Outcome of intracytoplasmic sperm injection in patients with polycystic ovary syndrome or isolated polycystic ovaries

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Objective: To determine the intracytoplasmic sperm injection (ICSI) and embryo transfer (ET) performance of patients with polycystic ovary syndrome (PCOS) and isolated polycystic ovarian (PCO) morphology.

Design: Case-control study.

Setting: IVF Center, Hacettepe University Faculty of Medicine.

Patient(s): Ninety-nine consecutive infertile women (n = 109 cycles) with PCOS and 58 patients (n = 58 cycles) with isolated PCO morphology were recruited. The control group consisted of 210 patients (n = 232 cycles) with isolated male factor infertility necessitating ICSI. All three groups were matched for female age and body mass index.

Intervention(s): Controlled ovarian hyperstimulation and ICSI.

Main Outcome Measure(s): Oocyte number, fertilization rate, embryo quality, clinical pregnancy rate, implantation rate, and ovarian hyperstimulation syndrome (OHSS).

Result(s): Six (5.5%) cycles in the PCOS group, 6 (10.3%) cycles in the PCO-only group, and 10 cycles (4.3%) in the control group were canceled. Despite a significantly lower total FSH dose used, a significantly higher serum E2 level was attained in both the PCOS and the PCO-only groups compared to the control group. The PCOS and PCO-only groups had significantly higher numbers of retrieved oocyte-cumulus complexes and metaphase II oocytes compared to the control group. The fertilization rates did not differ among the three groups. The mean number of embryos transferred was comparable among the three groups; however, the mean number of grade 1 embryos was significantly higher in the PCOS and PCO-only groups compared to the controls. The clinical pregnancy rates per ET of both the PCOS (66%) and the PCO-only (60%) groups were significantly higher than that of the control group (44%). However, the implantation rates were comparable among the three groups. Four cycles (3.7%) in the PCO group had OHSS necessitating hospitalization. The respective figures in the PCO-only and the control groups were 1 (1.7%) and 3 (1.3%).

Conclusion(s): Patients with the full-blown picture of PCOS or isolated PCO-only morphology behave exactly in the same manner during all stages of assisted reproduction. Owing to the availability of more fertilized oocytes and grade 1 embryos, patients with PCOS or PCO-only morphology are associated with higher clinical pregnancy rates per ET compared to patients with isolated male factor infertility. (Fertil Steril 2005;84:932–7. ©2005 by American Society for Reproductive Medicine.)

Key Words: PCOS, polycystic ovaries, assisted reproductive technologies, ICSI, OHSS

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disorder, affecting approximately 5%–7% of reproductive-age women (1–3). Assisted reproductive technologies (ART) are offered to women with PCOS failing to ovulate with clomiphene citrate followed by chronic low-dose gonadotropin protocols (4). In addition, ART may be considered when there is a severe accompanying infertility factor, such as severe male factor necessitating intracytoplasmic sperm injection (ICSI).

The ART performance of patients with PCOS, employing either IVF or ICSI, has been reported to be comparable to control groups mainly consisting of tubal factor or male factor infertility (5–10). Excessive response to gonadotropins manifested by possibly life-threatening ovarian hyperstimulation syndrome (OHSS) is a potential complication of controlled ovarian hyperstimulation (COH) in these patients (11).

Not infrequently polycystic ovaries (PCO) may be encountered at transvaginal ultrasonography without any evidence of anovulation, hyperandrogenism, or hyperandrogen-
emia. There is a paucity of data in the literature evaluating the ART performance of those so-called PCO-only patients.

The aim of this study was to compare the ICSI performance of patients with PCOS and PCO-only morphology with female age- and body mass index (BMI)–matched controls at a university IVF center.

**MATERIALS AND METHODS**

Ninety-nine consecutive infertile women with PCOS underwent 109 ICSI cycles. The second group had PCO-only morphology with regular documented ovulation and no evidence of clinical and laboratory hyperandrogenism (n = 58 patients and n = 58 cycles). The third group formed the controls: 210 patients (n = 232 cycles) with male factor infertility necessitating ICSI. The control group was matched in terms of female age and BMI with the former two groups.

The diagnosis of PCOS was made by the presence of any two of the following three criteria: polycystic ovaries, oligo- or anovulation, and clinical or biochemical evidence of hyperandrogenism (12). Polycystic ovary appearance was characterized as the presence of 12 or more follicles in each ovary, each measuring 2–9 mm in diameter, and/or increased ovarian volume (10 mL) at transvaginal ultrasonography (13). All patients in the three groups had severe male factor infertility necessitating ICSI using fresh ejaculated spermatozoa, defined as total ejaculate sperm count of <3 million and/or <2% normal morphology by Tygerberg strict criteria.

