Does metformin affect the ovarian response to gonadotropins for in vitro fertilization treatment in patients with polycystic ovary syndrome and reduced ovarian reserve? A randomized controlled trial

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Objective: To evaluate the effects of metformin on the ovarian response to gonadotropins given for in vitro fertilization (IVF) programs in patients with polycystic ovary syndrome (PCOS) and reduced ovarian reserve.
Design: Prospective, parallel, randomized, double-blind, placebo-controlled clinical trial.
Setting: Academic departments of obstetrics and gynecology, and a private IVF center.
Patient(s): Primary infertile patients with PCOS older than 35 years and/or with a basal follicle-stimulating hormone (FSH) level higher than 10 IU/L who were scheduled for IVF cycles.
Intervention(s): Gonadotropin-releasing hormone agonist flare-up protocol and high starting doses of recombinant FSH plus metformin or placebo tablets.
Main Outcome Measure(s): Primary end point: cancellation rate for low ovarian response. Secondary end-points: other clinical, biochemical, and reproductive data.
Result(s): Enrollment was stopped after 88 participants had been randomized and analyzed due to an unacceptable increased risk of poor ovarian response in the metformin arm. Statistically significant differences between the metformin and placebo groups were observed in the dose of gonadotropins used, peak estradiol levels, and the number of dominant follicles, retrieved oocytes, and metaphase II oocytes.
Conclusion(s): In patients with PCOS and reduced ovarian reserve, metformin worsened the response to gonadotropins, and its administration should be stopped before the start of controlled ovarian hyperstimulation for IVF programs.
Clinical Trials Identification Number: NCT01208740. (Fertil Steril® 2011;■:■–■. ©2011 by American Society for Reproductive Medicine.)

Key Words: Gonadotropins, infertility, IVF, metformin, PCOS, poor prognosis, poor responder

To date, the international consensus is against the use of metformin to induce ovulation to treat anovulatory infertility in women with polycystic ovary syndrome (PCOS), and the indication for metformin administration is restricted to patients with glucose intolerance (1). However, a recent online survey (http://www.ivf-worldwide.com/component/option,com_bfsurvey_pro/Itemid,141/catid,21/view,onepage) showed that a large proportion of infertile patients with PCOS who had failed to conceive after first-line treatments subsequently undergo in vitro fertilization (IVF) procedures that include the administration of metformin. Thus, it is common practice for gynecologists and endocrinologists to administer or sustain metformin treatment in infertile patients with PCOS who are scheduled for IVF programs, irrespective of their basal metabolic status or the clinical efficacy of the treatment.

Received February 15, 2011; revised June 19, 2011; accepted August 12, 2011.
S.P. has nothing to disclose. A.F. has nothing to disclose. A.D.C. has nothing to disclose. F.C. has nothing to disclose. A.T. has nothing to disclose. F.Z. has nothing to disclose.
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Published data on the effects of metformin during ovarian stimulation by gonadotropins are contradictory. Preliminary meta-analytic data (4) have demonstrated an improved ovarian response—that is, a shorter duration of ovarian stimulation and fewer gonadotropins used—in infertile patients with PCOS who were treated with metformin. However, more recently, in a meta-analysis that evaluated the effectiveness of metformin as a cotreatment during IVF cycles in women with PCOS, metformin reduced the risk of ovarian hyperstimulation syndrome (OHSS) by approximately 75% (3). To explain this effect, it has been hypothesized that metformin acts as a brake on the ovary through several, as yet unexplained, mechanisms (4). On the basis of these considerations, this clinical trial tested the hypothesis that metformin worsened the ovarian response to gonadotropins administered for IVF cycles in infertile patients with PCOS and reduced ovarian reserve.

MATERIALS AND METHODS

Population

Primary infertile patients with PCOS scheduled for IVF program and showing a reduced ovarian reserve were included in the study protocol. Infertile patients at their first IVF attempt were electively included.

Participants were defined as PCOS using international criteria (5), and as potential poor ovarian responders if they were of advanced age (i.e., ≥35 years) (6, 7), or had a basal level of serum follicle-stimulating hormone

(FSH) higher than 10 IU/L (8), or fulfilled both criteria. The indication for IVF was the lack of conception after 12 spontaneous or induced ovulatory cycles without any abnormality detected by standard investigations.

