Abstract. Adrenal involvement in polycystic ovarian disease was assessed by measuring dehydroepiandrosterone sulphate in 20 polycystic ovarian disease patients. The response of dehydroepiandrosterone sulphate to bromocriptine treatment was compared to that of placebo, both being given for one cycle on a double-blind, cross over basis. The mean basal DHEA-S was above the upper limit of the normal range (6793 nmol/l) in three patients. The mean basal dehydroepiandrosterone sulphate in the polycystic ovarian disease group was significantly higher than the mean of the normal control group ($P < 0.01$). Dehydroepiandrosterone sulphate showed a significant drop with bromocriptine as compared to placebo ($P < 0.001$) and a significant correlation with prolactin both before ($P < 0.001$) and after treatment with bromocriptine ($P < 0.001$). These findings support the hypothesis of adrenal involvement in polycystic ovarian disease and prove the significant effect of bromocriptine on the adrenal which might be of therapeutic value.

Involvement of the adrenal gland in polycystic ovarian disease (PCOD) has been recognized since Broster (1937) observed concurrent adrenal and ovarian hyperplasia during surgery. Similar conclusions were drawn from numerous functional studies involving adrenal suppression with dexamethasone (Abraham et al. 1976) or stimulation with ACTH (Gibson et al. 1980). It has been postulated that adrenal hyperfunction at the time of adrenarche may be responsible for the obesity and hirsutism in PCOD patients. Peripheral metabolism of increased adrenal androgens may result in increased oestrogen levels which provides the hormonal milieu for the development of PCOD (Goldzieher 1982).

In that dehydroepiandrosterone sulphate (DHEA-S) is almost exclusively secreted by the adrenal gland (Vande Wiele et al. 1963), elevation in its level may act as a marker of the adrenal involvement in PCOD. Several investigators (Buvat et al. 1982; Lobo et al. 1983) reported high DHEA-S levels in PCOD. Hyperprolactinaemia is a potential cause for such an elevation (Carmina et al. 1984). Evidence indicates that hyperprolactinaemia is not uncommon in PCOD (Wortsman & Hirschowitz 1980) which might reflect a central dopamine deficiency in these patients. The purpose of this study was to assess the degree of adrenal involvement in PCOD and its response to a dopaminergic agent. Bromocriptine and placebo were given on a double-blind, cross over basis to eliminate any biases and to balance out any possible disturbing time trend which might interfere with the real change produced by the drug.

Material and Methods

Twenty PCOD patients (18–35 years) were studied. Patients showed the features illustrated in Table 1.

The mean basal prolactin level of the PCOD group
Table 1.
Clinical, laboratory, ultrasonic and laparoscopic features of the PCOD group studied.

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perimenarchial oligomenorrhoea</td>
<td>15</td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>9</td>
</tr>
<tr>
<td>Oligomenorrhoea</td>
<td>7</td>
</tr>
<tr>
<td>Primary infertility</td>
<td>16</td>
</tr>
<tr>
<td>Obesity</td>
<td>16</td>
</tr>
<tr>
<td>Hirsutism and/or acne</td>
<td>15</td>
</tr>
<tr>
<td>Galactorrhoea</td>
<td>7</td>
</tr>
<tr>
<td>Enlarged ovaries by ultrasound</td>
<td>15</td>
</tr>
<tr>
<td>LH/FSH ratio more than 2</td>
<td>16</td>
</tr>
<tr>
<td>High testosterone</td>
<td>16</td>
</tr>
<tr>
<td>High androstenedione</td>
<td>16</td>
</tr>
<tr>
<td>Low or normal oestradiol-17β</td>
<td>16</td>
</tr>
<tr>
<td>High oestrone</td>
<td>7</td>
</tr>
</tbody>
</table>

was significantly higher than the mean of the normal control (18.6 + 4.4 vs 6.7 + 4.1 µg/l, \( P < 0.001 \)). Prolactin level was above the upper limit of the normal control (20 µg/l) in 9 patients.

Patients were subjected to repeated blood sampling in three consecutive cycles: the first without medication, the second and third with either placebo or bromocriptine on a double-blind, cross over basis. Amenorrhoic patients were studied for 3 consecutive months: the first without medication, the second and third with either bromocriptine or placebo on a double-blind cross over basis.

According to the patients' previous menstrual history and the date of her last menstrual period, each patient's cycle was divided into three phases: follicular, periovulatory and luteal. Three consecutive daily blood samples were taken during each phase. In amenorrhoic patients the 3 consecutive daily blood samples were separated by ten days intervals. Blood samples were taken at 8 a.m. under basal conditions aliquoting three smaller samples taken at 30-min intervals into one.

Patients were then given bromocriptine (or placebo) in a dose of 2.5 mg three times daily with meals (after building-up gradually to this dose) for one cycle or one month in amenorrhoic patients. Samples were collected at periods corresponding to those obtained before starting the treatment. Decision to start with this rather high dose of bromocriptine was based on review of the dosage used by other investigators in related conditions, the limited period of treatment and the design of the study as a double-blind cross over one. All patients received the same dose for the entire period of study. Ten patients showed side effects like dizziness, nausea, headache, confusion and fatigue. However, these side effects were not severe enough to stop the treatment in any of the patients.

Radioimmunoassay for DHEA-S was performed using \([^{125}I]\)RIA kits manufactured by Diagnostic Systems Laboratories (Webster, TX). The kit uses one antibody and a 30-min incubation. The lowest detectable level of DHEA-S that could be distinguished from the zero standard is 27 nmol/l at the 95% confidence limit. The intra-assay coefficient of variation was 7.4%. The inter-assay coefficient of variation was 7.9%.

