Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study

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BACKGROUND: Our aim was to investigate the effect of pre-treatment with metformin in women with polycystic ovary syndrome (PCOS) scheduled for IVF stimulation. METHODS: Seventy-three oligo/amenorrhoeic women with polycystic ovaries and at least one of the following criteria: hyperandrogenaemia, elevated LH/FSH ratio, hyperinsulinism, decreased SHBG levels or hirsutism, were studied. Normal weight and overweight patients were randomized separately in a prospective, randomized, double blind study. All patients were treated for at least 16 weeks with metformin (1000 mg bid) or placebo ending on the day of HCG injection. RESULTS: No differences were found in the primary end-points: duration of FSH stimulation 14.4 (13.1–15.7) versus 14.2 (12.6–15.7) days or estradiol on the day of HCG injection 6.8 (5.3–8.2) versus 7.6 (5.6–9.6) nmol/l in the metformin and placebo groups, respectively. The secondary end-points number of oocytes, fertilization rates, embryo quality, pregnancy rates and clinical pregnancy rates were equal. However, in the normal weight subgroup (BMI <28 kg/m², n = 27), pregnancy rates following IVF were 0.71 (0.63–0.79) versus 0.23 (0.15–0.31) in the metformin and placebo groups, respectively (P = 0.04). Overall clinical pregnancy rates were equal: 0.51 (0.34–0.68) versus 0.44 (0.27–0.62) in the metformin and placebo groups, respectively. However, in the normal weight subgroup, clinical pregnancy rates were 0.67 (0.43–0.91) and 0.33 (0.06–0.60), respectively (P = 0.06). CONCLUSIONS: Pre-treatment with metformin prior to conventional IVF/ICSI in women with PCOS does not improve stimulation or clinical outcome. However, among normal weight PCOS women, pre-treatment with metformin tends to improve pregnancy rates. Further studies in subgroups of PCOS women are required.

Key words: IVF stimulation/insulin-sensitizers/metformin/OHSS/polycystic ovary syndrome

Introduction

About 30–40% of infertile women have ovulation disorders. Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility, accounting for ~70% of cases (Adams et al., 1986; Hull, 1987; Knochenhauer et al., 1998). Traditionally clomiphene citrate (CC) has been first line therapy for ovulation induction. However, 20–30% of patients with PCOS are clomiphene resistant (Polson et al., 1989). Both insulin resistance and obesity are linked with clomiphene resistance (Lobo et al., 1982; Murakawa et al., 1999).

Hyperinsulinaemia and insulin resistance are present in the majority of women with PCOS (Dunaif et al., 1992; Utiger, 1996). Hence, efforts have focused on improving insulin sensitivity through diet and lifestyle modification, weight reduction and insulin-sensitizing drugs. Metformin, a biguanide originally used to treat type 2 diabetes, improves menstrual cyclicity and spontaneous ovulation rates in women with PCOS (Velazquez et al., 1994; Diamanti-Kandarakis et al., 1998; Morin-Papunen et al., 1998; Nestler et al., 1998; Glueck et al., 1999; Moghetti et al., 2000; Fleming et al., 2002; Haas et al., 2003; Harborne et al., 2003; Lord et al., 2003). There are two major (n = 61 and n = 90) prospective, randomized studies that compare metformin in combination with CC versus CC alone. In both studies, metformin increased ovulation rates in obese PCOS women (Nestler et al., 1998; El-Biely et al., 2001). In the latter study, which is not placebo controlled, metformin also increased pregnancy rates. In a randomized study (n = 56), metformin improved ovulation rates, cervical scores, endometrial thickness and cumulative pregnancy rates during CC stimulation (Kocak et al., 2002). Also, in a small
(n = 27) randomized study by Nestler’s group, metformin increased both ovulation rates and pregnancy rates in obese CC-resistant PCOS women (Vandermosten et al., 2001).

However, two small blinded, randomized studies (n = 20 and n = 26) did not verify increased spontaneous or CC response with metformin treatment (Ng et al., 2001; Sturrock et al., 2002). The study of Ng et al. (2001) was performed in lean, Chinese women [median body mass index (BMI) = 24 kg/m²]. A recent study (George et al., 2003) compared sequential 6 months’ combined treatment with metformin and CC with low dose gonadotrophin in CC-resistant PCOS women. In the metformin group, 40–45% of the patients improved menstrual and ovulatory function, while pregnancy rates were equal (16.7 versus 23.3%). However, gonadotrophin treatment resulted in a 4-fold increase in the cost per baby.

