

ORIGINAL ARTICLE

# *In vitro* fertilization following laparoscopic ovarian diathermy in patients with polycystic ovarian syndrome

NICOLA COLACURCI<sup>1</sup>, FULVIO ZULLO<sup>2</sup>, PASQUALE DE FRANCISCI<sup>1</sup>, ANTONIO MOLLO<sup>3</sup> AND GIUSEPPE DE PLACIDO<sup>3</sup>

From the <sup>1</sup>Institute of Gynaecology and Obstetrics, School of Medicine, Second University of Naples, the <sup>2</sup>Department of Gynaecologic and Pediatric Sciences, Catanzaro Medical School, University of Reggio Calabria, Reggio Calabria, Italy, and the <sup>3</sup>1st Department of Gynaecology and Obstetrics, 'Federico II' Medical School, University of Naples, Naples, Italy

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**Background.** To evaluate the *in vitro* fertilization outcome in patients with polycystic ovarian syndrome previously treated by laparoscopic ovarian diathermy.

**Methods.** We designed a prospective study to compare *in vitro* fertilization stimulation parameters and pregnancy rate for two groups of women with polycystic ovarian syndrome. In the first group, we included 23 patients previously treated by laparoscopic ovarian electrodiathermy (group A), in the second group we included 36 women who did not undergo surgical treatment (group B). All patients underwent the same ovarian hyperstimulation protocol and a standard *in vitro* fertilization and embryo transfer technique. In a limited number of women (five in group A and eight in group B) we measured the levels of sex steroids in follicular fluid. Statistical analysis was performed by means of chi-square test or Fisher's exact test to compare frequencies and by means of the Student's *t*-test or ANOVA test to compare means. Significance was set at  $p < 0.05$ .

**Results.** In group A we found a significantly higher ongoing pregnancy rate (28.6% in group A vs 7.3% in group B), a significantly lower estradiol peak level ( $1722.73 \pm 522.24$  in group A vs  $2314.48 \pm 692.60$  in group B), a trend for lower abortion rates and an improvement in the number of patients administered human chorionic gonadotropin than in group B. The levels of estradiol, testosterone and androstenedione in follicular fluid were significantly lower from small to intermediate and to large follicles in group A, while in group B only estradiol and androstenedione were different. Lower levels of androstenedione and testosterone were found in each follicular pool of group A, compared to the respective pool in group B.

**Conclusion.** We report a significantly better ongoing pregnancy rate after *in vitro* fertilization and embryo transfer procedures in women pretreated by means of laparoscopic ovarian electrocautery. These results may be related to lower androgen levels in the follicular fluid.

**Key words:** follicular fluid; *in vitro* fertilization; ovarian electrocautery; polycystic ovarian syndrome; steroids

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## Abbreviations:

PCOS: polycystic ovarian syndrome; LH: luteinizing hormone; IVF-ET: *in vitro* fertilization and embryo transfer; FF: follicular fluid; GnRH: gonadotropin-releasing hormone; E<sub>2</sub>: estradiol; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; BMI: body mass index; PR: pregnancy rate; RIA: radioimmunoassay; GnsIF: gonadotropin surge inhibiting factor; OMI: oocyte maturation inhibitor.

Polycystic ovarian syndrome (PCOS) is a common cause of female infertility. When PCOS is not responsive to clomiphene citrate, gonadotropin treatment and/or laparoscopic ovarian electrocautery are usually attempted (1-4). The use of ovarian electrocautery has become particularly popular owing to its ability to improve the reproductive outcome by reducing luteinizing hormone

(LH) and androgen levels (5–11), although it has been associated with the formation of postoperative adhesions (6, 12, 13). After six ovulatory cycles following the two different treatments and in the absence of other causes of infertility, the patients failing to conceive are referred to an *in vitro* fertilization and embryo transfer (IVF-ET) (14, 15). Yet no data exists on IVF outcome, or the concentrations of steroids in follicular fluid (FF) after ovarian electrocautery.

The purpose of this study was to compare the IVF stimulation parameters and the pregnancy rate for PCOS patients who had previously been treated by laparoscopic ovarian electrocautery to PCOS patients who had not undergone laparoscopic treatment. Furthermore, in a small number of patients we measured the levels of sex steroids in FF.

### Patients and methods

We included in this study PCOS women referred to our outpatient infertility clinic in the last two years. The diagnosis for PCOS was based on the typical ultrasonographic pattern evaluated in basal conditions (hyperechogenic central stroma with at least ten peripheral follicles <9 mm in diameter) (16), chronic anovulation, oligomenorrhea, hypertrichosis and infertility of at least two years. After at least six cycles stimulated with clomiphene citrate or gonadotrophins, the patients failing to conceive underwent laparoscopy. Women with no other form of infertility except PCOS were treated either by laparoscopic ovarian electrocautery according to the Gjonnaess technique (2) (group A) or by controlled ovarian stimulation (group B). After at least six ultrasonographically documented ovulatory cycles either spontaneous or with gonadotrophin stimulation, 23 patients in group A and 36 patients in group B were referred to our IVF program within 9 months of surgery. All women were treated using a standard gonadotrophins stimulation protocol including a long-acting gonadotropin-releasing hormone (GnRH) analogue. Human chorionic gonadotropin (10,000 IU i.m.) was administered when serum E<sub>2</sub> concentrations reached a mean of 150 to 200 pg/ml per follicle of 15 mm or more, when at least two follicles >17 mm in diameter. Eggs were collected 35 hours later and the embryo transfer 48 hours later. The luteal phase was supported by i.m. progesterone in oil (50 mg/day).

