Reproductive Sciences
2019, Vol. 26(10) 1336-1342

DOI: 10.1177/1933719118765985
journals.sagepub.com/home/rsx
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Impact of Metformin on IVF Outcomes in Overweight and Obese Women With Polycystic Ovary Syndrome: A Randomized Double-Blind Controlled Trial

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Abstract

Objectives: To evaluate the impact of metformin on in vitro fertilization (IVF) outcomes in overweight and obese women with polycystic ovary syndrome (PCOS). **Methods:** This was a randomized double-blind placebo-controlled study (ClinicalTrials.gov: NCT 02910817) carried out in a University IVF Center. The study included 102 overweight and obese women (body mass index [BMI] >24 kg/m^2) with PCOS who underwent their first fresh autologous IVF-embryo transfer cycle and agreed to participate in the study. The study participants were randomized into 2 groups: metformin group received metformin (1000 mg per day) at the start of controlled ovarian stimulation (COH) until the day of the pregnancy check, and placebo group received placebo tablets in the same duration. The primary outcome measure was the total number of retrieved oocytes. **Results:** Both groups were homogenous in baseline demographic characteristics. Metformin group versus the placebo group demonstrated decrease in the mean number of the retrieved oocytes (9.06 $\pm$ 4.23 vs 16.86 $\pm$ 8.3, $P < .01$) and similar live birth rate (LBR; 25.5% vs 17.6%, $P = .34$). The number of fertilized oocytes was lower in the metformin group (5.65 $\pm$ 2.66 vs 9 $\pm$ 4.55, $P < .01$). However, the fertilization rate was similar in both groups (62.3% vs 53.4%, $P = .10$). There was no difference in the implantation rate (15.7% vs 11.8%, $P = .32$), multiple pregnancy rate (13.4% vs 3.9%, $P = .08$), or miscarriage rate (23.5% vs 35.7%, $P = .46$). No cases of ovarian hyperstimulation syndrome (OHSS) were observed in both groups. **Conclusion:** Short-term administration of metformin to overweight or obese women with PCOS undergoing IVF decreased number of the retrieved oocytes but did not improve the LBR.

Keywords

metformin, polycystic ovary syndrome, obesity, overweight, in vitro fertilization

Synopsis

Metformin use could decrease the number of retrieved oocytes in overweight and obese women with polycystic ovary syndrome undergoing IVF.

Introduction

Polycystic ovary syndrome (PCOS) is the most frequent cause of anovulatory infertility in women of reproductive age, accounting for about 10% prevalence.[1] The women with PCOS may have some metabolic and reproductive abnormalities including insulin resistance (IR) with hyperinsulinemia.[2] Patients are diagnosed to have PCOS, according to Rotterdam criteria, when 2 of the following are present: chronic oligo-ovulation or anovulation, clinical or biochemical hyperandrogenism, and ultrasound polycystic ovaries.[3] The primary mechanism of infertility in PCOS is chronic anovulation, and in vitro fertilization (IVF) is considered the last resort for some women with PCOS.[4] Infertile anovulatory women with PCOS should have trials for ovulation induction to achieve pregnancy, passing by weight reduction, clomiphene citrate (CC), and gonadotropin's minimal stimulation before attempting IVF trial.[5]

Obesity and IR are frequent features of PCOS. It is estimated that 88% of the obese women with PCOS are insulin resistant.[6-8] The IR which occurs more frequently in

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overweight and obese women with PCOS is suggested to be associated with compromised infertility management such as CC resistance and adverse fertility outcomes.[9,10]

Insulin-sensitizing agents, such as metformin, have been used to improve insulin sensitivity and reduce hyperinsulinemia with subsequent reduction in the ovarian hyperandrogenism associated with PCOS.[11,12] Metformin, a biguanide medication, is the first line to treat obese patients with non-insulin-dependent diabetes mellitus.[13] Metformin mostly acts through suppression of hepatic gluconeogenesis and enhancing the peripheral glucose uptake, thereby decreasing circulating insulin concentrations.[14]