All patients underwent controlled ovarian hyperstimulation consisting of luteal-long leuprolide acetate (Lucrin; Abbott Cedex, Istanbul, Turkey) with oral contraceptive pretreatment (Lo-ovral; Wyeth, Istanbul, Turkey) and recombinant FSH (Gonal-F; Serono, Istanbul, Turkey) using the step-down protocol. The starting dose of gonadotropin was determined based on female age, antral follicle count at baseline transvaginal ultrasonography, day 3 FSH and E2 levels, BMI, and previous ovarian response, if available. Ovarian response was monitored with frequent serum E2 measurements and transvaginal ultrasonography, as described previously (14). The criterion for hCG (Profasi; Serono) administration was the presence of 3 or more follicles exceeding 17 mm in diameter.

Oocyte retrieval was carried out under local anesthesia using vaginal ultrasound–guided puncture of follicles 36 h after hCG administration. Standard procedures were carried out for gamete-embryo handling, and day 3 embryo transfer (ET) was performed in all cases using soft catheter. Luteal phase was supported by daily vaginal P suppositories (Cronine; Serono) starting one day after oocyte pick-up.

Despite stepping-down and careful titrating of the FSH dose, coating was employed for unexpected hyperresponse. Hyperresponse was defined as serum E2 level >4,000 pg/mL, irrespective of whether hCG criteria were fulfilled or not (≥3 follicles ≥17 mm in diameter). For coating, gonadotropin injections were stopped, leuprolide-acetate was continued, and serum E2 level was measured daily. When serum E2 level dropped below 4,000 pg/mL, hCG was administered at a dose of 10,000 IU. When the serum E2 level increased very rapidly in the presence of follicles not fulfilling the hCG criteria, “early” coating was also undertaken even with serum E2 <2,500 pg/mL.

Cycle cancellation was undertaken when significant E2 drop and cessation of follicular growth were noted during stepping down of the FSH dose. Significant E2 drop was assumed to be 30% of the preceding E2 level. Cycle cancellation was also undertaken with total fertilization failure or arrest of preembryonic development.

Embryos were graded on day 3 according to a 1–4 scoring system (with 1 being the best), which was based on fragmentation, cell symmetry, and blastomere number. The embryos with even blastomeres and no fragmentation were graded as grade 1, the embryos with even blastomeres and <30% fragmentation as grade 2a, the embryos with uneven blastomeres and no fragmentation as grade 2b, the embryos with uneven blastomeres and <30% fragmentation as grade 2ab. The embryos with 30%–50% fragmentation and >50% fragmentation were graded as grade 3 and 4 embryos, respectively (15). Embryos with grades 1–3 were considered as transferable.

Clinical pregnancy was defined as the presence of an intraspinous gestational sac at transvaginal ultrasonography. Symptomatic patients with moderate or severe OHSS were hospitalized (11).

The statistical analyses were performed using Statistics Package for Social Sciences version 12.0 (SPSS, Chicago, IL). The chi-squared and Fisher exact tests were used to analyze nominal variables in the form of frequency tables. Normally distributed (Kolmogorov-Smirnov test) parametric variables were tested by the analysis of variance (ANOVA) using Bonferroni test for post hoc analysis. Non-normally distributed metric variables were analyzed by the Kruskal-Wallis test and Mann-Whitney U test. P values of ≤0.05 were considered statistically significant. Values were expressed as mean ± SD, unless stated otherwise.

**RESULTS**

All three groups were comparable in terms of the baseline characteristics, including female age, BMI, and duration of infertility (Table 1). Six (5.5%) cycles in the PCOS group, 6 (10.3%) cycles in the PCO-only group, and 10 (4.3%) cycles in the control group were canceled (P > 0.05).

Despite a significantly lower total FSH dose used, a significantly higher serum E2 level was attained in both the PCOS and PCO-only groups compared to the control group (Table 2). Although the mean number of follicles greater than 17 mm in diameter at hCG administration was comparable among the three groups, the mean number of follicles...
with diameters of 15–17 mm and 10–14 mm were significantly higher in the PCOS and PCO-only groups compared to the control group ($P < .05$; Table 3). The need for coasting was significantly higher in the PCOS ($n = 10$ cycles) and PCO-only ($n = 7$ cycles) groups compared to the control group ($n = 8$ cycles) ($P < .05$). In all three groups, the coasting period was 1 day in 17 patients, 2 days in 5 patients, and 3 days in 3 patients.