For each cycle we analyzed the number of patients not administered human chorionic gonadotrophin, E<sub>2</sub> peak, number of oocytes collected, fertilization rate, number of transferred and frozen

embryos, pregnancy rate (PR) per cycle and per transfer, ongoing PR and abortion rate.

In a limited number of cases (five in group A and eight in group B) we collected follicular fluid samples directly into an empty tube before any washing procedure. After oocyte retrieval the samples with blood were discarded and those remaining were put together into three pools depending on the follicular size (1=follicles of less than 13 mm; 2=follicles between 13 and 17 mm; 3=follicles more than 17 mm) and the volumes were recorded. Samples were centrifuged to remove cells and debris and the supernatants immediately frozen at -20°C for storage until assay.

Measurements of follicular fluid steroid hormones were performed using the specific Coat-A-Count radioimmunoassay (RIA) kits (Diagnostic Products Corporation, Medical System, Italy).

Statistical analysis was performed by means of chi-square test or Fisher's exact test to compare frequencies and by means of Student's *t*-test or ANOVA test to compare means. All values are given as means ± standard deviation. Significance was set at  $p < 0.05$ .

### Results

No clinical or hormonal differences were found between group A and B before IVF-ET cycles (Table I). A total of 28 cycles in group A and 47 cycles in group B were studied (Table II). hCG was given in all 28 cycles in group A, but it was not given owing to excessive response (E<sub>2</sub> >3,500 pg/ml) in 6 out of 47 cycles in group B.

Serum E<sub>2</sub> peak concentration in group B (2314.48 ± 692.60) was significantly higher than in group A (1722.73 ± 522.24).

Although the total pregnancy rate showed only a trend of improvement in group A, the ongoing pregnancy rate per cycle was significantly better in patients previously treated by ovarian diathermy (28.6% vs 7.3%). The abortion rate was 11.1% in group A and 40% in group B (one out of nine

Table I. Basal clinical and hormonal parameters of PCOS women treated by laparoscopic ovarian electrocautery (group A) and PCOS women who did not undergo surgical treatment (group B)

|                                       | Group A<br>(mean ± s.d.) | Group B<br>(mean ± s.d.) |
|---------------------------------------|--------------------------|--------------------------|
| Number of patients                    | 23                       | 36                       |
| Age (years)                           | 28.2 ± 6.8               | 32.3 ± 5.6               |
| Duration of infertility (years)       | 3.9 ± 1.1                | 4.5 ± 1.3                |
| BMI (Kg/m <sup>2</sup> )              | 27.2 ± 5.1               | 28.7 ± 6.0               |
| Luteinizing hormone (mIU/ml)          | 11.2 ± 7.1               | 15.9 ± 10.3              |
| Follicle stimulating hormone (mIU/ml) | 6.9 ± 2.4                | 8.8 ± 3.1                |
| Testosterone (ng/ml)                  | 0.59 ± 0.39              | 0.78 ± 0.34              |

Table II. IVF-ET outcome in PCOS women treated by laparoscopic ovarian electrocautery (group A) and in PCOS women who did not undergo surgical treatment (group B)

|   | A              | B              | <i>p</i> |
|---|----------------|----------------|----------|
| Number of cycles                        | 28             | 47             |          |
| No hCG given (%)                        | 0/28 (0)       | 6/47 (12.8)    | n.s.     |
| Peak E <sub>2</sub> (pg/ml) (mean±s.d.) | 1722.73±522.24 | 2314.48±692.60 | <0.05    |
| Number of oocytes/pickup                | 7.4 (207/28)   | 10.1 (414/41)  | n.s.     |
| Fertilization rate (%)                  | 72.1           | 57.3           | n.s.     |
| Number of embryos                       | 149            | 237            | –        |
| Number of embryos/transfer              | 3.19 (89)      | 3.42 (140)     | n.s.     |
| Frozen embryos                          | 60             | 97             |          |
| Total pregnancy rate/cycle (%)          | 32.1 (9/28)    | 10.6 (5/47)    | n.s.     |
| Total pregnancy rate/transfer (%)       | 32.1 (9/28)    | 12.2 (5/41)    | n.s.     |
| Ongoing pregnancy rate/cycle (%)        | 28.6 (8/28)    | 7.3 (3/41)     | <0.05    |
| Abortion rate (%)                       | 11.1 (1/9)     | 40 (2/5)       | n.s.     |

pregnancies vs two out of five pregnancies) and all three abortions occurred within 12 weeks of gestation.

