Bromocriptine Treatment in Anovulation with Decreased Ratio of Follicle Stimulating Hormone to Luteinizing Hormone and with Hyperandrogenism

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Abstract

Twenty-six anovulatory women of polycystic ovarian (PCO)-type were treated with bromocriptine (Br) at a daily dose of 5 mg for 2 months. Ovulatory cycles were resumed in 18 (69.2%) women (Br-responders). No difference between pretreatment serum levels of FSH, LH, PRL and estradiol and FSH/LH ratios in Br-responders and nonresponders was observed. The geometric mean of circulating androstenedione (A-dione) in Br-responders (2.58 ng/ml) appeared higher than that in nonresponders (2.11 ng/ml) but was not statistically significant. The geometric mean of dehydroepiandrosterone sulfate (DHEA-S) in Br-responders (1652 ng/ml) was lower (p<0.01) than that in nonresponders (2582 ng/ml). The ratio of DHEA-S to A-dione (D/A ratio) exhibited a highly significant between-group difference (p<0.001) (646 and 1222 for Br-responders and nonresponders, respectively). Br-nonresponders with high DHEA-S levels and D/A ratios tended to hyperproduction of adrenal androgen, and Br-responders with high A-dione levels and low D/A ratios to hyperproduction of ovarian androgen. The present study indicates that Br is effective in PCO-type women presumably with ovarian androgen hyperproduction. The efficacy of Br, when applied to PCO-type women, could be predicted with their D/A ratios.

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1980; Suginami et al., 1986a), have been applied to PCO-type anovulation. The efficacy, rationale, and adverse effects of the treatments have been reviewed (Yen, 1980; Coney, 1984; Goldzieher and diZerega, 1985). Recent literature has indicated the effectiveness of bromocriptine mesilate (Br) in PCO-type anovulation (Spruce et al., 1984; Mori et al., 1985; Taketani et al., 1986). The present study was conducted to reassess the efficacy of Br in PCO-type women, to prospectively differentiate women responding to Br from others and to analyze, if possible, its action mechanisms.

Materials and Methods

Patients

The tentative participants in the study were 73 anovulatory women, aged 21–34 yrs and showing monophasic and low basal body temperature (BBT) profiles for at least 40 days preceding their first visit. All gave informed consent. Peripheral blood (10 ml) was obtained at 1330–1500 h prior to physical examinations. The time of blood sampling was so decided in order to eliminate diurnal variations in the hormonal estimates and due to our convenience since our infertility clinic was open from 1330 to 1700 h. Serum levels of LH, FSH, prolactin (PRL), estradiol (E2), androstenedione (A-dione), and dehydroepiandrosterone sulfate (DHEA-S) were determined by radioimmunoassays (RIAs). The participants visited us after a 1 month observation period, when BBT was recorded without medication.

The following criteria, based on the clinical course during the observation period and serum hormonal levels at the first visit, were employed for selection of the actual participants in Br treatment; 1) a monophasic and low BBT profile during the observation period, 2) increased circulating LH >20 mIU/ml, 3) normal FSH <20 mIU/ml, 4) decreased FSH/LH ratio <0.5, 5) normal PRL <25 ng/ml, and 6) increased A-dione >1.5 ng/ml and/or DHEA-S >1500 ng/ml.

To 26 women who fulfilled the criteria was administered a daily dose of 5 mg Br b.i.d. for 2 months. Of the 26 women 9 (34.6%) and 3 (11.5%) had clinical manifestations of hirsutism and obesity, respectively. Ovulation was diagnosed when a BBT chart exhibited a high phase persisting for more than 12 consecutive days (Lenton et al., 1984) at least once during the treatment period, or when pregnancy ensued.

Determination of serum hormonal levels

Serum hormonal levels were determined by RIAs. For the determination of serum LH, FSH, and PRL, the appropriate Daiichi RIA kits (Daiichi Radioisotopes Lab.) were used. E2 was determined with CIS RIA kits (Commissariat a L'Energie Atomique, France; distributed by the Green Cross Corp.). A-dione and DHEA-S were assayed with the appropriate RIA kits produced by the Teikoku Hormone Co. Assays were performed according to the manuals included in the kits. The intra- and interassay coefficients of variation were less than 7% and 15%, respectively, for all the assays.

Evaluation of the data

All the hormonal estimates were logarithmically transformed (Gaddum, 1945). Ratios of FSH to LH (FSH/LH ratio) and of DHEA-S to A-dione (D/A ratio) were calculated and similarly transformed. The transformed estimates and ratios were evaluated with Student's t-test and analysis of variance. For assessment of difference in incidence, the $\chi^2$-test with Yates correction was employed. $P$ values less than 0.05 were regarded as statistically significant.