Several studies investigated the effects of metformin administration in PCOS, and the results are still conflicting.[8,15] Some of them demonstrated that metformin co-treatment in women with PCOS was associated with reduced number of retrieved oocytes and better fertilization and pregnancy rates.[15] In contrary to that, Stadtmauer et al could not find a significant difference when they used metformin co-treatment with regard to the number of retrieved oocytes, fertilization, and pregnancy rates.[16] A worldwide survey could not find any clear evidence to support the use of metformin in improving IVF outcomes in women with PCOS.[17]

The most common side effects recorded with metformin therapy are gastrointestinal disturbances such as nausea or diarrhea. Gradual administration of metformin, according to the severity of symptoms, can be used to adjust and to minimize the possible side effects.[18]

The PCO is the most known risk for an exaggerated response to controlled ovarian stimulation (COH). The COH in women with PCOS may result in a significant number of follicles with a higher risk of ovarian hyperstimulation. However, a large number of the retrieved oocytes can be immature.[19] Metformin can be used as an adjuvant in PCOS to decrease the risk of ovarian hyperstimulation syndrome (OHSS) because of its effect in reducing the ovarian androgens.[20,21]

The ASRM/ESHERE consensus recommended restricting the use of metformin to women with glucose intolerance.[4] However, it is recorded that metformin has commonly been administrated as a co-treatment with COH in women with PCOS who undergo IVF.[22] It is not yet clear which group will benefit from metformin administration during IVF cycle.

In the current study, we hypothesize that metformin may improve IVF outcomes in the overweight and obese women with PCOS by reducing the IR and hyperandrogenism. Therefore, the study aims to evaluate the impact of metformin on IVF outcomes in overweight and obese women with PCOS.

Materials and Methods

Study Type, Setting, and Duration

The current study was a randomized double-blind controlled trial (Clinical Trials. Gov: NCT 02910817) conducted in a University IVF Center during the period from January 1, 2015, to December 31, 2016. The institutional ethical review board approved the study, and we obtained a written informed consent from all participants before enrollment.

Study Population

The study participants were recruited from the IVF center. All women who attended the center for first planned fresh embryo transfer IVF cycles were invited to participate in the study. We included women with PCOS who were less than 39 years, overweight, and obese with body mass index (BMI) >24 kg/m^2. They were diagnosed as having PCOS according to Rotterdam criteria,[3] by the finding of at least 2 of the following: basal ultrasound polycystic ovary (12 or more follicles ranging from 2 to 9 mm), hyperandrogenism (clinical and biochemical), and anovulation or oligoovulation (less than 9 ovulatory cycles per year). All patients had normal thyroid-stimulating hormone (TSH), prolactin, and day 3 follicular-stimulating hormone (FSH) levels.

Exclusion criteria were diabetes mellitus, renal or liver disease, documented tubal factor or pelvic adhesions, elevated 17α hydroxyprogesterone level, and FSH more than 10 IU/mL. We also excluded the women who started program or medications to reduce their weight and those whose partners had abnormal semen parameters according to the World Health Organization parameters (WHO, 2010).[23] Hysterosalpingography or office hysteroscopy was performed to confirm normal uterine cavity, and we excluded the patients with uterine abnormalities.

Sample Size

In a retrospective data analysis conducted by Stadtmauer et al, metformin improved the clinical pregnancy rate (CPR) 21/30 (70%) compared to CPR in the placebo group 9/30 (30%).[16] Based on these results, the sample size was calculated using the G power program at a statistical significance 0.05 and power 90%. The estimated sample size in each group was 51 women.

Randomization

The randomization was done by computer-generated random table. Eligible women who gave their informed consent were randomized to either group I (metformin group) or group II (placebo group). Allocation concealment was done using serially numbered closed opaque envelopes. Each envelope was labeled with a serial number and had a card noting the intervention type. Allocation never changed after opening the closed envelopes.