Cycle cancellation due to significant E$_2$ drop and cessation of follicular growth was undertaken in 6 patients in the PCOS group and 5 in the PCO-only group. One patient in the PCO-only group had unexpected total fertilization failure and did not reach ET. The etiology of cycle cancellation in the control group was poor ovarian response ($n = 1$) or total fertilization failure combined with arrest of preembryonic development ($n = 9$).

The PCOS and PCO-only groups had significantly higher numbers of retrieved oocyte-cumulus complexes and metaphase II oocytes compared to the control group ($P < .05$; Table 3). However, the number of metaphase II oocytes/number of total oocyte-cumulus complexes ratio and the fertilization rate did not differ among the three groups (Table 3). The mean number of embryos transferred was comparable among the three groups; however, the mean number of grade 1 embryos was significantly higher in the PCOS and PCO-only groups compared to the controls ($P < .05$; Table 3). The rate of cycles in which embryo cryopreservation could be undertaken did not differ among the three groups.

The clinical pregnancy rates per ET of both PCOS (66%) and PCO-only (60%) groups were significantly higher than that of the control group (44%) (Table 3). The implantation rates were comparable among the three groups. The multiple pregnancy rates were 48%, 48%, and 41%, respectively. The respective figures for miscarriage were 12%, 33%, and 14% ($P < .05$, PCO-only group versus PCOS and control groups).

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCOS</th>
<th>PCO-only</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>99</td>
<td>58</td>
<td>210</td>
</tr>
<tr>
<td>No. of cycles</td>
<td>109</td>
<td>58</td>
<td>231</td>
</tr>
<tr>
<td>No. of canceled cycles (n, %)</td>
<td>6 (5.5)</td>
<td>6 (10.3)</td>
<td>10 (4.3)</td>
</tr>
<tr>
<td>Female age (y)</td>
<td>30.5 ± 4.8</td>
<td>30.0 ± 4.8</td>
<td>30.6 ± 3.7</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>26.8 ± 4.7</td>
<td>25.4 ± 4.9</td>
<td>26.1 ± 3.5</td>
</tr>
<tr>
<td>Duration of infertility (m)</td>
<td>94.4 ± 62.7</td>
<td>88.9 ± 53.7</td>
<td>92.8 ± 53.1</td>
</tr>
</tbody>
</table>

*Note: All are not significant. Values are expressed as mean ± SD or n (%).*

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### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCOS</th>
<th>PCO-only</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of stimulation (d)</td>
<td>10.1 ± 1.7</td>
<td>10.0 ± 1.7</td>
<td>10.2 ± 2.6</td>
</tr>
<tr>
<td>Total dose of FSH used (IU)</td>
<td>2,049.7 ± 906.9</td>
<td>2,071.1 ± 1,000.2</td>
<td>2,483.6 ± 1,107.6$^a$</td>
</tr>
<tr>
<td>$E_2$ level on the day of hCG administration (pg/mL)</td>
<td>3,168.4 ± 1,620.2</td>
<td>3,361.3 ± 2,421.9</td>
<td>2,340.5 ± 1,582.2$^a$</td>
</tr>
<tr>
<td>No. of follicles &gt;17 mm in diameter at hCG administration</td>
<td>3.8 ± 2.4</td>
<td>3.9 ± 3.2</td>
<td>3.5 ± 2.1</td>
</tr>
<tr>
<td>No. of follicles 15–17 mm in diameter at hCG administration</td>
<td>5.7 ± 4.1</td>
<td>5.1 ± 2.6</td>
<td>3.7 ± 3.0$^a$</td>
</tr>
<tr>
<td>No. of follicles 10–14 mm in diameter at hCG administration</td>
<td>10.8 ± 6.9</td>
<td>11.4 ± 6.3</td>
<td>7.1 ± 5.3$^a$</td>
</tr>
<tr>
<td>Endometrial thickness at hCG administration (mm)</td>
<td>11.3 ± 2.3</td>
<td>11.3 ± 2.0</td>
<td>10.9 ± 2.2</td>
</tr>
</tbody>
</table>

*Note: Values are expressed as mean ± SD. NS = not significant. $^a$ Statistically different from PCOS and PCO-only group.*

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Four cycles (3.7%) in the PCOS group had OHSS necessitating hospitalization. The respective figures in the PCO-only and the control groups were 1 (1.7%) and 3 (1.3%) (P < 0.05).