Statistical analysis was performed by calculating the mean and standard deviation and comparing the difference between 2 means using the Student's t-test. Correlation between 2 variables was assessed by performing the linear regression and the correlation coefficient (r).

### Results

**Baseline cycle**

Three patients had their DHEA-S values (mean of 9 samples) above the normal range (6793 nmol/l). The mean basal DHEA-S value of the whole group was significantly higher than the mean of the age and weight-matched normal control, as shown in Fig. 1.

The three patients with high basal DHEA-S values showed the following clinical and hormonal characteristics:

1) Obesity (% ideal body weight was 164, 158 and 122%).
2) Two patients had amenorrhoea and galactorrhoea and one patient had oligomenorrhoea.

3) Hyperprolactinaemia (basal prolactin level above 20 ng/ml).

4) High testosterone in two patients (above 4.65 nmol/l).

5) High androstenedione in one patient (above 16.57 nmol/l).

With bromocriptine there was a significant decrease in DHEA-S. One patient (out of three) still had her mean value above the normal range. Compared to placebo the decrease in DHEA-S with bromocriptine therapy was statistically significant \( (P < 0.001) \), as shown in Fig. 2. Prolactin values showed a significant drop with bromocriptine treatment (from 18.6 ± 4.4 to 6.05 ± 2.07, \( P < 0.001 \)). Luteinizing hormone values also significantly dropped with bromocriptine (from 24.2 ± 9 to 15.3 ± 4.3 IU/l, \( P < 0.001 \)).

The decrease in DHEA-S levels occurred both in patients with elevated as well as normal basal levels and was more or less equal in both the hyperprolactinaemic \( (P < 0.02) \) and the normoprolactinaemic subgroups \( (P < 0.001) \) (Fig. 3).

DHEA-S was the only androgen with a significant correlation with prolactin both before \( (r = 0.658, P < 0.001) \) and after treatment with bromocriptine \( (r = 0.533, P < 0.001) \). The DHEA-S relation to basal LH/FSH ratio was suggestive but not conclusive. The difference between the luteal and periovulatory phase values was higher than the follicular phase difference following bromocriptine treatment.

Three patients ovulated under bromocriptine treatment. Ovulation was documented by basal body temperature charts, luteal phase progesterone more than 5 µg/l and a pre-menstrual endometrial biopsy.

One of the patients with high basal DHEA-S, that was markedly reduced with bromocriptine, showed evidence of ovulation at the end of the treatment cycle.

The changes in the hormonal values with bromocriptine were not different in amenorrhoeic patients vs those with oligomenorrhoea or irregular menses. Neither were they different between patients who showed galactorrhoea and those who did not.
Discussion

The aetiology of the elevation of DHEA-S in PCOD remains to be settled. ACTH administration to PCOD patients ruled out the possibility of a mild form of congenital adrenal hyperplasia as the cause of DHEA-S elevation (Horrocks et al. 1983). A subtle, incomplete 3β-hydroxysteroid dehydrogenase deficiency may exist in some hirsute oligomenorrhoeic women who have baseline elevation of serum DHEA-S as well as Δ5-androstenedione and 17-hydroxy-progesterone (Lobo & Goebelsmann 1981). The high level of oestrogen in PCOD may interfere with the enzyme 3β-hydroxysteroid dehydrogenase or there may be an alteration in the factors controlling adrenal androgen secretion in PCOD (Horrocks et al. 1983).

Several investigators (Bassi et al. 1977; Vermeulen et al. 1977; Carmina et al. 1984) have presented data linking serum concentration of prolactin to adrenal androgen production. Vermeulen et al. (1977) found plasma DHEA-S to be significantly higher \((P < 0.001)\) in women with elevated prolactin than normal controls. Hyperprolactinaemia is thought to selectively stimulate adrenal cortical androgen production (Carter et al. 1977). This is further supported by finding prolactin receptors in the adrenal gland (Marshall et al. 1976).

Carter et al. (1977) investigated the effects of bromocriptine on prolactin and androgen levels in hyperprolactinaemic women with galactorrhoea and amenorrhoea. They found that associated with the bromocriptine-induced fall in mean prolactin levels, there was a significant fall in DHEA-S \((P < 0.0005)\) and DHEA \((P < 0.01)\), while testosterone and androstenedione were unchanged. The insignificant drop in DHEA-S with bromocriptine observed in our study correlates with Seib et al. (1984) findings who reported that DHEA-S levels declined in normoprolactinaemic PCOD patients given bromocriptine and in whom ovulation occurred.

It is concluded from our findings that the adrenal gland is involved in PCOD and that bromocriptine decreases the adrenal contribution to the androgenic pool in PCOD. Although the pathophysiology of adrenal involvement in PCOD cannot be settled yet, our data point to the role of prolactin and implicate a central dopamine deficiency as a probable aetiologic factor. However, a direct effect of prolactin on the adrenal gland cannot be excluded. The occurrence of ovulation in PCOD patients with high basal DHEA-S and in whom DHEA-S markedly dropped with bromocriptine is significant. It suggests an aetiologic role of DHEA-S in anovulation in PCOD patients and the possible therapeutic effect of bromocriptine on these patients.

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Dr Gamal H. El Tabbakh is currently a fellow to Department of Obstetrics & Gynaecology, NY Medical School, Valhalla, NY, USA.

References


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Dr Gamal El-Tabbakh,
El-Shatby Maternity Hospital,
El-Shatby,
Alexandria,
Egypt.