The specific exclusion criteria were age >45 years, basal FSH levels >30 IU/L, body mass index (BMI, kg/m^2) ≥30, organic pelvic disease, and/or abnormality of the partner's semen. Other exclusion criteria were previous or concurrent major medical illness, abuse of alcohol, and current or previous use of any drug with a hormonal/metabolic action (a washout period of at least 3 months was considered appropriate before enrollment). Women who intended to start a diet or a specific program of physical activity were also excluded.

Randomization

All patients were allocated randomly to two independent arms (metformin and placebo groups) by centralized computer software. The randomization process was made by using random permuted block to ensure that, at any point in the trial, roughly equal numbers of participants were allocated to two comparison groups. The block size was constant of four (i.e., two patients per treatment within each block of size four were constantly allocated). The random allocation sequence was concealed in a closed, dark envelope until the interventions were assigned (9). The clinicians, investigators, and patients remained blinded to the treatment assignment until the end of the study.

Protocol

The metformin group received metformin at a dosage of 500 mg three times daily, whereas the placebo group was treated with corn-flour placebo tablets (three tablets daily). The metformin and placebo tablets were identical in size, appearance, and taste. The drug and the placebo were packaged in the pharmacy of the Department of Obstetrics and Gynecology of the University of Catanzaro, and they were labeled according to participant number. Patients were instructed to take the tablets with their meals, starting 1 month before the beginning of controlled ovarian hyperstimulation (COH) and continuing until a positive pregnancy test or menstrual bleeding occurred.

In each patient, the COH consisted of a gonadotropin-releasing hormone agonist (GnRH-a) flare-up protocol with a personalized step-down gonadotropin regimen. In particular, leuprolide acetate (1 mg daily) was administered subcutaneously from day 3 of the spontaneous or progesterone-induced menstrual cycle until oocyte maturation. For the first 5 days, a daily starting dose of 300 IU of recombinant FSH was also given subcutaneously.

From day 6 of COH, patients were monitored every 3 days by serial transvaginal ultrasonography and serum assay of estradiol (E_2) levels, and the dose of recombinant FSH was adjusted in accordance with the ovarian response. Monitoring was performed daily when the follicles reached 15 mm in diameter. When at least three leading follicles with a mean diameter greater than 18 mm were present, 250 μg of recombinant human chorionic gonadotropin (hCG) was injected subcutaneously 24 hours after the last injection of recombinant FSH to complete the oocyte maturation.

The cycle was canceled if there was a low ovarian response or in patients at high risk of OHSS. A low ovarian response was considered to be indicated by the presence of fewer than three follicles with a diameter ≥14 mm after 10 days of recombinant FSH, or by failure to attain the criteria for administration of recombinant hCG. A high risk of OHSS was indicated by a serum E_2 value >4,000 pg/mL and/or >20 follicles with a mean diameter >10 mm on a day on which recombinant hCG was given. Patients were considered and defined to be poor responders when a cycle was canceled owing to a low ovarian response, or fewer than three oocytes were retrieved at pick-up.

Oocyte retrieval was performed by using vaginal ultrasonography 36 hours after injection of recombinant hCG. The retrieved oocytes were washed, and the mature oocytes were classified by an experienced biologist on the basis of the presence of a first polar body (metaphase II: MII oocytes). On the same day as oocyte retrieval, samples of follicular fluid were collected and stored for further analysis.

The MII oocytes were inseminated more than 4 hours after recovery with 10,000–20,000 motile spermatozoa and were incubated at a temperature of 37°C in 5% CO_2 in air. Fertilization was assessed 20 hours after insemination. The zygotes were scored using four grades (Z1 to Z4) according to the number of nucleolar precursor bodies, the presence or absence of a halo, and the alignment of the nuclei in relation to the polar bodies (10). Embryos that did not cleave after 24 hours were considered to be arrested. Two days after insemination, the embryos were graded according to standardized criteria based on percent fragmentation and cell counts (11), and up to three of the best-quality embryos were transferred into the uterus. The luteal phase was supported by natural progesterone (50 mg daily), injected intramuscularly. Serum β-hCG levels were assessed on day 14 after embryo transfer.

