Cabergoline influences ovarian stimulation in hyperprolactinaemic patients with polycystic ovary syndrome

Enrico Papaleo¹, Nicola Doldi, Lucia De Santis, Guido Marelli, Elena Marsiglio, Simone Rofena and Augusto Ferrari

Department of Obstetrics and Gynecology, San Raffaele Scientific Institute, University of Milan, Italy

¹To whom correspondence should be addressed at: Dept of Obstetrics and Gynecology, San Raffaele Scientific Institute, University of Milan, Via Olgettina 60, 20132 Milan, Italy. E-mail: enrypap@hotmail.com

BACKGROUND: Polycystic ovary syndrome (PCOS) is characterized by abnormal gonadotrophin secretion, in particular an elevated serum concentration of LH, depressed FSH, and an LH/FSH ratio of ≥2. Mild, transient hyperprolactinaemia is frequently associated with PCOS (30% of patients); furthermore, it can be observed during the late follicular and luteal phases of both natural and stimulated cycles. It is suggested that a reduction of the dopamine inhibitory effect might raise both prolactin (PRL) and LH.

METHODS AND RESULTS: We compared ovarian stimulation in two groups of hyperprolactinaemic (hyperPRL)–PCOS patients; one group was treated with cabergoline, reducing PRL plasma concentrations to the range normally observed during ovulation induction. In the untreated hyperPRL–PCOS group, we noted a reduced total number of ampoules of recombinant FSH (P < 0.04), fewer days to reach HCG administration (P < 0.04), and significantly higher peak oestrogen plasma concentrations (P < 0.03) compared with the treated group. By ultrasound examination the same group showed significantly higher ovarian volume and an increased total number of follicles of every size. In untreated hyperPRL–PCOS patients, four cycles out of 65 were cancelled due to mild ovarian hyperstimulation syndrome (OHSS) that occurred during ovulation induction. Only one cycle out of 42 in the patients treated with cabergoline was cancelled. No significant differences in pregnancy rate nor in multiple pregnancy were found.

CONCLUSION: Our data suggest a dopaminergic control of LH release and support the use of cabergoline in the management of such patients, in order to provide better clinical control of ovarian response and consequently a reduction of the risk of OHSS, with no decrease in pregnancy rate.

Key words: cabergoline/hyperprolactinaemia/ovulation induction/PCOS

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disease of unknown aetiology most frequently associated with anovulation. The classification of the syndrome is based on clinical and endocrine features with a well known ultrasound ovarian pattern. Obesity, hirsutism, oligomenorrhoea with chronic anovulation and hyperandrogenaemia are variably associated with abnormal gonadotrophin secretion, an elevated serum concentration of LH, depressed FSH and an LH/FSH ratio of ≥2 (Adams et al., 1986; Erickson et al., 1992; Jacobs et al., 1996; Doldi et al., 1999). Thirty percent of patients with PCOS show mild hyperprolactinaemia (Duignam, 1976; Falaschi et al., 1977; Corenblum and Taylor, 1982; Isik et al., 1997).

Furthermore, a transient rise in plasma prolactin (PRL) concentrations can be observed during the late follicular and luteal phases of both natural and stimulated cycles (Doldi et al., 2000). It is known that hypothalamic dopamine is the major inhibitor of PRL secretion in humans (Webster, 1999) and there may be a possible, if controversial, role for central dopaminergic mechanisms in the release of LH. Several investigators (Falaschi et al., 1986; Prelevic et al., 1987) also indicated a dopaminergic control on gonadotrophin secretion, and suggested that a reduction of the dopamine inhibitory effect might cause abnormal PRL and LH secretion, and found in hyperPRL–PCOS patients. Few studies have analysed the effect of treatment with a dopamine agonist on the ovarian response of patients with polycystic ovarian changes and mild, elevated serum PRL concentrations.

In order to better understand the influence of dopaminergic control in PCOS, we retrospectively evaluated the clinical effect of cabergoline, a potent dopamine agonist and inhibitor of PRL secretion, on ovarian response (ovarian size, number of follicles developed, peak oestradiol at HCG administration) during recombinant FSH (rFSH) stimulation protocols in such patients.
Materials and methods

Patients
Forty-four couples undergoing procreation medical assisted (PMA) attempts in our Reproductive Endocrinology Center were enrolled in the study. Female patients were investigated by hysterosalpingography and some of them also by laparoscopy and hysteroscopy. All the male partners had normal semen quality according to World Health Organization (WHO) criteria (World Health Organization, 1992). All couples had failed to conceive in the last two years. At least four cycles with clomiphene citrate, with no further infertility treatment, had been performed.