Estradiol, testosterone and Δ<sub>4</sub> androstenedione were significantly lower from small to intermediate and to large follicles in group A, while in group B significance was found only for estradiol and androstenedione (Table III). In group A statistically significant (*p*<0.05) lower levels of testosterone and Δ<sub>4</sub> androstenedione were found in each pool when compared with the respective pool in group B.

**Discussion**

According to our knowledge, this is the first study which compares IVF outcome and FF steroid content in infertile patients with PCOS pretreated by laparoscopic ovarian electrocautery, with those of untreated PCOS women with similar clinical and hormonal parameters, and stimulation protocol.

Considering that laparoscopic ovarian diathermy has become a common second line treatment for ovulation induction in PCOS women, and that the technique has been reported (12, 13) to induce post operative adhesions, it may be import-

ant to evaluate the IVF outcome after this treatment.

Women with PCOS in our IVF program had all failed to conceive after treatment with clomiphene citrate and during six documented ovulatory cycles following diagnostic laparoscopy with or without ovarian diathermy. According to Urman et al. (14) and Homburg et al. (15), this is an appropriate indication for IVF-ET treatment, in particular employing a GnRH analogue in the stimulation protocol.

We reported a significantly (*p*<0.05) better ongoing pregnancy rate in our series in the IVF-ET cycles of those PCOS women pretreated by means of laparoscopic ovarian electrocautery.

The reproductive benefits of this kind of surgery have been widely demonstrated (6, 9, 11–13, 17, 18, 19) and our study is the first trial reporting a better pregnancy rate, a reduced abortion rate and a reduced trend for hyperstimulation (significantly lower serum E<sub>2</sub> peak with the same stimulation protocol and lower cancellation rate) also in IVF cycles performed within 9 months of surgery.

Since testosterone and Δ<sub>4</sub> androstenedione levels in the follicular fluid were significantly lower in patients treated by ovarian diathermy, this may explain the improved oocyte quality. This androgenized follicular microenvironment might be related to the decrease in LH levels induced by ovarian electrocautery, probably via a paracrine activation in the production of a gonadotropin surge inhibiting factor (GnsIF) as suggested by Balen & Jacobs (20).

The reduction in LH has been widely reported as the main mechanism by which reproductive outcome is improved after ovarian electrocautery (21–23).

Our FF steroids' data might offer an alternative explanation to the direct induction by LH of an untimely initiation of meiosis (21, 24) resulting in an aged oocyte with a poor reproductive potential.

This mechanism of premature resumption of meiosis could not be directly triggered by LH, but by the LH-induced antral hyperandrogenism. The

Table III. Follicular fluid concentrations of estradiol (E<sub>2</sub>), progesterone (P), testosterone (T), and Δ<sub>4</sub> androstenedione (Δ<sub>4</sub>) from follicles of different sizes (mean±s.d.)

| Follicular size | E <sub>2</sub> (ng/ml) |                | P (ng/ml)     |               | T (ng/ml)      |                       | Δ <sub>4</sub> (ng/ml) |                        |
|-----------------|------------------------|----------------|---------------|---------------|----------------|-----------------------|------------------------|------------------------|
|                 | A <sup>a</sup>         | B <sup>a</sup> | A             | B             | A <sup>a</sup> | B                     | A <sup>a</sup>         | B <sup>a</sup>         |
| <13 mm          | 475.3±171.5            | 552.5±175.0    | 5475.9±1482.6 | 5362.3±1660.4 | 12.1±3.8       | 18.7±5.9 <sup>b</sup> | 39.3±13.9              | 66.0±12.3 <sup>b</sup> |
| 13–17 mm        | 318.3±112.7            | 397.6±145.8    | 5060.6±1206.2 | 4742.7±1169.5 | 11.4±3.8       | 18.1±6.0 <sup>b</sup> | 30.3±12.1              | 52.1±11.1 <sup>b</sup> |
| >17 mm          | 273.1±106.3            | 222.6±93.2     | 6410.4±1658.1 | 6046.7±1537.5 | 10.2±3.8       | 17.4±6.4 <sup>b</sup> | 21.1±10.7              | 39.3±13.4 <sup>b</sup> |

<sup>a</sup> Significant stepwise change of steroids in follicles of increasing size within each group A and B, *p*<0.05.

<sup>b</sup> Significant difference between steroid levels in group A and in group B, *p*<0.05.

latter, in fact, might be involved in the paracrine control of the factors inhibiting the final maturation events of the oocyte such as the cellular coupling between oocyte and coronal cells and the oocyte maturation inhibitor (OMI) (25).

If our data are confirmed by a larger prospective series, we may conclude that in infertile PCOS women, when an adequate diagnostic-therapeutic preoperative approach is followed, an ovarian electrocautery at the time of diagnostic laparoscopy (7) may be recommended, not only for the high rate of spontaneous ovulation, but also for a better outcome in IVF cycles.

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### Address for correspondence:

Prof. Nicola Colacurci  
Via Manzoni 88  
80124, Napoli  
Italy