Study Intervention

The eligible women were allocated to either group I (metformin group) received 2 tablets of metformin 500 mg (Cidophage, Chemical Industries Development Co, Egypt) or group II (placebo group) received 2 placebo tablets with the same shape, color, and consistency. This dose was decided according to our

experience and practice as well as the expected tolerance of the patients to metformin avoiding the reported adverse effects. The patients and the attending physicians did not know the assigned group. We instructed the patients to have 2 tablets per day (morning and evening) starting from the date of COH until the day of pregnancy check (14 days starting from the embryo transfer day). If pregnancy test was positive, the patient was instructed to continue having the medication during the first 12 weeks of gestation in both groups.

The IVF Protocol

Patients were kept on low-dose oral contraceptive pills (OCPs) containing 0.03 mg of ethinylestradiol and 3 mg of drospirenone (Yasmin, Bayer Schering Pharma, Germany), for at least 2 weeks. We downregulated the pituitary using GnRH agonist 0.5 mg/day (Lupron, Rameda pharmaceutical, Egypt). We instructed the women to stop taking OCPs after 4 days of Lupron overlap. With the start of menstruation (Lupron menstruation), the patients had a basal ultrasound examination to exclude the presence of ovarian cyst and to evaluate the endometrial thickness.

We started COH using recombinant FSH (r-FSH) (Gonal-F Merk Serono Pharmaceutical, Egypt) on the third day of menstruation, and since then, the GnRH-agonist dose was reduced to 0.25 mg per day. The starting dose of FSH was 150 IU, which was increased, decreased, or not changed according to the ovarian response on day 5 of the start of COH.

In both groups, monitoring with ultrasound examination and E2 levels were initiated on day 5 of COH. According to the ovarian response, we started to step up or step down of the gonadotropin dose. We continued patients monitoring using transvaginal ultrasound and estradiol level (E2) at least every other day or every day in some patients according to the ovarian response to the COH. Human chorionic gonadotropin (Choriomon, IBSA Pharmaceutical, Egypt) 10 000 IU was administered when 4 leading follicles were at least 15 to 17 mm mean diameter.

Oocyte retrieval under general anesthesia was performed 36 hours after hCG administration. The intracytoplasmic sperm injection (ICSI) was performed in all the mature oocytes 6 hours after the retrieval. We transferred the best quality cleavage stage embryos (day 3 embryos). We standardized the number of the embryos transferred to the patient enrolled in the study to 3 (the best 3 cleavage stage embryos). The luteal phase was supported by intramuscular progesterone (Protogest, IBSA Pharmaceutical, Egypt) 25 mg twice daily.

After 14 days counting from the day of ET, we assessed the serum hCG levels and the pregnant women were instructed to continue having the study medication until the end of the first 12 weeks of pregnancy in both groups. We remeasured the serum hCG levels 48 hours later in the women with positive hCG to early predict ectopic pregnancy and early exclusion of pregnancy loss. After 4 weeks starting from the hCG check day, the patients were examined by transvaginal ultrasound to confirm the presence of cardiac pulsation and to exclude the possibility of higher rate pregnancies. Serum b-hCG was assessed 14 days after ET.

Study Outcomes

The primary outcome of the study was the number of retrieved oocytes (total number of retrieved oocytes regardless its maturity). The secondary outcomes included the fertilization rate (defined as the number of the fertilized oocytes divided by the total number of the retrieved oocytes per 100), number of embryos (the number of the fertilized, 2pn oocytes), implantation rate (defined as the total number of the sacs divided by the total number of the transferred embryos per 100), CPR (defined as the number of the cases with at least on sac in or out the uterus divided by the cycles initiated per 100), miscarriage rate (the number of the cases with miscarriage divided by the number of clinical pregnancies per 100), and LBR (defined as the total number of the cases with at least 1 baby born after 24=weeks of gestation divided by the total number of the cycles initiated per 100). The miscarriage was defined as pregnancy loss within 12 weeks of gestation starting from the day of oocyte fertilization.

Statistical Analysis

The data were collected and entered into a Microsoft Access database and then analyzed using the Statistical Package for Social Science (SPSS Inc, Chicago, Illinois, version 21). The outcome variables were calculated using Student t test. For dichotomous variables, chi-square was used to estimate the significance value. For analysis, $P < .05$ was considered to be significant.