Assessments

At entry into the study, a case history was collected for each patient, and all patients underwent anthropometric measurements, clinical evaluation, collection of venous blood during the early proliferative phase (days 2 to 3) of spontaneous or progesterone-induced withdrawal uterine bleeding for metabolic and hormonal assessments, and pelvic ultrasonography (including ovarian size and morphology, and antral follicular count). At the end of the study, the reproductive results, safety, and compliance with the treatments were evaluated (12).

Statistical Analysis and Calculation of Sample Power

The primary end point of the current clinical trial was the rate of cancellation due to low ovarian response. One goal of the proposed study was to test the null hypothesis that the cancellation rate due to low ovarian response was lower in the metformin group. The criterion for statistical significance (alpha) was set at 0.05. The test was two-tailed, which meant that an effect in either direction would be interpreted.

On the basis of our previous experience (13), the rate of cancellation of cycles due to low ovarian response in aged patients who undergo COH for IVF is approximately 0.17. A reduction of this incidence to 0.07 was assumed to be clinically relevant, and therefore we conjectured that administration of metformin should lead to an absolute decline of 0.10 in the cancellation rate for low ovarian response. Thus, we needed to enroll at least 165 patients in each arm to yield a statistically significant result with a power of 80%. To allow for an unpredictable number of withdrawals, we decided to enroll a total of 175 patients per arm in the expectation that at least 165 patients would remain. The power analysis and the calculation of sample size were performed using Sample Power, release 2.0 (SPSS, Inc.).

At study design, four interim analyses were planned, once every time 25% of the patients had completed their participation in the study. The Lan and DeMets spending function that approximates an O'Brien-Fleming boundary was used (14). At each interim analysis, the sample size was recalculated.

The data were analyzed using the per-protocol and the intention-to-treat (ITT) methods on the basis of treatment receipt and treatment assignment, respectively. For categorical variables, the Pearson chi-square or Fisher's exact test was performed, as appropriate. The normal distribution of continuous variables was evaluated with the use of the Kolmogorov-Smirnov test. Data were expressed as the median and interquartile range (IQR) with min–max values, and differences between groups were analyzed using the Mann-Whitney U test. A Cox proportional-hazards model was used to calculate the hazard risk and its 95% confidence interval (CI) for cancellation of cycles in patients who received metformin or placebo. The number needed to harm (NNH) was calculated for the cancellation rate and poor ovarian response (StatsDirect, release 2.4.3; StatsDirect Ltd.).

$P<0.05$ was considered statistically significant, and a trend was defined as $P \geq .05 < .09$. The Statistics Package for Social Science (SPSS 14.0.1, 18 Nov 2005; SPSS Inc.) was used for all statistical analyses.

RESULTS

Early Termination of Enrollment

The trial started in January 2009 and was stopped prematurely in October 2010 on the advice of the data safety and monitoring committee because of concerns about safety at the first interim analysis. Our final analysis involved the first 88 patients (44 for each arm) who had been enrolled and randomized. At the interim analysis, it was calculated that, if the study had continued to the planned enrollment of

330 patients, the probability of a poor response would have been greater than 48% in the metformin-treated group.

Clinical and Biochemical Data

Figure 1 shows the flow-diagram of the randomized controlled trial in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (9). The per protocol and ITT analyses were equivalent because there were no withdrawals from the study. After randomization, the two arms did not differ with respect to the main anamnestic, anthropometric, clinical, or biochemical data (Table 1).

The proportion was similar among the groups of women with hyperandrogenism: 19 of 44 (43.2%) versus 22 of 44 (50.0%) for the metformin and placebo groups, respectively (P=.139); oligoamenorrhea: 34 of 44 (77.3%) versus 36 of 44 (81.8%) for the metformin and placebo groups, respectively (P=.597); and polycystic ovaries: 39 of 44 versus 42 of 44 (95.5%) for the metformin and placebo groups, respectively (P=.237).

No statistically significant difference between the metformin and placebo groups was detected with respect to the distribution of patients who were aged ≥35 years (10 of 44 [22.7%] vs. 14 of 44 [31.8%], respectively), had a basal serum FSH level higher than 10 IU/L (4 of 44 [9.1%] vs. 3 of 44 [6.8%], respectively), or fulfilled both criteria (30 of 44 [68.2%] vs. 27 of 44 [61.4%], respectively) (P=.503). No statistically significant differences between groups were observed in relation to the mean ovarian size and antral follicular count (see Table 1).

