Bromocriptine treatment during early human pregnancy: effect on the levels of prolactin, sex steroids and placental lactogen

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Abstract. To elucidate the role of prolactin (Prl) in the endocrinology of early human pregnancy, 28 healthy women were given 5.0–7.5 mg of bromocriptine daily for two weeks between weeks 6–9 of normal gestation. Plasma Prl, oestradiol-17β (Oe2), progesterone (P), testosterone (T) and human placental lactogen (hPL) were measured before, and one and two weeks after the start of bromocriptine, and they were compared with those in 22 control women who were followed similarly but without bromocriptine treatment. Bromocriptine treatment induced a significant Prl depression at one week (7.3 ± 4.3 ng/ml vs 23.7 ± 11.4 ng/ml) and two weeks (5.3 ± 2.5 ng/ml vs 31.9 ± 16.4 ng/ml). Oe2, P, T and hPL levels, however, showed no significant differences between the groups. Two women undergoing bromocriptine treatment (7.1%) and one control woman (4.5%) experienced spontaneous incomplete abortion during the study period, but these three already had a low Oe2 level and a low/undetectable hPL level at the beginning of the study. It is obvious that neither maternal 'hypoprolactinaemia' nor bromocriptine during early human pregnancy interfere with the normal progress of pregnancy or with the normal synthesis of sex steroids and hPL at this time.

A certain amount of prolactin (Prl) is necessary for progesterone production by human granulosa cells in tissue culture; however, both subnormal and high local Prl concentrations have an inhibitory effect (McNatty et al. 1974). This phenomenon has also been confirmed in vivo, since both hyperprolactinaemia (Friesen et al. 1973) and bromocriptine-induced hypoprolactinaemia (Schulz et al. 1976, 1978; Bohnet et al. 1977) led to deficient luteal function or anovulation in non-pregnant women. Prl may also be involved with the secretion of androgens (Carter et al. 1977; Rubin et al. 1977; Bassi et al. 1977; Kandeel et al. 1978). During human pregnancy, the level of Prl exceeds the non-pregnant level after 32–36 days from conception (Barberia et al. 1975), yet it is not known whether this Prl rise is crucial for the normal progress of early pregnancy and for the normal production of sex steroids and peptide hormones. The present study was therefore designed to determine the effects of bromocriptine on the plasma levels of prolactin, oestradiol, progesterone, testosterone and human placental lactogen during early human pregnancy.

Materials and Methods

Fifty healthy women admitted for legal abortion between weeks 6–9 of gestation volunteered for this study after being fully informed about its purpose and course (Table 1). The pregnancies were uncomplicated, with the uterine sizes comparable with the duration of amenorrhoea. Twenty-eight women were given bromocriptine (Parlodel®, Sandoz Ltd., Basel, Switzerland) orally at a dose of 5 to 7.5 mg daily for two weeks, and 22 women served as controls. After the study period of two weeks, all women underwent an uncomplicated abortion with vacuum curettage (n = 47) or with hysterotomy (n = 3). Venous blood samples were collected into heparinized tubes before and one and two weeks after the start of the
trial. Plasma was separated by centrifugation and kept frozen at −20°C until assayed. Plasma prolactin (PRL) was assayed with CEA-IRE-SORIN kits (Department des Radioelements, 91190 Gif-sur-Yvette, France), as described elsewhere (Hammond et al. 1977a). Oestradiol-17β (Oe2), progesterone (P) and testosterone (T) were determined by radioimmunoassays using iodinated ligands (Hammond et al. 1977b). Human placental lactogen (hPL) was measured with a radioimmunoassay kit (Nor-diclab Ltd., Oulu, Finland). To make the hPL assay sensitive enough for early pregnancy samples the following modifications were made: the tracer hPL was diluted 5-fold in male serum and the antiserum 10-fold. The standard inhibition curve was prepared with hPL concentrations from 5 to 250 μg/l. The reagents were incubated for 48 h at +4°C. With this system, hPL concentrations down to 10 μg/l could be accurately measured. Student’s t-test was employed for the statistical analysis of the results.

Results

Hormonal findings
Before the start of the trial, mean hormonal concentrations were similar in both groups (Table 2). Bromocriptine significantly lowered (P < 0.001) the individual and mean PRL levels at one and two weeks. The mean Oe2, P, T and hPL levels did not differ between the groups either at one or two weeks of the trial (Table 2).

Table 1.
Clinical data (mean ± SD) of the patient population.