Results

One hundred and twelve women were approached to participate in the study. Ten women have been excluded: 5 of them had associated tubal or male factor infertility and 3 women had medical diseases. Moreover, 2 women declined participation in the study. We randomly assigned the remaining 102 women into both groups (Figure 1, the study flowchart).

Both groups were homogenous in baseline demographic characteristics with no significant differences in mean age, body mass index, and duration of infertility (Table 1).

Table 2 summarizes the cycle and ovarian stimulation clinical data before oocytes retrieval in both groups. They were similar in the terms of antral follicular count (AFC), serum FSH, luteinizing hormone (LH), prolactin, and TSH. There were no significant differences in the total gonadotropin doses used in COH in both metformin and placebo groups (1708.1 ± 533.42 vs 1856.69 ± 761.63, $P = .23$). When compared to the placebo group, the estimated estradiol level on the day of the hCG trigger was significantly lower in the metformin group (2109.22 ± 817.75 vs 2965.88 ± 1517.30, $P < .01$).

Table 3 compares reproductive IVF outcomes between both groups. There were no canceled cycles in both groups. In

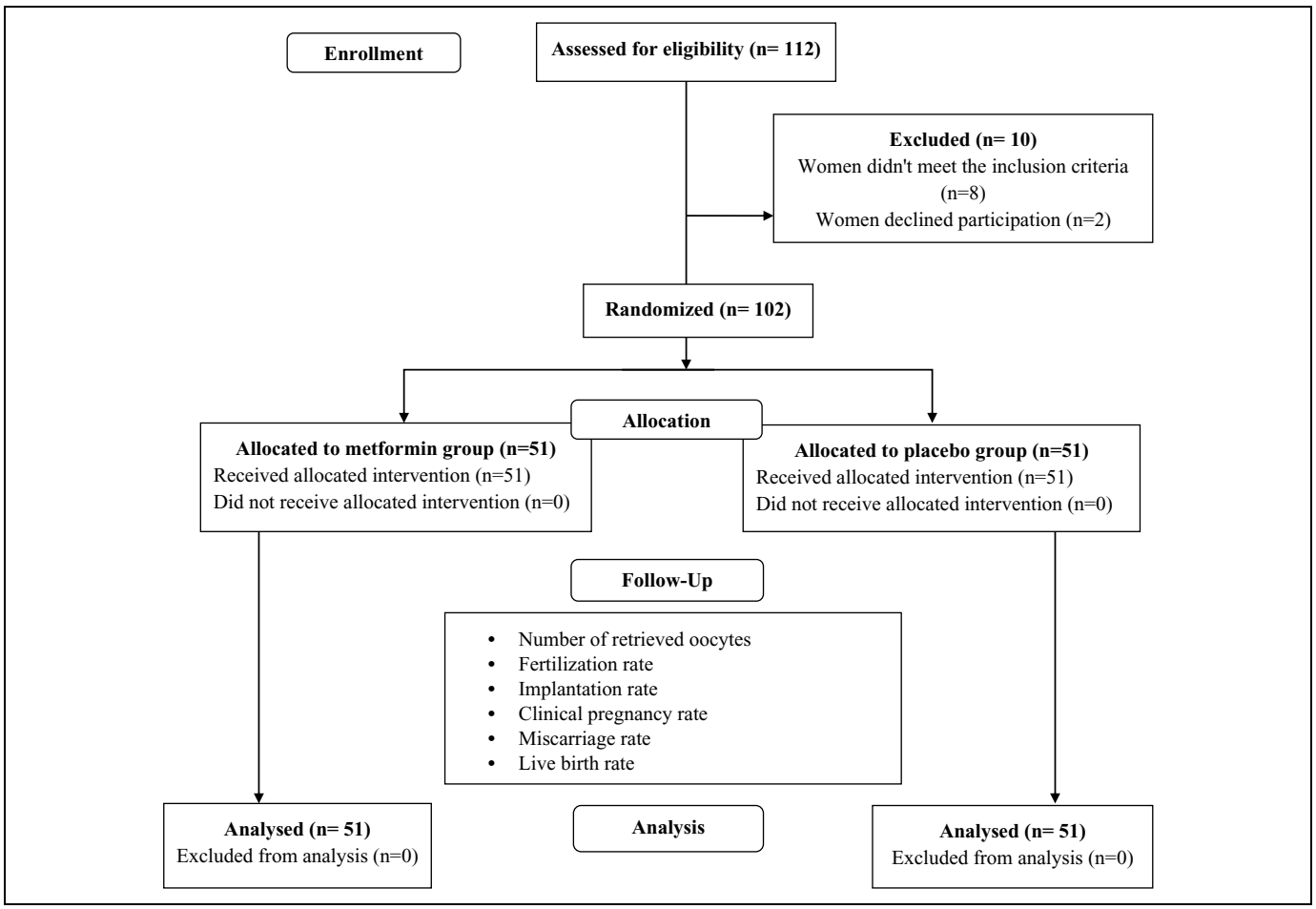

Figure 1. The study flowchart.

comparison with the placebo group, women who received metformin had statistically significant lower total number of retrieved oocytes (9.06 ± 4.23 vs 16.86 ± 8.30, $P < .01$) and fertilized (2pn) oocytes (5.65 ± 2.66 vs 9 ± 4.55, $P < .01$). The fertilization rate was higher in the metformin group, but this did not reach a statistical significance (62.3% vs 53.4%, $P = .10$).

Despite transferring an equal number of embryos to every case, there was no statistically significant difference in the implantation and the multiple pregnancy rates between both groups. Moreover, no significant differences could be detected between both groups regarding CPR, miscarriage rate, or LBR.