Safety Data

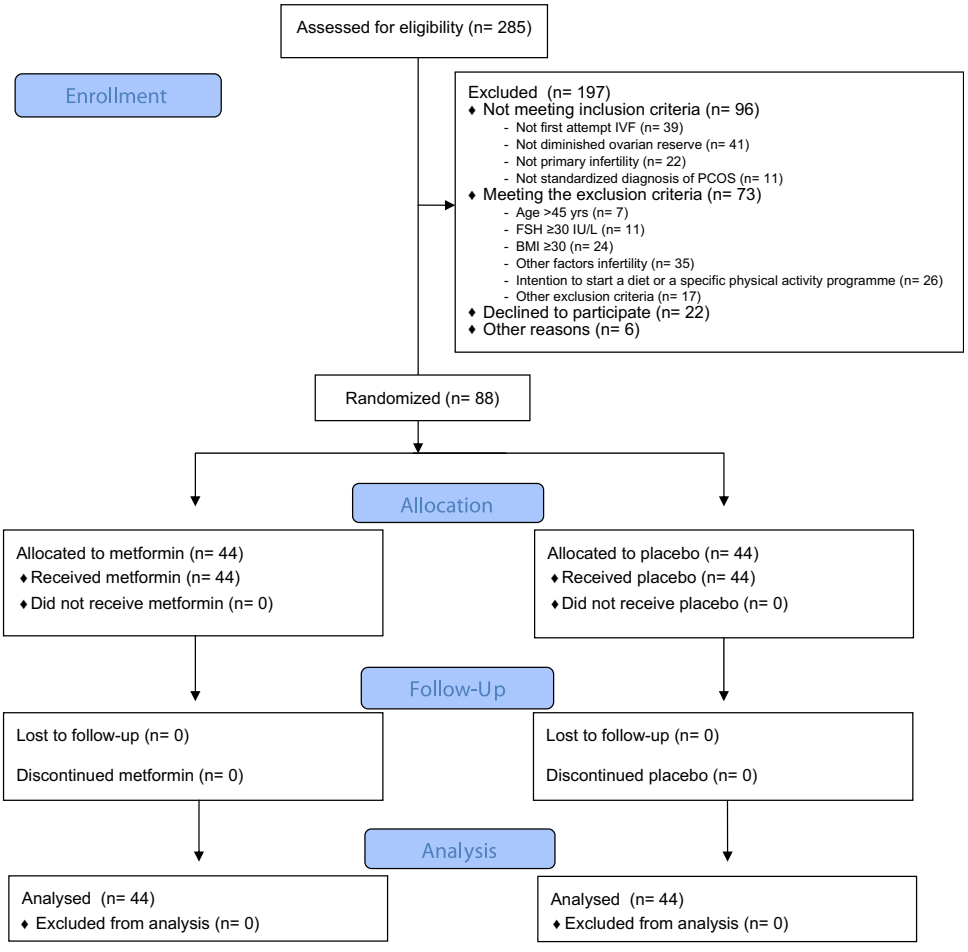
No patient discontinued the assigned treatment as a result of drug-related adverse experiences. In general, both metformin and the placebo were well tolerated, and only common minimal adverse experiences were reported. In particular, 10 of 44 (22.7%) and 3 of 44 (6.8%) patients from the metformin and placebo group, respectively, reported gastrointestinal symptoms (P=.036).

Reproductive Data

Table 2 shows the reproductive results obtained in the two groups. The rate of canceled cycles tended to be higher in the metformin than in the placebo group: 13 (29.5%) of 44 and 6 (13.6%) of 44, respectively (P=.089). In all cases, the cycles were canceled as a result of a low ovarian response; no cycle was canceled because of a high risk of

FIGURE 1

Flow diagram of the randomized controlled trial according to the CONSORT guidelines (9). The reason for which the single exclusion causes exceed the total number is that each subject could have more than one exclusion causes.



Palomba. Metformin in PCOS and reduced ovarian reserve. Fertil Steril 2011.

TABLE 1

Effect of metformin on ovarian response to gonadotropins for in vitro fertilization treatment in patients with polycystic ovary syndrome and reduced ovarian reserve: main anthropometric, clinical, and biochemical data.

