td>
</tr>
<tr>
<td>Normal sella</td>
<td>67</td>
<td>40</td>
</tr>
<tr>
<td>$n = 9$</td>
<td>(55–81)</td>
<td>(34–52)</td>
</tr>
<tr>
<td>Abnormal sella</td>
<td>74</td>
<td>58</td>
</tr>
<tr>
<td>$n = 19$</td>
<td>(62–88)</td>
<td>(49–70)</td>
</tr>
</tbody>
</table>
Regular spontaneous menstruations returned in 3 women after they had stopped breastfeeding. The prolactin concentration in serum was within the normal range in one of them while the other 2 had slightly raised prolactin levels (Table 3). None of the women used any contraception after the pregnancy. One of them (Case 1) conceived but had an early abortion. Case 3 had short luteal phases (8–10 days) according to the basal body temperature chart and inadequate luteal phase progesterone concentrations in serum (below 20 nmol/l).

Signs of tumour enlargement during pregnancy were found in 4 women at the post-partum X-ray examination. The clinical course and outcome of these pregnancies have been described previously (Bergh et al. 1978a,b; Nillius et al. 1980). Sellar X-rays 12 to 21 months after the pregnancy showed evidence of tumour regression in 3 of the 4 women. In one of them (Case 3, Table 3) the sella turcica had changed during pregnancy from Grade B4 to B4E but one year after the delivery, without any treatment, there was re-calcification of the sella and the erosion had disappeared.

Radiological signs of tumour regression were also found in 2 other women with evidence of tumour enlargement during pregnancy. A 25 year old woman with primary amenorrhoea developed severe headache from the second trimester of pregnancy but the visual fields remained normal. The headache disappeared post-partum but X-ray examination showed a change in the appearance of the pituitary fossa from Grade B2 to B5E. After

### Table 3.

Clinical details in 3 women who regained spontaneous menstruations after a bromocriptine-induced pregnancy.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age years</th>
<th>Amenorrhoea months</th>
<th>Bromocriptine treatment (5 mg/d) months</th>
<th>Prolactin Before treatment</th>
<th>Prolactin After treatment</th>
<th>Sella turcica</th>
<th>Observation time after pregnancy, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>36</td>
<td>6</td>
<td>13</td>
<td>38</td>
<td>25</td>
<td>Normal B0</td>
<td>2</td>
</tr>
<tr>
<td>Case 2</td>
<td>30</td>
<td>24</td>
<td>4</td>
<td>35</td>
<td>10</td>
<td>Normal B0</td>
<td>1</td>
</tr>
<tr>
<td>Case 3</td>
<td>28</td>
<td>6</td>
<td>4</td>
<td>49</td>
<td>20</td>
<td>Asymmetrical B4</td>
<td>2</td>
</tr>
</tbody>
</table>
6 months of breastfeeding bromocriptine therapy (5 mg daily) was re-instituted resulting in normal prolactin levels and regular ovulatory menstruations. After discontinuation of bromocriptine 21 months later the patient remained normoprolactinaemic and has continued to have regular menstrual bleedings. Sellar X-ray one year after bromocriptine therapy was stopped showed evidence of regression.

A 35 year old woman with 13 years' amenorrhoea and an uneventful pregnancy had signs of tumour enlargement post-partum despite a sella turcica which was judged to be normal before pregnancy. After 5 months of breastfeeding bromocriptine therapy was re-instituted (5 mg daily) and regular menstrual bleedings returned. Re-examination of the pituitary fossa 22 months later showed signs of regression (Fig. 2). Her prolactin level before treatment was 111 μg/l and before bromocriptine was re-instituted 59 μg/l. Discontinuation of the bromocriptine therapy after 2 years resulted in an increase of the prolactin levels to 109 μg/l within 2 weeks. A fourth woman also had evidence of tumour enlargement at the post-partum X-ray examination (sella Grade B4→B4E) despite a completely uneventful pregnancy. The patient had normal prolactin levels and regular menstruations during treatment with bromocriptine but two years after the delivery the sellar X-ray was unchanged. No tumour complications occurred in the other 24 women who experienced 27 term pregnancies in all.