**DISCUSSION**

There are a limited number of studies evaluating the ART performance of patients with PCOS or PCO-only ovaries (5–10, 16–19). In those studies where IVF or ICSI have been performed for PCOS-associated infertility, it is generally noted that the outcome is similar to other forms of infertility (19). In patients with PCOS compared to controls mainly consisting of tubal factor or male factor infertility, more follicles are produced and more oocytes are retrieved with a lower dose of total gonadotropins; however, in general, implantation and pregnancy rates are noted to be comparable (5–10, 18).

In this study, we noted that patients with PCOS or isolated PCO morphology had even more favorable ICSI outcome compared to controls with male factor infertility. Both PCOS and PCO-only groups had more oocytes retrieved, fertilized oocytes, and grade 1 embryos transferred, resulting in a significantly higher clinical pregnancy rate per transfer compared to controls.

Intrinsic abnormalities of the oocyte or abnormal endocrine in vivo milieu have been postulated to contribute errors in folliculogenesis, oocyte, and embryo quality in patients with PCOS (20). Abnormal expression of growth differentiation factor 9 (GDF-9) was reported in oocytes from PCOS patients (21). GDF-9 is an important oocyte-derived growth factor that is not only involved in early follicular development but also appears to have a role in controlling cumulus expansion in the preovulatory follicle (22). Regarding abnormal endocrine in vivo milieu, exposure to increased circulating concentrations of LH and insulin has been associated with abnormal granulose cell function (20). Despite these abnormalities of folliculogenesis and granulose cell function, oocyte and embryo quality appear not to be impaired in ART (7). Oocyte quality, as judged by fertilization and embryo development rates, has been noted to be similar to controls (7). Indeed, blastocyst cell numbers were found to be significantly higher, following a titrated gonadotropin regimen, in women with PCOS than in those with tubal infertility (20). In contrast, lower fertilization rates with IVF have been noted in other studies (6, 16, 17, 23).

In concordance with previous studies, we noted that despite significantly lower FSH consumption, serum E2 level on the day of hCG was higher in both the PCOS and the

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**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCOS</th>
<th>PCO-only</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of oocyte-cumulus complexes</td>
<td>15.5 ± 7.3</td>
<td>15.3 ± 6.4</td>
<td>11.7 ± 6.1a</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>No. of metaphase II oocytes</td>
<td>13.4 ± 7.1</td>
<td>13.1 ± 5.6</td>
<td>10.3 ± 5.8a</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Metaphase II oocytes/total oocytes (%)</td>
<td>87</td>
<td>86</td>
<td>87</td>
<td>NS</td>
</tr>
<tr>
<td>2-pronucleated/metaphase II oocytes (%)</td>
<td>72</td>
<td>67</td>
<td>70</td>
<td>NS</td>
</tr>
<tr>
<td>No. of 2 pronucleated oocytes</td>
<td>10.1 ± 5.4</td>
<td>9.1 ± 5.2</td>
<td>7.2 ± 4.4a</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>No. of transferred grade 1 embryos</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.2</td>
<td>0.7 ± 0.1a</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>No. of transferred grade 1 embryos/no. of embryos transferred (%)</td>
<td>33.3</td>
<td>34.2</td>
<td>24.6a</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>No. of transferred grade 2 embryos</td>
<td>2.0 ± 0.1</td>
<td>2.1 ± 0.3</td>
<td>2.2 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>No. of embryos transferredc</td>
<td>3.2 ± 1.1</td>
<td>3.2 ± 1.3</td>
<td>3.0 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>No. of cycles with embryo freezing (n, %)</td>
<td>39 (35.8)</td>
<td>14 (24.1)</td>
<td>64 (28.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancy/embryo transfer (%)</td>
<td>66.0</td>
<td>59.6</td>
<td>44.3a</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>28.8</td>
<td>24.3</td>
<td>23.1</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple pregnancy rate (%)</td>
<td>48</td>
<td>48</td>
<td>41</td>
<td>NS</td>
</tr>
<tr>
<td>Twin (%)</td>
<td>39</td>
<td>44</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Triplet (%)</td>
<td>9</td>
<td>4</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Miscarriage rate (n, %)</td>
<td>8 (11.8)</td>
<td>9 (33.3)b</td>
<td>14 (14.1)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>No. of OHSS requiring hospitalization (n, %)</td>
<td>4 (3.7)</td>
<td>1 (1.7)</td>
<td>3 (1.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Note:** Values are expressed as mean ± SD, unless stated otherwise. NS = not significant; OHSS = ovarian hyperstimulation syndrome.