Pre-treatment with metformin in low-dose gonadotrophin stimulation favours mono-follicular development and reduces estradiol levels (De Leo et al., 1999). However, a small study (n = 16 in each group) did not verify this or any effect of metformin on ovarian response during a low dose step-up protocol using recombinant FSH (Yarali et al., 2002). However, the study suggested that metformin might restore spontaneous ovulation without improvement in insulin resistance.

Two studies have evaluated the effect of metformin treatment prior to IVF. In a retrospective study of 46 women undergoing 60 cycles of IVF treatment, metformin-treated women had more mature oocytes (18 versus 13), increased fertilization rates (64 versus 43%) and higher clinical pregnancy rates (70 versus 30%) than controls (Stadtmann et al., 2001). And in a small open-label randomised crossover trial, metformin increased the number of oocytes collected among insulin-resistant, obese PCOS women (Fedorecsik et al., 2003).

To clarify the effect of pre-treatment with metformin in PCOS women scheduled for IVF/ICSI treatment, we performed a prospective, randomized double-blind study. We treated the women for at least 16 weeks ending on the day of HCG injection. According to our hypothesis, reduced insulin resistance and androgen levels in the 85 day period during which the primordial follicles achieve pre-ovulatory status should facilitate the IVF process.

Materials and methods

Patients

Seventy-three consecutive, infertile women with PCOS referred for treatment at the IVF-unit at Trondheim University Hospital between January 2001 and June 2002 were recruited. All patients had polycystic ovaries (PCO) with at least 10 follicles 2–10 mm in diameter, and increased density and area of ovarian stroma determined by the use of ultrasound (Adams et al., 1986). All the patients had oligo/amenorrhoea, defined as either menstruation periods between 32 and 42 days (30%), an interval of between 42 days and 6 months (47%), or >6 months between periods (23%). In addition, at least one of the following five criteria had to be fulfilled: testosterone >2.0 nmol/l (65%), sex hormone-binding globulin (SHBG) <30 nmol/l (60%), LH/FSH ratio >2 (38%), fasting insulin C-peptide >1.0 nmol/l (41%) or hirsutism (37%). Hirsutism was defined as the need to remove unwanted facial hair at least once a week. Exclusion criteria were diabetes mellitus, renal insufficiency (creatinine >130 µmol/l), liver disease (alanine aminotransferase >80 U/l) or treatment with oral glucocorticoids. Patients with hyperprolactinaemia, abnormal thyroid function tests, congenital adrenal hyperplasia and androgen-secreting tumours were excluded. Of the 73 patients randomized, 41 patients (60%) had undergone a laparoscopy. Of these patients, 12 (29%) had tubal disease and three (7%) had endometriosis in addition to PCOS. Twenty-two (31%) of the couples had an additional male factor. Twelve couples were treated with microinjection (ICSI) and 49 with IVF. Seventy-three percent of the women were para 0, and 27% were para I. The mean duration of infertility was 4.0 (3.4–4.6) years. Except for testosterone levels and the free testosterone index (FTI) in the lean subgroup, there were no significant differences between the study groups regarding inclusion criteria and demographics (Tables I and II).

Protocol

At inclusion, all participants received both written and individual oral diet and lifestyle counselling. All the women, and especially obese women, were encouraged to increase their physical activity. The dietary advice resembles the advice given to type 2 diabetic patients. The patients were treated with metformin 500 mg (Metformin®, Weifa, Oslo, Norway) or placebo two capsules bid (gradually increasing the dose during the first 2 weeks) for at least 16 weeks ending on the day of ovulation induction with HCG injection. The IVF/ICSI treatment cycle was started with spontaneous or progesterone-induced withdrawal bleeding (Norethisterone 5 mg tid for 4 days; Primolut®, Schering AG, Berlin, Germany). At cycle day 20, downregulation with a GnRH analogue was started (nafarelin 800 µg daily; Synarel®, Searle, USA). Following at least 14 days of downregulation, stimulation with recombinant FSH (rFSH; Puregon®, Organon, The Netherlands) was performed. The starting dose of FSH was 100 IU daily in normal weight women (BMI <28 kg/m² at screening) or 150 IU daily in obese women (BMI ≥28 kg/m²). The first monitoring was performed at cycle day 10; thereafter individual dosing was allowed in accordance with clinical response. In cases of threatening ovarian hyperstimulation syndrome (OHSS), FSH was withdrawn for 4 days (`coasting’), and HCG injection was not given until estradiol was <10.0 nmol/l. Ovulation was induced with 5000 IU of HCG (Pregnyl®, Organon, The Netherlands) and follicles were aspirated (ovum pick up, OPU) 34–36 h later. Collected oocytes were fertilized in vitro by IVF or ICSI. A maximum of two embryos was transferred on the third day of the cycle. Luteal phase was supported with progesterone vaginally for 2 weeks (Progestan® 200 mg tid, Organon, The Netherlands). The Committee for Medical Research Ethics of Health Region IV, Norway, and The Norwegian Medicines Agency approved the study. Written informed consent was obtained from patients before inclusion in the study, and the Declaration of Helsinki was followed throughout the study.