Groups	Metformin (n = 44)	Placebo (n = 44)
Age (y)	40 (4.8; 31–42)	39 (5; 30–43)
Duration of infertility (mo)	27 (5; 13–38)	30 (6; 14–37)
BMI (kg/m^2)	25.4 (6.0; 18.5–29.7)	26.0 (6.5; 17.9–29.6)
WHR	0.85 (0.06; 0.72–1.1)	0.84 (0.14; 0.75–1.4)
Ferriman-Gallwey score	11.4 (4; 8–19)	12.0 (5; 8–22)
FSH (IU/L)	12.0 (3.9; 4.2–17.6)	11.0 (4.0; 2.0–11.0)
LH (IU/L)	16.5 (4.0; 6.0–19.0)	17.0 (3.9; 4.6–20.0)
E_2 (pg/mL)	56.4 (26.5; 33.4–88.0)	57.2 (20.0; 34.2–79.1)
P (ng/mL)	1.5 (0.5; 1.0–2.2)	1.4 (0.6; 0.9–1.8)
17-OHP (μg/L)	5.6 (1.5; 2.6–6.8)	5.5 (1.7; 2.8–6.9)
PRL (ng/mL)	7.2 (3.0; 5.3–12.0)	7.0 (4.0; 5.1–12.5)
TSH (μU/mL)	2.5 (1.3; 0.8–4.3)	2.3 (1.4; 0.7–4.5)
T (ng/mL)	5.0 (3.5; 2.5–7.7)	5.0 (2.4; 3.0–7.5)
A (ng/mL)	6.3 (1.5; 3.0–7.2)	6.2 (1.8; 3.4–7.7)
DHEAS (ng/mL)	2,679.5 (544.0; 2,408.1–3,009.4)	2,621.0 (520.3; 2,308.7–3,125.6)
SHBG (nmol/L)	27.0 (11.5; 18.0–37.6)	27.5 (12.0; 18.1–38.4)
FAI (%)	19.5 (8.2; 9.5–34.8)	20.2 (6.9; 10.3–33.0)
Fasting glucose (mmol/L)	4.7 (1.0; 2.9–5.9)	4.9 (0.9; 3.1–5.7)
Fasting insulin (μU/mL)	27.0 (12.5; 15.2–52.3)	26.8 (15.3; 14.7–49.9)
Ovarian size (cm^3)	12.5 (4.0; 6.7–15.4)	12.3 (4.5; 6.3–15.0)
Total AFC (no.)	13.5 (5.0; 0–21)	14.0 (6.0; 0–24)

Note: Data expressed as median (IQR; range). Data are not statistically significantly different between two groups. 17-OHP = 17α-hydroxyprogesterone; A = androstenedione; AFC = antral follicle count; BMI = body mass index; DHEAS = dehydroepiandrosterone sulfate; E_2 = 17β-estradiol; FAI = free androgen index; FSH = follicle-stimulating hormone; IQR = interquartile range; LH = leuteinizing hormone; P = progesterone; PRL = prolactin; SHBG = sex hormone–binding globulin; T = testosterone; TSH = thyroid-stimulating hormone; WHR = waist-to-hip ratio.

Palomba. Metformin in PCOS and reduced ovarian reserve. Fertil Steril 2011.

the development of OHSS. The hazard risk for cancellation of a cycle for low ovarian response under metformin treatment was 1.52 (95% CI, 0.96–2.21). Considering the cancellation of a cycle for low ovarian response as a treatment-related event, the NNH was 7 (range: 7–70).

The rate of poorly responding patients was statistically significantly higher in the metformin group than in the placebo group: 19 of 44 (43.2%) and 9 of 44 (20.5%), respectively (P=.022). In particular, in 16 of 44 (36.4%) and 7 of 44 (15.9%) patients in the metformin and placebo groups, respectively, COH produced fewer than three periovulatory follicles on a day on which recombinant hCG was given (P=.029). In 3 of 44 (6.8%) and 2 of 44 (4.5%) patients in the metformin and placebo groups, respectively, fewer than three oocytes were retrieved at pick-up (P=.680). The hazard risk for poor ovarian response under metformin treatment was 1.63 (95% CI, 1.08–2.41). Considering the poor ovarian response as a treatment-related event, the NNH was 5 (range: 3–32).

In no case, 0 of 44 (0.0%), from the metformin group and in two cases, 2 (4.5%) of 44, from the placebo group a mild degree of OHSS developed (P=.247). No patients required hospital admission. The doses of gonadotropins used (P<.001) and the duration of ovarian stimulation (P=.071) were higher in the metformin than in the placebo group, although statistical significance was not obtained for the latter parameter.