Results

Twenty-six (35.6%) of the 73 tentative participants fulfilled the criteria and entered Br treatment. Eighteen (69.2%) of the 26 women who underwent Br treatment ovulated (Br-responders), while the remaining 8 (30.8%) did not respond to Br (Br-non-responders). Six (40.0%) of 15 infertile Br-responders conceived during Br treatment.

Individual pretreatment hormone concentrations FSH/LH and D/A ratios are shown in Figs. 1–3 and their geometric means and 95% confidence limits in Table 1. No statistical difference between Br-responders and nonresponders was observed.
Responders (n=18)  Non-responders (n=8)

Fig. 1. Individual serum levels of LH (left), FSH (middle) and FSH/LH ratio (right) before Br treatment. Closed and open circles represent Br-responders and non-responders, respectively. None of the geometric means of the three parameters exhibited a between-group difference.

Fig. 2. Individual serum levels of PRL (left) and E₂ (right) before Br treatment. See the legend for Fig. 1. None of the geometric means of the two parameters exhibited a between-group difference.
Fig. 3. Individual serum levels of A-dione (left) and DHEA-S (middle) and D/A ratio (right) before Br treatment. See the legend to Fig. 1. Shadows represent the ranges for normal ovulating women (early follicular phase). Although the distribution of serum A-dione levels appeared different between groups, its geometric means were not statistically different. Serum DHEA-S levels in Br-nonresponders were all above 2000 ng/ml, while a considerable number of responders had normal DHEA-S levels. The geometric mean of circulating DHEA-S in Br-nonresponders was significantly higher (p<0.01) than that in responders. The between-group difference in D/A ratios was highly significant (p<0.001).

Table 1. Endocrinological profiles of the subjects before entering Bromocriptine treatment. Geometric means and 95% confidence limits (in blackets) are presented.

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<thead>
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<th>Br-responders (n=18)</th>
<th>Br-nonresponders (n=8)</th>
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<tbody>
<tr>
<td>LH (mIU/ml)</td>
<td>41.6 (34.7–49.9)</td>
<td>47.3 (31.7–70.6)</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>11.3 (10.1–12.6)</td>
<td>10.7 (8.4–13.7)</td>
</tr>
<tr>
<td>FSH/LH ratio</td>
<td>0.27 (0.23–0.31)</td>
<td>0.25 (0.17–0.36)</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>11.9 (9.7–14.6)</td>
<td>13.7 (9.9–19.1)</td>
</tr>
<tr>
<td>E₂ (pg/ml)</td>
<td>43.8 (35.3–54.2)</td>
<td>61.0 (28.5–130.3)</td>
</tr>
<tr>
<td>A-dione (ng/ml)</td>
<td>2.58 (2.17–3.06)</td>
<td>2.11 (1.67–2.67)</td>
</tr>
<tr>
<td>DHEA-S (ng/ml)</td>
<td>1652 (1343–2032)*</td>
<td>2582 (2254–2958)</td>
</tr>
<tr>
<td>D/A ratio</td>
<td>646 (530–787)**</td>
<td>1222 (1016–1469)</td>
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* p<0.01 vs. Br-nonresponders
** p<0.001 vs. Br-nonresponders
either in the distributions of individual estimates or in the geometric means as far as serum concentrations of LH, FSH, PRL and E₂ and FSH/LH ratios were concerned (Figs. 1 and 2, Table 1). However, serum A-dione and DHEA-S concentrations and D/A ratios were of contrast (Fig. 3, Table 1). Serum A-dione concentrations in Br-responders were distributed in the range between 1.80 and 6.55 ng/ml, while those in nonresponders were in the range between 1.43 and 3.07 ng/ml. Although the distributions appeared different, the geometric means for A-dione in the two groups (2.58 and 2.11 ng/ml for Br-responders and non-responders, respectively) were not different. Serum DHEA-S concentrations in Br-responders were less than 2220 ng/ml, except for 2 cases showing 3780 and 3891 ng/ml. Moreover, 7 of the 18 Br-responders had serum DHEA-S concentrations compatible with those in normal menstruating women during the early follicular phase (<1500 ng/ml). In contrast, all the Br-nonresponders had increased DHEA-S concentrations (2147–3351 ng/ml). The geometric means of serum DHEA-S concentrations in Br-responders and nonresponders (1652 and 2582 ng/ml, respectively) were significantly different (p<0.01). Consequently, the between-group difference in D/A ratios (646 and 1222 for Br-responders and nonresponders, respectively) was also significant (p<0.001).