Randomization

Randomization was performed by our hospital pharmacy; it was performed in blocks of four and stratified according to BMI <28 kg/m² or BMI ≥28 kg/m². Patients were treated with identical capsules of metformin or placebo. Randomization codes were kept in the pharmacy until the last patient had finished the IVF procedure (October 2002).

Assays

Blood samples were drawn from the patients in the fasting state from an antecubital vein between 8.00 and 10.00 a.m. Samples were centrifuged within 30 min and serum was stored at −78°C until the assays described below were performed. Plasma glucose was analysed
on the day of the blood sampling using a glucose dehydrogenase method after protein precipitation using reagents and calibrators delivered by the manufacturer (Merck Granustest 250 reagent kit, E Merck, Darmstadt, Germany). Testosterone was analysed on the Elecsys 2010 analyser by an electrochemiluminescent assay using the reagents, calibrators and dilutes delivered by the supplier (Boehringer Mannheim, Germany) with a lower and upper detection limit of 0.1 and 52.0 nmol/l. Androstenedione and insulin C-peptide were analysed on the immulite 2000 analyser by a solid phase, competitive chemiluminscent immunoassay using the reagents and calibrators supplied by the manufacturer (Diagnostic Products Corporation, Los Angeles, CA). The lower and upper detection limits were 1.0 and 35 nmol/l for androstenedione, and 0.17 and 2.3 nmol/l for insulin C-peptide. Estradiol was analysed on the immulite 2000 analyser by a competitive immunoassay using the reagents and calibrators supplied by the manufacturer (Diagnostic Products Corporation). The lower and upper detection limits were 0.07 and 7.34 nmol/l. SHBG, LH, FSH and prolactin were analysed on an immulite 2000 analyser by a

<table>
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<th>Variable</th>
<th>Treatment group</th>
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<th>P</th>
<th>BMI &gt;28 kg/m²</th>
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<tr>
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<td>4.0</td>
<td>3.3–4.6</td>
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<td></td>
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<td>31</td>
<td>4.2</td>
<td>3.1–5.3</td>
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<tr>
<td>Total ovarian volume (ml)</td>
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<td>22.5</td>
<td>19.6–25.4</td>
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<td>14</td>
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<td>14</td>
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<td>2</td>
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<td>10</td>
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<td>0.8–1.2</td>
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<td>0.19–0.24</td>
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<td>138–191</td>
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<td>0.9–1.3</td>
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<tr>
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<td>Metformin</td>
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<td>1.0</td>
<td>0.9–1.2</td>
<td>0.6</td>
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<td>Glucose (nmol/l)</td>
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<td>4.9</td>
<td>4.7–5.0</td>
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CI = 95% confidence interval.

Table I. Basic variables and fulfilment of inclusion criteria according to study group and BMI

Table II. Baseline endocrine variables according to study groups and BMI
immunometric assay using reagents and calibrators delivered by the supplier (Diagnostic Products Corporation). The lower and upper detection limits were 3 and 180 nmol/l (SHBG), 0.05 and 200 mIU/l (LH), 0.1 and 170 mIU/l (FSH), and 11 and 3180 mIU/l (prolactin). FTI was calculated as total testosterone/SHBG and multiplied by 10.

Statistical analysis

Retrospective analyses from our database at the infertility unit regarding IVF treatment of PCOS patients were used for calculating standard differences for our primary end-points: total number of days of FSH stimulation and serum estradiol on the day of HCG injection. A treatment effect of $\pm 3$ days or $\Delta$-estradiol $\pm 3.5$ nmol/l was considered to be of clinical significance. Thirty-two patients would be needed in each group to detect such changes with a 80 percentage power and with a $P$-value of 0.05.