Statistically significant differences between groups were observed with respect to the peak levels of E_2 (P=.001) and the numbers of dominant follicles (P=.002), retrieved oocytes (P=.009), and MII oocytes (P=.017). No further statistically significant differences in reproductive data were detected between the two groups.

DISCUSSION

To the best of our knowledge, ours is the first randomized controlled trial to investigate the effect of metformin on a specific subgroup of PCOS women with reduced ovarian reserve. The optimal management of infertile women with PCOS who are scheduled for IVF remains under debate (15). Traditionally, PCOS is considered to be related to an exaggerated ovarian response; as a consequence, several methods have been proposed to reduce the risk of OHSS and multiple pregnancy. On the other hand, recommendations are totally lacking regarding the management of infertile patients with PCOS and diminished ovarian reserve.

A representative sample of patients who fulfilled the diagnostic criteria for PCOS (5), were at their first attempt of IVF, and had predictors of a potential poor response to ovarian stimulation were enrolled. In this regard, even though the concept of a poor prognosis has varied greatly among studies (8, 16, 17), we chose to use two accredited and easy applicable criteria to select our sample: advanced female age and/or high basal serum FSH levels (8). Further biochemical and morphologic markers of the ovarian response to IVF have been proposed in infertile women (8, 16, 17), but their clinical value in PCOS is not completely known. In fact, markers such as antimüllerian hormone (AMH) and antral follicular count are deeply influenced by the ovarian size and morphology, which are impaired in a large proportion of PCOS patients. In our study, 88.6% and 95.5% of the patients in the metformin and placebo arms, respectively, had polycystic ovaries (5). However, during initial ultrasonographic assessment, we evaluated the antral follicular count that confirmed the lack of difference between groups.

TABLE 2

Effect of metformin on ovarian response to gonadotropins for in vitro fertilization treatment in patients with polycystic ovary syndrome and reduced ovarian reserve: reproductive results.

Groups	Metformin (n = 44)	Placebo (n = 44)	*P* value
Stimulation length (d)	13 (4; 9–15)	11 (4; 9–14)	.071
Gonadotropins dose (IU)	3,900 (1,462.5; 1,835–4,200)	2,400 (1,656; 2,100–4,125)	<.001
Dominant follicles on day of ovulation triggering (no.)	4 (4; 1–10)	6 (4; 2–12)	.002
Cancellation rate (no., %)	13/44 (29.5)	6/44 (13.6)	.089
Peak E_2 levels on day of ovulation triggering (pg/mL)	480.0 (503.8; 124.3–1,200)	733.5 (342.5; 230–1,400)	.001
Retrieved oocytes (no.)	3 (3.5; 0–8)	5 (4; 1–10)	.009
MII oocytes (no.)	2.3 (1.5; 0–6)	4 (2.5; 1–7)	.017
Fertilization rate (no., %)	157/205 (76.6)	248/328 (75.6)	.798
Zygote quality (no., %)			.659
Z1	72/157 (45.9)	99/248 (39.9)	
Z2	40/157 (25.5)	57/248 (23.0)	
Z3	29/157 (18.5)	53/248 (21.4)	
Z4	16/157 (10.2)	39/248 (15.7)	
Cleaved embryo quality (no., %)			.766
Grade 1	65/157 (41.4)	85/248 (34.3)	
Grade 2	33/157 (21.0)	64/248 (25.8)	
Grade 3	32/157 (20.4)	49/248 (19.8)	
Grade 4	14/157 (8.9)	30/248 (12.1)	
Grade 6	13/157 (8.3)	20/248 (8.1)	
Transferred embryos (no. per fertilized oocytes, %)	61/157 (38.9)	92/248 (37.1)	.722
Implantation rate (no. per transferred embryos, %)	26/61 (42.6)	34/92 (37.0)	.482
Clinical pregnancy rate (no. per started cycles, %)	13/44 (29.5)	16/44 (36.4)	.496
Ongoing pregnancy rate (no. per started cycles, %)	11/44 (25.0)	14/44 (31.8)	.637
Multiple pregnancies rate (no. per pregnancies, %)	1/12 (8.3)	2/15 (13.3)	.742
Live-birth rate (no. per started cycles, %)	12/44 (27.3)	13/44 (29.5)	.816

Note: Data expressed as number and percentage and analyzed with the Pearson chi-square test or the Fisher's exact test, or as median and interquartile range (IQR) with min-max values and analyzed using the Mann-Whitney *U* test. E_2 = 17β-estradiol; MII = metaphase 2.