All the women fulfilled our criteria for the diagnosis of PCOS: a history of anovulatory infertility and/or oligomenorrhea or amenorrhea, a Ferriman score >7 for hirsutism, hyperandrogenaemia, elevated concentration of LH or an LH/FSH ratio of ≥2, increased ovarian volume and ≥10 follicles of 2–8 mm in diameter at ultrasound examination. They all had mild, increased serum PRL concentrations (mean 31.5 ± 3.1 ng/ml) measured in the mid and/or late follicular phase and in the mid luteal phase of the menstrual cycle before ovarian stimulation. No organic lesion (serum PRL values >50 ng/ml) or medication was responsible for the increased PRL concentrations.

Eighteen patients (group A: mean PRL concentration = 32.8 ± 3.6 ng/ml) were treated with cabergoline (Dostinex®, 0.5 mg, 1/2 tablet per week) before ovarian stimulation, up to the decrease of plasma PRL concentrations (12.5 ± 2.8 ng/ml), and continued the therapy during the long protocol ovarian stimulation. Twenty-six patients (group B: mean PRL concentration = 31.1 ± 3.2 ng/ml) underwent an ovarian stimulation programme without treatment of hyperprolactinaemia.

Stimulation protocol
All women were treated by a long protocol. It consisted of gonadotrophin-releasing hormone (GnRH) agonist (Triptorelin, Decapeptyl®, IPSEN) at the dose of 0.1 mg/day s.c., administered on day 21 after a progestin-induced withdrawal bleed or spontaneous menstruation.

At the next menstrual flow the oestriadiol serum concentration was measured and ultrasound examination of the ovaries performed. If oestradiol plasma concentration was <60 pg/ml and there were no follicles or cyst >10 mm diameter, gonadotrophin treatment was started. If ovarian quiescence was not achieved, a further examination was performed 1 week later.

Gonadotrophin stimulation consisted of one ampoule per day of FSH (rFSH, Gonalf 75 UI®, Serono, Rome, Italy) for the first 5–7 days (low dose scheme for PCOS treatment).

Adjustment of the dose (increase of 37.5–75 UI of rFSH) was based on the individual response. Final dosage of the oocyte was效应 with 5000 UI of human chorionic gonadotrophin (HCG, Profasi®, Serono, Rome, Italy) when there were at least 2 follicles >16 mm.

Intra-uterine insemination was performed 32–36 h after HCG administration.

Statistical analysis
All results are reported as the mean ± standard deviation. Differences in the mean values for individual hormone measurements were assessed by using analysis of variance and the two-tailed group t-test.

Results
As shown in Table I, the two groups of patients were similar. No significant differences in age, FSH and LH concentration, testosterone or androstenedione values were found. The two groups presented similar increased serum PRL concentrations before GnRH analogue/rFSH treatment. Group A had PRL values in the normal range (12.5 ± 2.8 ng/ml), following treatment with cabergoline.

We analysed 107 ovulatory GnRH analogue/rFSH/HCG cycles (group A: 42 cycles, mean = 2.33/patient; group B: 65 cycles, mean = 2.50/patient). We noted (Table II) that in group B (without cabergoline treatment) the total number of ampoules of rFSH per cycle was significantly lower (P < 0.04) with fewer days of stimulation before HCG administration (P < 0.04), and peak serum oestradiol concentrations were significantly higher (P < 0.03) compared with group A (cabergoline treatment). Serum concentrations of progesterone on the day of HCG administration were not significantly different between the two groups. Furthermore, by ultrasound examination, hyperPRL–PCOS patients developed more follicles of every size (<10 mm: 4.3 ± 0.9 versus 4.8 ± 1.3; 10–15 mm: 5.8 ± 1.8 versus 7.5 ± 1.5; >15 mm: 4.8 ± 0.7 versus 5.2 ± 1.0) on the day of HCG administration compared with treated hyperPRL–PCOS patients. These differences were statistically significant (P < 0.04; P < 0.03; P < 0.03).

In group B, four cycles out of 65 (6.2%) developed mild ovarian hyperstimulation syndrome (OHSS) compared with only one cycle out of 42 (2.4%) in group A; all five cycles were cancelled. There was a total of eight pregnancies in group A (three multiple pregnancies) compared with 11 pregnancies in group B (five multiple pregnancies). This difference was not significant.

Discussion
Several investigators have supported the idea that mild, transient hyperprolactinaemia and PCOS are not a distinct entity (Falaschi et al., 1977; Corenbloom and Taylor, 1982; Prelevic et al., 1987; Isik et al., 1997). A mild central dopamine deficiency could cause an increase of both PRL and LH in patients with PCOS, and the inhibiting effect of hypothalamic dopamine, and dopamine agonists, on PRL is well documented.

Cabergoline, a new long-acting ergoline D2 agonist derivative, has been in use for six years. Compared with other dopamine agonists, it seems that cabergoline is well tolerated and appears to have similar efficacy in PRL suppression and restoration of gonadal function (Paoletti et al., 1994; Ciccarelli et al., 1997; Webster, 1999). Furthermore, no increase in miscarriage rate, congenital malformation, distribution of birthweights and sex ratio within the expected range was observed (Robert et al., 1996). Clinical data concerning dopamine influence on gonadotrophin release, in particular LH, are still controversial.