Secondary end-points were number of oocytes, total gonadotrophin dose used, fertilization rates, embryo quality, pregnancy rates, clinical pregnancy rate and live birth rates. Embryo quality was evaluated as the mean cleavage rate representing the mean number of blastomeres at day 3 among normally fertilized embryos (two pronuclei). A good quality embryo was defined as an embryo either transferred or frozen. Pregnancy was defined by positive urine HCG on day 14 after embryo transfer. Clinical pregnancy was defined as a verified intrauterine gestational sac by ultrasound performed in week 7.

SPSS for Windows version 11.0 (Chicago, IL) was used for all statistical analyses. Mann–Whitney tests and $\chi^2$ tests were used to compare groups. Values are given as means and 95% confidence intervals (CIs). No adjustments for multiple testing were performed. $P$-values <0.05 were considered significant.

Results

Patient flow

Seventy-three women with PCOS were randomized. Four patients withdrew for personal or economic reasons, leaving 35 in the metformin group and 34 in the placebo group. During 16 weeks of pre-treatment, four women in the metformin group and two in the placebo group became pregnant spontaneously (Figure 1). Thus, 63 women started gonadotrophin-stimulation, 31 in the metformin group and 32 in the placebo group. These patients are subject to our per protocol analyses. Two women were excluded before OPU, one due to threatening OHHS and one with only one follicle developing. Four patients dropped out before embryo transfer (ET), two due to OHHS and two due to lack of good quality embryos. The remaining 57 patients had ET (Figure 1).

Analyses are made per-protocol, i.e. among the 63 women who started IVF stimulation. In addition, analyses of pregnancy rates, clinical pregnancy rates and live birth rates are also made as intention to treat analysis among the total of 73 randomized patients.

Baseline characteristics

There was no significant difference between the study groups at inclusion regarding age, duration of infertility, parity, BMI and inclusion criteria (Tables I and II). In the normal weight subgroup ($n = 27$), more patients in the metformin group fulfilled the testosterone criteria. This led to higher testosterone levels and FTI index at inclusion in lean metformin-treated women (Tables I and II).

Primary end-points

In the total study population, duration of FSH-stimulation was 14.4 (13.1–15.7) versus 14.2 (12.6–15.7) days in the metformin and placebo groups, respectively. Estradiol on the day of HCG injection was 6.8 (5.3–8.2) versus 7.6 (5.6–9.6) nmol/l, respectively, with no significant difference between the groups.
In the normal weight subgroup, duration of FSH stimulation was 15.8 (13.7–17.9) versus 14.2 (11.5–16.8) days, and estradiol on the day of HCG injection was 5.8 (4.1–7.5) versus 5.7 (2.9–8.4) nmol/l, respectively. In the obese subgroup, duration of FSH-stimulation was 13.4 (11.7–14.8) versus 14.6 (12.4–16.8) days, and estradiol on the day of HCG injection was 7.5 (5.2–9.6) versus 9.1 (6.3–11.8) nmol/l.

Secondary end-points

The total FSH dosages used were 1883 (1510±2056) versus 2039 (1529±2548) IU in the metformin and placebo groups, respectively (Table III). In the normal weight subgroup, total FSH dosages were 1671 (1253±2089) versus 1483 (1049–1917) IU and in the obese group 1981 (1584–2279) versus 2463 (1643–3283) IU. In the total study group, the number of oocytes collected was 13.9 (11.1±16.7) in the metformin group versus 13.1 (10.7±15.5) in the placebo group (Table IV). In the normal weight subgroup, 13.1 (8.9±17.3) versus 9.7 (6.8±12.7) oocytes were collected (P = 0.19), and in the obese subgroup 14.6 (10.4±18.9) versus 15.2 (11.9±18.5), respectively.

Fertilization and embryo quality

In the total study population, no differences were found in fertilization rates 0.53 (0.45±0.60) versus 0.55 (0.46±0.63), mean cleavage 5.1 (4.7±5.6) versus 5.3 (4.9–5.7) and number of good embryos 2.6 (1.8–3.4) versus 3.4 (2.1–4.7) in the metformin and placebo groups, respectively (Table IV). There were four patients with only one embryo available for transfer, all four in the placebo group (P = 0.12). The rest of the patients (53) had two embryos transferred. The total number of cycles

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CI = 95% confidence interval.