Differences in the incidences of women with increased circulating A-dione and DHEA-S and those having increased D/A ratios were assessed in Br-responders and nonresponders. With a cut-off point of 2.0 ng/ml for circulating A-dione, the numbers of women with excessive A-dione were 12 (66.7%) and 5 (62.5%), respectively, with no statistical significance (Table 2). With a cut-off point of 2000 ng/ml for circulating DHEA-S, the numbers of women with excessive DHEA-S were 5 (27.8%) and 8 (100.0%), respectively. The difference was significant (p<0.005) (Table 3). With a cut-off point of 1000 for D/A ratios, 3 (16.7%) and 6 (75.0%) of Br-responders and nonresponders, respectively, belonged to the high D/A ratio group. The difference in the incidences was significant (p<0.025) (Table 4). Although the significance was higher for DHEA-S than for D/A ratios, fewer Br-responders belonged to the high D/A ratio group than to the high DHEA-S group.

**Table 2.** Incidence of women with elevated circulating A-dione between Br-responders and nonresponders. A cut-off point of 2.0 ng/ml was employed.

<table>
<thead>
<tr>
<th></th>
<th>Circulating A-dione</th>
<th>Total</th>
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<tbody>
<tr>
<td>&gt;2.0 ng/ml</td>
<td>12 (66.7%)</td>
<td>18</td>
</tr>
<tr>
<td>&lt;2.0 ng/ml</td>
<td>6 (33.3%)</td>
<td>8</td>
</tr>
</tbody>
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(Χ²-Yates=0.06, p>0.05)

**Table 3.** Incidence of women with elevated circulating DHEA-S between Br-responders and nonresponders. A cut-off point of 2000 ng/ml was employed.

<table>
<thead>
<tr>
<th></th>
<th>Circulating DHEA-S</th>
<th>Total</th>
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<tbody>
<tr>
<td>&gt;2000 ng/ml</td>
<td>5 (27.8%)</td>
<td>13 (72.2%)</td>
</tr>
<tr>
<td>&lt;2000 ng/ml</td>
<td>8 (100.0%)</td>
<td>0 (0.0%)</td>
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(Χ²-Yates=8.85, p<0.005)

**Table 4.** Incidence of women with elevated D/A ratios between Br-responders and nonresponders. A cut-off point of 1000 was employed.

<table>
<thead>
<tr>
<th></th>
<th>D/A Ratio</th>
<th>Total</th>
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<tbody>
<tr>
<td>&gt;1000</td>
<td>3 (16.7%)</td>
<td>15 (83.3%)</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>6 (75.0%)</td>
<td>2 (25.0%)</td>
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(Χ²-Yates=5.95, p<0.025)

Discussion

PCO-type anovulaton is characterized by
Elevated LH, normal FSH, decreased FSH/LH ratio, and hyperandrogenism. All of the 26 actual participants in the study fulfilled the previously mentioned criteria and were diagnosed as PCO-type anovulation. In spite of the well-known endocrinologic characteristics of PCO-type anovulation, its etiology is not completely understood. It is now rather well recognized that ovarian morphology, such as multiple atretic follicles and thickened tunica albuginea, and aberrated gonadotropin secretion in PCO-type anovulation are not primary but secondary to increased androgen production regardless of whether its production site is the adrenal or the ovary (Yen, 1980; Goldzieher and diZerega, 1985).

Thus, the source of androgen excess in PCO-type anovulation is controversial. Although the determination of androgen levels in the adrenal and ovarian veins could provide a definite answer to the question (Kirschner and Jacobs, 1971), the intervention is too invasive to be employed in such a study as the present one. Instead, we measured in the study circulating DHEA-S as a representative androgen of adrenal origin and A-dione as a marker reflecting ovarian androgen production. The reason why we chose these androgens to be measured is that more than 90% of circulating DHEA-S in normal women is derived from the adrenals (Abraham, 1974) and that A-dione is the most abundant androgen in the follicular fluid (Braily et al., 1984), admitting that A-dione is produced also by the adrenals (Abraham, 1974). It is likely that the enhancement of adrenal androgen production contributes to an increase in circulating A-dione (Braily et al., 1984). If this is the case, women with excessive adrenal androgens would possess higher D/A ratios than women with excessive ovarian androgens.

Interestingly, serum levels of DHEA-S and A-dione in Br-nonresponders were higher than, and compatible to, those in responders, respectively. Consequently, the geometric mean of D/A ratios in nonresponders was significantly higher than that in responders. Therefore, one could judge that Br-nonresponders might hyperproduce adrenal androgen. This is supported by the fact that 2 Br-nonresponders, who underwent corticosteroid therapy after completion of the study, both resumed ovulation.

On the other hand, all the Br-responders had elevated serum A-dione levels and quite a number of them had normal serum DHEA-S levels. The implication of the results would be that they might have hyperandrogenism not due to an adrenal contribution. There is another major site of androgen production besides the adrenals, i.e. the ovaries. Thus, Br-responders might hyperproduce ovarian androgen.