Although the mechanism is not clear, many authors (Klibanski et al., 1984; Falaschi et al., 1986; Chapman et al., 1987; Matsuzaki et al., 1994; Paoletti et al., 1996) have demonstrated an inhibitory role of dopamine, and its agonists, on LH secretion and androgen concentrations both in normal and hyperPRL women. According to its capacity to reduce LH secretion, dopamine agonists were proposed as a useful
Table I. Clinical and hormonal data from hyperprolactinemic patients with polycystic ovary syndrome

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>18</td>
<td>26</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.4 ± 2.6</td>
<td>30.8 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.5 ± 1.9</td>
<td>23.9 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>FSH concentration (mIU/ml)</td>
<td>5.3 ± 1.6</td>
<td>5.9 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>LH concentration (mIU/ml)</td>
<td>9.4 ± 2.6</td>
<td>9.7 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Testosterone concentration (nmol/l)</td>
<td>4.5 ± 0.9</td>
<td>4.8 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Androstenedione concentration (nmol/l)</td>
<td>13.4 ± 0.7</td>
<td>13.1 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>PRL concentration (ng/ml)</td>
<td>32.8 ± 3.6</td>
<td>31.1 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>PRL concentration (ng/ml) post-treatment</td>
<td>12.5 ± 2.8</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.

PRL = prolactin

Group A = treatment; group B = no treatment; NS = not significant.

Table II. Characteristics of ovarian response to rFSH/HCG in both treated and non-treated patients undergoing the ovarian stimulation programme

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>18</td>
<td>26</td>
<td>–</td>
</tr>
<tr>
<td>Cycles (n)</td>
<td>42</td>
<td>65</td>
<td>–</td>
</tr>
<tr>
<td>Total number of ampoules of FSH</td>
<td>20.7 ± 7.8</td>
<td>16.2 ± 5.7</td>
<td>P &lt; 0.04</td>
</tr>
<tr>
<td>Day of HCG administration</td>
<td>12.3 ± 3.6</td>
<td>10.4 ± 2.1</td>
<td>P &lt; 0.04</td>
</tr>
<tr>
<td>Oestradiol concentration (pg/ml) at HCG</td>
<td>1150 ± 665</td>
<td>1457 ± 654</td>
<td>P &lt; 0.03</td>
</tr>
<tr>
<td>Progesterone concentration (pg/ml) at HCG</td>
<td>1.2 ± 0.4</td>
<td>1.0 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Number of follicles &lt;10 mm</td>
<td>4.3 ± 0.9</td>
<td>4.6 ± 1.3</td>
<td>P &lt; 0.04</td>
</tr>
<tr>
<td>Number of follicles 10–15 mm</td>
<td>5.8 ± 1.8</td>
<td>7.5 ± 1.5</td>
<td>P &lt; 0.03</td>
</tr>
<tr>
<td>Number of follicles &gt;15 mm</td>
<td>4.8 ± 0.7</td>
<td>5.2 ± 1.0</td>
<td>P &lt; 0.03</td>
</tr>
<tr>
<td>OHSS</td>
<td>1</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Cumulative pregnancy</td>
<td>8</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>3</td>
<td>5</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are means ± standard deviation.

NS = not significant; OHSS = ovarian hyperstimulation syndrome.

The aim of our study was to evaluate PCOS patients with mild increased serum PRL concentrations who were participating in an ovulation induction programme, and to quantify the clinical effect of cabergoline on the outcome of ovarian stimulation. We compared mild hyperPRL–PCOS patients (group A) treated with the dopamine agonist cabergoline during rFSH/HCG administration with untreated hyperPRL–PCOS patients (group B).

We found that: (i) despite a reduced total number of ampoules of rFSH and fewer days to reach HCG administration, peak oestrogen plasma concentrations were significantly higher in the untreated hyperPRL–PCOS patients; (ii) by ultrasound examination, group B presented a significantly higher ovarian volume and an increased total number of follicles of every size; (iii) four cases of ovarian hyperstimulation syndrome lead to the suspension of treatment in group B compared with only one case in group A; (iv) no significant differences were observed either in cumulative pregnancy rate or in multiple pregnancy rate.

Our data support the evidence of a dopaminergic component in the control of LH release in PCOS patients, and suggest that a pre-treatment with cabergoline reduces ovarian response to rFSH, without affecting pregnancy rate or increasing the possibility of multiple pregnancy. Although these data are not statistically significant, this approach should be further investigated as a potentially important option for limiting the risk of OHSS in the clinical handling of such patients.

References


Received on March 30, 2001; accepted on August 7, 2001