Spontaneous pregnancies were those occurring during the pre-treatment period. Fifty-seven patients had embryo transfer (never more than two embryos). Pregnancy rate = βHCG day 14. Clinical pregnancy rate = gestational sac by ultrasound per started cycle. Live birth rate is per treatment cycle started.
with freezing was not significantly different: four in the metformin group (21 embryos frozen) versus seven cycles in the placebo group (51 embryos frozen). No differences in fertilization or embryo parameters were found in subgroup analysis.

**Pregnancy rates**

Among the 63 women who started IVF stimulation, pregnancy rates were 0.58 (0.50–0.66) versus 0.47 (0.39–0.55), clinical pregnancy rates 0.48 (0.40–0.56) versus 0.44 (0.36–0.52), and the live birth rate 0.39 (0.31–0.47) versus 0.34 (0.26–0.42), in the metformin and placebo groups, respectively (Table IV).

In subgroup analysis, pregnancy rates in the normal weight subgroup were higher in the metformin group 0.71 (0.63–0.79) versus 0.23 (0.15–0.31) in the placebo group \( (P = 0.04) \). The clinical pregnancy rates were 0.57 (0.49–0.65) versus 0.23 (0.15–0.31) \( (P = 0.12) \), and live birth rates 0.43 (0.35–0.51) versus 0.15 (0.07–0.23) \( (P = 0.12) \), respectively. In the obese subgroup, there were no differences regarding pregnancy and live birth rates, but rather a tendency toward higher rates in the placebo group. There were six twin clinical pregnancies in the metformin group versus five in the placebo group. There were three healthy twin births in the metformin group and two in the placebo group.

**Spontaneous pregnancies**

There were six spontaneous pregnancies during the 16 weeks of pre-treatment, four in the metformin group and two in the placebo group. All six spontaneous pregnancies occurred among normal weight PCOS women. Mean duration of infertility in these six women was somewhat shorter than for the rest of the study group: 2.4 years versus 4.1 years. Mean age was 30.7 years, mean BMI was 24.5 kg/m², mean fasting insulin C-peptide at inclusion was 0.6 nmol/l and mean serum testosterone at inclusion was 2.4 nmol/l among these six women.

**Intention to treat analysis**

In intention to treat analysis, the total of 73 randomized women, clinical pregnancy rates were 0.51 (0.34–0.68) versus 0.44 (0.27–0.62) in the metformin and placebo groups. In subgroup analyses, the clinical pregnancy rate in normal weight women \( (n = 33) \) was 0.67 (0.43–0.91) versus 0.33 (0.06–0.60) \( (P = 0.06) \), and in obese women \( (n = 40) \) it was 0.37 (0.13–0.61) versus 0.52 (0.29–0.76) in the metformin and placebo groups, respectively.

**Weight reduction and adverse effects**

Mean BMI at inclusion was 28.6 (26.9–30.4) versus 29.9 (27.9–31.9) kg/m² in the metformin and placebo groups, respectively. In the normal weight subgroup, mean BMI was 24.5 (23.5–25.6) versus 24.4 (22.6–26.2) in the obese group 32.0 (30.2–33.9) versus 33.7 (32.1–35.3), respectively. In the metformin group, BMI was reduced by –1.0 kg/m², and in the placebo group by –0.3 kg/m² \( (P = 0.03) \). In subgroup analysis the change in BMI was significant in normal weight women only, –0.6 kg/m² versus +0.2 kg/m² \( (P = 0.035) \). In the obese group, weight reduction was –1.4 kg/m² versus –0.6 kg/m² \( (P = 0.15) \). Twenty women in the metformin group and five in the placebo group reported minor gastrointestinal side effects, of which five women in the metformin group reduced the metformin dose from 2000 to 1500 mg daily. In the placebo group, none reduced the study medication. No patients dropped out of the study due to side effects of the medication.