<table>
<thead>
<tr>
<th></th>
<th>Bromocriptine</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.3 ± 8.9</td>
<td>25.9 ± 7.1</td>
</tr>
<tr>
<td>Nulliparous/parous</td>
<td>16/12</td>
<td>13/9</td>
</tr>
<tr>
<td>Gestational age (weeks) at start of study</td>
<td>7.7 ± 0.9</td>
<td>7.8 ± 0.9</td>
</tr>
</tbody>
</table>

Table 2.
Concentrations (mean ± SD and range) of prolactin, oestradiol, progesterone, testosterone and human placental lactogen in bromocriptine and control groups. The number of samples is given in parentheses on the right.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>One week</th>
<th>Two weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bromocriptine</td>
<td>Control</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>Prolactin (μg/l)</td>
<td>27.3 ± 8.9 (26)</td>
<td>21.1 ± 12.9 (21)</td>
<td>7.3* ± 4.3 (16)</td>
</tr>
<tr>
<td>Oestradiol (nmol/l)</td>
<td>1.81 ± 0.93 (26)</td>
<td>1.81 ± 1.18 (21)</td>
<td>1.90 ± 0.95 (16)</td>
</tr>
<tr>
<td>Progesterone (nmol/l)</td>
<td>61.9 ± 1.93 (26)</td>
<td>60.6 ± 15.8 (21)</td>
<td>64.6 ± 16.8 (16)</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>2.93 ± 1.00 (14)</td>
<td>2.32 ± 0.91 (14)</td>
<td>2.66 ± 0.95 (14)</td>
</tr>
<tr>
<td>hPL (μg/l)</td>
<td>a30.3 ± 17.8 (14)</td>
<td>b32.4 ± 15.6 (14)</td>
<td>c98.6 ± 13.4 (14)</td>
</tr>
</tbody>
</table>

a Undetectable in 7 women.  b Undetectable in 7 women.  c Undetectable in 2 women.  d Undetectable in 1 woman.
Clinical outcome

During the study period of two weeks, pregnancy ended in spontaneous incomplete abortion in two of the 28 women (7.1%) undergoing bromocriptine treatment and in one of the 22 control women (4.5%) \( (P > 0.05) \). At the onset of the study these three women already had Oe2 levels (0.19, 0.24 and 0.54 nmol/l, respectively) which were clearly lower than the lowest Oe2 concentration of 0.77 nmol/l in women with continued pregnancy. Two of them had undetectable hPL levels. Their P levels, however (32.9, 38.9 and 54.5 nmol/l, respectively) fell within the range of 32.8–90.8 nmol/l found in women with continued pregnancy. These three women were excluded from the comparison of the hormonal findings between the bromocriptine and control groups. Twenty women treated with bromocriptine (71.4%) and 9 control women (40.9%) complained of severe nausea and/or vomiting.

Discussion

Because bromocriptine treatment is usually stopped as soon as pregnancy is diagnosed, data about the effects of bromocriptine on PRL secretion during pregnancy are scanty (Griffith et al. 1978). In one report, PRL levels were not suppressed when an acromegalic woman was given 10 mg of bromocriptine daily throughout pregnancy (Bigazzi et al. 1979). In our study, 5.0–7.5 mg of bromocriptine daily significantly lowered maternal plasma PRL concentrations in healthy women during normal early pregnancy. Similar bromocriptine treatment has been known to suppress PRL levels to below 2.2 µg/l in healthy non-pregnant women (Schulz et al. 1976, 1978), and compared with that, PRL suppression in our study was not so marked. The women in the bromocriptine group were, however, significantly ’hypoprolactinaemic’, because their mean plasma PRL concentrations were only 30.8% (at one week) and 16.6% (at two weeks) of the respective level in the untreated group. It is likely, therefore, that our procedure is valid for determining the effects of ’hypoprolactinaemia’ during early human gestation.

Spontaneous abortion occurred in both the ’hypoprolactinaemia’ group (2/28) and in the control group (1/22) and only in women whose Oe2 and hPL levels were already low at the onset of PRL suppression. This is taken as evidence that neither maternal ‘hypoprolactinaemia’ nor bromocriptine treatment predispose women to spontaneous abortion. This finding is in keeping with a report of normal pregnancies in women with defective PRL secretion (Turkington 1972) and with a report of normal PRL levels in women with subsequent abortion (Ylikorkala et al. 1979). In some other studies however PRL level was initially low, and fell before abortion (Schmidt-Gollwitzer & Saxena 1975; Jovanovic et al. 1978).

There appears to be three phases of P production in early pregnancy (Yoshimi et al. 1969; Tulchinsky & Hobel 1973; Mishell et al. 1973). At first, all the P comes from the ovaries, and this period probably does not last beyond weeks 5 or 6 of gestation. There is then a period extending to weeks 10–12 when both the ovaries and trophoblast contribute to the total production, and finally, the placenta becomes the dominant P source. The Oe2 patterns resemble those of P (Tulchinsky & Hobel 1973; Mishell et al. 1973). Circulating T levels also rise in early pregnancy, partly due to the foeto-placental contribution (Gandy 1976). In our study, the samples during bromocriptine intake were taken on average at 8.7 ± 1.1 (mean ± s.d) and 9.7 ± 1.1 weeks of gestation, when the Oe2 and P production was gradually shifting from the corpus luteum to the foeto-placental unit. Apart from a significant PRL suppression, Oe2, P, T and hPL levels were similar in the bromocriptine and control groups. This suggests that neither maternal ’hypoprolactinaemia’ nor bromocriptine interfere with the normal synthesis of sex steroids by the corpus luteum and/or foeto-placental unit during early human gestation.

Acknowledgments

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References


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