Discussion

Pregnancy in a woman with a prolactinoma is associated with increased risk of pituitary tumour complications. However, studies during recent years have shown that the incidence of such complications are surprisingly low (Nillius et al. 1980, review). More recently, it has even been suggested that pregnancy may have a beneficial effect on hyperprolactinaemia (Isaacs 1979). Resolution of hyperprolactinaemia or resumption of ovulatory function after bromocriptine-induced pregnancies occurred in 10 of 23 hyperprolactinaemic women studied by Jacobs & Thobani (in press). Many of these women had prolactinomas. In contrast only 3 of our 28 hyperprolactinaemic patients resumed regular menstruations and only one conceived spontaneously. An explanation for this may be that our patients had rather high pre-treatment prolactin levels in serum. Jacobs & Thobani (in press) found a significant association of remission with pre-treatment prolactin levels of below 40 μg/l.

After pregnancy and lactation, 19 of our 28 patients had lower prolactin levels than before treatment. This has also been found by other investigators (Zárate et al. 1979; Rjosk et al. 1980). It is evident from the post-pregnancy prolactin concentrations that the potent stimulatory effect of pregnancy and lactation on the pituitary lactotrophs did not make the prolactin hypersecretion worse. Thorner et al. (1975) discouraged their hyperprolactinaemic patients with suspected pitui-
tary tumours to breastfeed to avoid the stimulatory
effect of suckling on the pituitary. Our prolacti-
inoma patients have been allowed to breastfeed
and we have not seen any untoward effects of this
practice. In our opinion there is no reason to
withhold hyperprolactinaemic women from the
advantages of breastfeeding.
Radiological signs of tumour enlargement were
found at the post-partum sellar X-ray in 4 of our
28 patients but only one of them had symptoms
during pregnancy. The subtle radiographic
changes probably represent growth of a pituitary
adenoma. However, it is not known whether simi-
lar changes of the sellar appearance may occur
during pregnancy in the healthy population. In 3
of the 4 patients with pregnancy-induced sellar
enlargement, radiological regression occurred
within 2 years after the delivery. We have pre-
viously described a prolactinoma patient who dur-
ing pregnancy developed visual field defects, which
regressed after reinitiation of bromocriptine
(Bergh et al. 1978a). However, serious pituitary
tumour complications during pregnancy are rare
(Nillius et al. 1980, review).
Bromocriptine seems to prevent growth of pro-
 lactinomas and may even cause regression of such
tumours (Nillius 1980, review). Some investigators
have therefore maintained bromocriptine therapy
during pregnancy in patients with prolactinomas to
prevent tumour growth (Yuen 1978; Coelingh
Bennink 1979). In the few cases where this has
been done, the bromocriptine treatment has had
no untoward effects on the pregnancy or the
foetus. However, bromocriptine crosses the human
placenta and inhibits the prolactin increase in the
mother and foetus during pregnancy (Bigazzi et al.
1979; Coelingh Bennink 1979). The low incidence of
complications during pregnancy in patients with
prolactinomas, found in this and other studies, do
not justify prophylactic bromocriptine therapy
during pregnancy. However, if serious tumour
complications occur reinitiation of bromocriptine
may be the treatment of choice (Bergh et al.
1978a).
Recent studies have shown that bromocriptine
can safely be used as primary treatment for infertile
women with hyperprolactinaemia, even in the
presence of radiological signs of a microadenoma
or a macroadenoma without suprasellar extension
(Nillius et al. 1980, review). This study confirms
that the risk for serious pituitary tumour compli-
cations during a bromocriptine-induced pregnancy
is small. It is uncommon that the pregnancy makes
the condition worse. On the other hand, resolution
of hyperprolactinaemia after a bromocriptine-
induced pregnancy seems to be an unfrequent
finding.

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