**Discussion**

This is the first prospective, randomized, double-blind, placebo-controlled study evaluating the effect of pre-treatment with metformin in PCOS women undergoing IVF stimulation. The aim of the study was to investigate whether metformin treatment would normalize the IVF stimulation process in PCOS women. According to our hypothesis, reduced hyperandrogenaemia and insulin resistance in PCOS women should facilitate FSH stimulation. This was evaluated by the duration of gonadotrophin stimulation and estradiol levels on the day of HCG injection. We found no such effects of metformin in either the total study population or in the normal weight or obese subgroups. Our results are partially in agreement with the studies of Stadtmauer et al. (2001) and Fedorcsák et al. (2003), although these investigate two quite different patient populations of PCOS patients. In the Stadtmauer study, patients had a mean BMI of 26.5 kg/m², which corresponds well with our normal weight subgroup. The study by Fedorcsák consisted of obese, verified insulin-resistant PCOS patients with a mean BMI of 32.0 kg/m². Both the Stadtmauer study and our study are probably more heterogeneous with regard to insulin resistance.

Stadtmauer et al. (2001) found more mature oocytes and more 4-cell embryos in the metformin-treated group. These findings are not supported by our study. We have also performed more analysis with regard to number and proportion of 4- and 8-cell embryos in the study groups and subpopulations, but we do not find a higher rate of cell division in any group. Fedorcsák et al. (2003) found that metformin treatment did not change the amount of gonadotrophin used, but the mean number of oocytes collected was increased (8.6 versus 4.6) by metformin. This is not confirmed by the present study. However, we notice a non-significant 25% reduction (–600 IU) in the total gonadotropin consumption in obese, metformin-treated women (Table III), while in the normal weight group the daily doses were similar. This might represent a type II error. In the study of Stadtmauer et al. (2001), the amount of gonadotrophin used was the same, but, as previously mentioned, the Stadtmauer study population seem to be more like our normal weight subgroup. Our conclusion is that we could not find any significant differences with regard to stimulation, oocytes or embryo parameters.

The finding of an increased pregnancy rate through IVF in normal weight PCOS women is interesting, but difficult to explain. We would like to interpret this finding with caution and emphasize that the clinical pregnancy rate and live birth rate was not significantly increased. The power for studying the clinical pregnancy rate and live birth rate in this study was low. Looking thoroughly at the data in our study, we find that in the
normal weight group, all three patients with only one embryo available for transfer was in the placebo group.

In the normal weight subgroup, baseline testosterone levels and FTIs were elevated in the metformin group. This skewed distribution could have affected our results. However, we have performed control analyses with patients grouped according to levels of testosterone ≥2.0 or ≤2.0 nmol/l. These analyses did not alter our results.

PCOS patients are a heterogeneous group, and the findings of our study confirm this. In fact, we find more differences between the normal weight and obese patients than between metformin- and placebo-treated patients. Fasting insulin C-peptide and free androgen levels are higher in obese PCOS women. Obese women need higher gonadotrophin doses and have a higher serum estradiol level on the day of HCG. All six spontaneous pregnancies during the pre-treatment period occurred among the 33 normal weight PCOS women and none among the 40 obese women. Any study of treatment of PCOS patients should be aware of the striking differences between normal weight and obese PCOS women when designing studies. The high pregnancy rate in the normal weight metformin-treated PCOS women should be confirmed in larger studies. Such studies should also be designed to find explanations for a possible metformin effect other than stimulation or embryo parameters.

In the present study, metformin treatment ended on the day of HCG injection. Our study was designed to validate the effect of metformin pre-treatment, i.e. from the hypothesis that normalizing the endocrine changes in PCOS women during the 85 days for the primordial follicles to achieve pre-ovulatory status would facilitate the IVF process. Thus, we chose 16 weeks of pre-treatment. Possibly, a continued metformin treatment through the luteal phase and into pregnancy could have affected the results. Hopefully, appropriately designed studies to answer this question will be performed in the future.

In our inclusion criteria, we defined oligomenorrhea as cycle length above 32 days. In retrospect, we would prefer to have defined this as above 35 days. However, all patients except one would meet this criterion. This patient reported cycle length between 32 and 36 days. She had typical polycystic ovaries, severe hyperandrogenism and elevated C-peptide.

Finally, we notice live birth rates as high as 39% following IVF treatment in metformin-treated women versus 34% in the placebo group. The fact that PCOS women are a subgroup of IVF women with a good ovarian reserve might be of importance. Additionally, the diet and lifestyle counselling given to all the participants might have contributed to the overall good results regarding IVF treatment in the present study.

Conclusions

Pre-treatment with metformin for 16 weeks does not facilitate IVF stimulation or improve the outcome during IVF treatment. However, in normal weight PCOS women, metformin might increase pregnancy rates. Our findings need to be confirmed in future studies. We would recommend that future studies stratify according to BMI.

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