There were 2 seemingly exceptional cases in Br-responders. Their serum DHEA-S levels were as high as 3780 and 3891 ng/ml, which were more than those in Br-nonresponders. These enormously elevated serum DHEA-S levels might indicate hyperproduction of adrenal androgen. Their D/A ratios were, however, as low as 577 and 1049, respectively, since they had also elevated A-dione levels (6.55 and 3.71 ng/ml, respectively). The former D/A ratio was far below the 95% confidence limits of Br-nonresponders (1016–1469), and in the range of the 7 responders with elevated A-dione and normal DHEA-S levels (386.4–720.0). Although circulating DHEA-S is mostly of adrenal origin in normal women, the ovarian contribution to it is not negligible as suggested by its increase during the periovulatory
phase under adrenal suppression by dexamethasone (Abraham, 1974). It might be reasonable to assume that considerable amount of circulating DHEA-S is of ovarian origin in a situation where ovarian androgen production is excessive. This could be true of at least to one of these 2 exceptional cases.

Thus, the present study indicated the effectiveness of Br for ovulation induction in PCO-type women presumably hyperproducing ovarian androgen. Similar results were shown by Taketani et al. (1986), although, unlike the present study, they included both normo- and hyperprolactinemic PCO women in their study. They also classified PCO into 2 subgroups, namely ovarian and adrenal types, on the basis of circulating DHEA-S levels. They defined women with elevated DHEA-S more than 2000 ng/ml as the adrenal type and the remainder as ovarian type, and demonstrated a higher incidence of Br-responsive women of the ovarian type.

We previously conducted a study to assess the efficacy of Br in normoprolactinemic anovulation (Suginami et al., 1986b). It consisted of measurement of hormonal levels through a day-night period and at metoclopramide (MCP) provocation, followed by chronic Br administration. Br therapy was effective in cases of nocturnal hyperprolactinemia and in those showing exaggerated PRL secretion in response to MCP. The implication would be that an increase in circulating PRL during sleep or in a certain condition might be a factor in disturbed ovulation as in cases of apparent hyperprolactinemia, and its reduction by Br was supposed to be instrumental in the resumption of ovulatory cycles. It is not known whether the same argument is applicable to the present study since its protocol did not include the hormonal assessment during sleep or at MCP provocation. The mechanism by which Br resumed ovulatory cycles in PCO-type women presumably of the ovarian androgen hyperproduction type remains to be elucidated.

Although Br appears to be effective in a fraction of PCO-type women as suggested in the present study and by others (Spruce et al., 1984; Mori et al., 1985; Taketani et al., 1986), there is a challenging report by Buvat et al. (1986). They performed a double blind controlled study on the efficacy of Br in PCO, where they treated PCO women with either Br or a placebo, measured various hormones before and during treatment, and assessed differences between hormonal and clinical effects in the 2 groups. They found no between-group difference except a steady decline in circulating PRL in the Br-treated group. Furthermore, they reported no difference between Br-responsive and nonresponsive groups in hormonal estimates both before and during Br treatment except lower A-dione levels in the Br-responsive group at 3 months of Br treatment. They claimed that the only significant effect of Br therapy in PCO was to lower the serum PRL concentration. Their results clearly contrast with ours and we do not know the reason for the discrepancy. It is, however, possible that they could have found a difference between Br-responders and nonresponders if they had introduced D/A ratios as we did in the present study.

In order to explore a marker for prospective indication of Br treatment in PCO-type women, incidences of women with an increase in circulating PRL during sleep or in a certain condition might be a factor in disturbed ovulation as in cases of apparent hyperprolactinemia, and its reduction by Br was supposed to be instrumental in the resumption of ovulatory cycles. It is not known whether the same argument is applicable to the present study since its protocol did not include the hormonal assessment during sleep or at MCP provocation. The mechanism by which Br resumed ovulatory cycles in PCO-type women presumably of the ovarian androgen hyperproduction type remains to be elucidated.

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women are, therefore, likely to be excluded from Br therapy when the classification based only on circulating DHEA-S is performed prospectively. The number of women likely to be excluded from the treatment is reduced by introducing a classification based on D/A ratios with a cut-off point of 1000. Thus, the last parameter would be the most suitable to use in the prospective selection of PCO-type women entering Br treatment.

We conclude that Br causes ovulatory cycles to be resumed in PCO-type women having excessive circulating androgens presumably of ovarian origin. However, its action mechanism is not yet understood and has to be elucidated. The D/A ratio could be used as a marker to locate the site of enhanced androgen production and could be utilized as a marker to predict the efficacy of Br when applied to PCO-type women.

References