a Statistically different from PCOS group and PCO-only groups.

b Statistically different from PCOS and control group.

| Mean ± SEM. |

PCO-only groups. Metaphase II oocyte quality, in terms of fertilization and embryo development, was not impaired following ICSI in both the PCOS and the PCO-only groups. Fertilization rate was comparable among the three groups. Because significantly more oocytes were retrieved in the PCOS and PCO-only groups, significantly more 2-pronucleated oocytes were available.

Of note, owing to the greater number of embryos available, significantly more grade 1 embryos were transferred in the PCOS and PCO-only groups compared to the controls, resulting in significantly higher clinical pregnancy rates in the PCOS and PCO-only groups. However, implantation rates were comparable among the three groups. We therefore conclude that the presence of either PCOS or PCO-only ovaries is a favorable prognostic finding during counseling before ART.

Patients with PCO-only ovaries are not infrequently encountered. The presence of PCO has been reported in 23% of 257 “normal” volunteers (24). There is a paucity of data on the ART performance of ovulatory PCO-only patients. Engmann et al. (5) compared the outcome of a course of up to three cycles of IVF treatment in 46 women (97 cycles) who had PCO but who had no clinical symptomatology associated with PCOS with that of 145 women (332 cycles) who had normal ovarian morphology on ultrasound examination. On average, women with PCO produced more follicles, oocytes, and embryos than the women with normal ovaries, but the fertilization, cleavage, and miscarriage rates were similar. Adjusted for age, the odds of achieving a pregnancy within three cycles of treatment in a woman with PCO were 69% higher than those of a woman with normal ovaries (odds ratio (OR): 1.69; 95% confidence interval (CI) 0.99–2.90; P= .05), and the odds of achieving a live birth were 82% higher (OR: 1.82; 95% CI 1.05–3.16; P=0.03). The authors concluded that the outcome of IVF treatment for women with PCO seen on ultrasound examination may be better than that for women with normal ovaries. In concordance with those findings, the presence of PCO was a favorable prognostic sign in our study, associated with significantly higher clinical pregnancy rate per ET compared to the controls with isolated male factor infertility.

The mean numbers of embryos transferred in the PCOS, PCO-only, and control groups were 3.2 ± 1.1, 3.2 ± 1.3, and 3.0 ± 1.2, respectively. The respective multiple pregnancy rates were 48%, 48%, and 41%. Owing to these exceedingly high multiple pregnancy rates in all three groups, we currently consider transferring two, rather than three embryos on day 3 in such favorable patients. The miscarriage rate was significantly higher in the PCO-only group; this may be due to a type 1 error resulting from the limited sample size of the PCO-only group.

As a routine policy, we take five parameters into consideration when deciding the starting dose of FSH. These include female age, number of antral follicles, BMI, serum FSH and E₂ levels, and previous ovarian response, if available. Both lean and obese patients with PCOS or PCO-only ovaries are a challenge to COH for ART. In such patients the therapeutic window for “optimal” COH is narrow; cycle cancellation due to either OHSS or significant E₂ drop may be encountered while titrating the dose of FSH. In our study, we needed to cancel the cycle due to significant E₂ drop and cessation of follicular growth in 6 and 5 patients in the PCOS and PCO-only groups, respectively.

We noted that the number of small (10–14 mm in diameter) and medium-sized (15–17 mm in diameter) follicles, rather than large (>17 mm in diameter) follicles, were increased in PCOS and PCO-only groups, contributing to the need for coating and risk of OHSS. Coasting is an effective strategy to avoid OHSS in hyperresponders (25–27). As might be expected, we noted that significantly more cycles needed to be coasted in the PCOS and PCO-only groups. Despite careful titrating of the FSH dose and coating, when necessary, moderate to severe OHSS requiring hospitalization was encountered in 4, 1, and 3 patients in the PCOS, PCO-only, and control groups, respectively (P>.05).

We conclude that patients with the full-blown picture of PCOS or isolated PCO-only morphology behave exactly in the same manner during all stages of ART. Owing to the availability of more fertilized oocytes and grade 1 embryos, patients with PCOS or PCO-only morphology are associated with higher clinical pregnancy rates per ET compared to patients with isolated male factor infertility.

REFERENCES