Palomba. Metformin in PCOS and reduced ovarian reserve. Fertil Steril 2011.

The rate of cancellation due to low ovarian response was our primary end point, and we designed our randomized controlled trial under the hypothesis that metformin should lead to a 10% reduction in this end point. It was anticipated that a sample of 330 subjects would be required to obtain a power of 80%.

The most noteworthy finding of the present clinical trial was the increased rate of poor response to gonadotropins under metformin treatment. The first interim analysis revealed an incidence of poor response of 43.2% under metformin. In addition, metformin increased the risk of a poor ovarian response to 63%, with a NNH of 7. For this reason, after 25% of the anticipated patients had been enrolled, the trial was stopped because of concerns about safety that were raised at the first interim analysis. At the same time, the sample size recalculation was performed considering a difference of 16% in the primary end point. In this regard, considering the sample size at the first interim analysis, we obtained a poststudy power of 96% for cancellation rate due to poor response.

In our trial, metformin decreased the ovarian response to gonadotropins without affecting the quality of the embryos or the main reproductive results, including the live-birth data. In particular, patients who received metformin tended to have a higher rate of canceled cycles and a slightly higher risk of cycle cancellation than the placebo group, and metformin increased the overall rate and the hazard risk for a poor response significantly. In addition, the dose of gonadotropin used was increased, whereas the peak level of E_2 and the number of dominant follicles, retrieved oocytes, and MII oocytes were decreased under metformin.

The role of metformin with respect to the improvement of embryo quality, implantation, and the rate of miscarriage is supported by the preliminary data (18), but it remains controversial. Here we detected no effect of metformin on rates of fertilization, implantation, and miscarriage, or on the quality of the zygote/cleaved embryo, transferred embryos (19) or on pregnancy, multiple pregnancy, OHSS, or live-birth rates (3).

Currently, the mechanisms that underlie the decreased response to gonadotropins that is induced by metformin in potential low responders can be only hypothesized. The effects on the ovary that are induced by metformin have been explained in terms of the improvement in systemic metabolism that is related to the use of metformin. However, this has never been confirmed in experimental studies (4). An increasing number of papers have been published in recent years that demonstrate a direct effect of metformin on the ovary (4). Published data (2, 3) seem to suggest that metformin acts to regulate the ovarian response to exogenous gonadotropins, improving the environment of the ovary through local actions on ovarian steroidogenesis (20–22), and on autocrine/paracrine insulin-related signaling (23–27). In fact, two main mechanisms have been proposed: improvement of ovarian resistance to insulin and reduction of intrafollicular androgen levels.

In a recent experimental study (28) we found that metformin exerts effects on insulin-like growth factors (IGFs) and IGF-binding proteins (IGFBPs), as suggested previously by Stadtmauer et al. (29). In theory, this activity can block the synergic action of FSH and IGF on granulosa cells (28), which is the basis of the

effectiveness of growth hormone (GH)/GH-releasing factors in poor responders (16, 29). On the other hand, given that androgens enhance the expression of FSH receptors on granulosa cells (30, 31) and can be used to prime ovaries before IVF (32, 33), the reduction in androgen levels that is induced by metformin could contribute to the low response to stimulation. Finally, less well-tested hypotheses suggest that metformin affects other factors that modulate the ovarian response and serve as a sensitive marker of IVF outcomes, such as leptin (34), antimüllerian hormone (35, 36), and vascular endothelial factors (37).

In conclusion, our findings, although limited to infertile PCOS patients with reduced ovarian reserve, demonstrate that metformin worsens the ovarian response to gonadotropins administered for IVF programs. On the basis of the current data, we can advise clinicians about metformin use in infertile patients with PCOS who are scheduled for gonadotropin COH when is suspected or confirmed a reduced ovarian reserve. In these patients, the coadministration of metformin with gonadotropins should be avoided, or it should be stopped before the start of treatment to avoid an unjustified increase in the risk of a poor ovarian response.

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