Table 1. The Baseline Characteristics of the Study Participants.[a]

Characteristics	Metformin Group (n = 51)	Placebo Group (n = 51)	*P* Value
Age (years)	31.1 ± 3.7	31.89 ± 3.6	.61
BMI (kg/m^2)	33.8 ± 4.4	32.9 ± 6.7	.11
Duration of infertility (years)	2.5 ± 1.1	2.79 ± 1.4	.38

Abbreviation: BMI, body mass index.
[a]All data are presented as mean ± standard deviation.

Discussion

To the best of our knowledge, the present study is the first randomized placebo-controlled study evaluating the effects of short-course metformin co-treatment in overweight and obese women with PCOS undergoing IVF. We demonstrated that metformin coadministration during COH in overweight and obese women with PCOS was associated with a significant decrease in the number of retrieved oocytes along with reduced number of fertilized oocytes.

We did not find any significant impact of metformin on implantation, multiple pregnancies, fertilization, miscarriage, clinical pregnancy, and LBRs. We suggest that metformin administration during IVF cycles in the prospective hyperresponsive patients does not have beneficial effects in the overweight and obese women with PCOS.

Our patients were overweight and obese with PCOS, and so it is expected that they have a high prevalence of IR along with hyperinsulinemia.[6,24] Metformin, an insulin-sensitizing agent, has been widely used in the treatment of PCOS to lower insulin and blood sugar levels since IR and hyperinsulinemia play a

Table 2. Cycle Clinical Data Before Oocyte Retrieval in Both Study Groups.[a]

Variables	Metformin Group (n = 51)	Placebo Group (n = 51)	*P* Value
Basal E2 (pg/mL)	25.16 ± 17.8	23.59 ± 8.4	.57
Total AFC	34.35 ± 13.77	30.43 ± 16.89	.21
FSH (mIU/mL)	6.59 ± 1.95	6.05 ± 2.06	.18
LH (IU/L)	7.44 ± 2.11	7.63 ± 2.74	.85
PRL (ng/mL)	12.84 ± 5.64	10.08 ± 5.51	.14
TSH (μU/mL)	1.51 ± 0.81	1.79 ± 0.78	.21
Peak E2 (pg/mL)	2109.22 ± 817.75	2965.88 ± 1517.30	<.001[b]
Total gonadotropin dose	1708.1 ± 533.42	1856.69 ± 761.63	.23

Abbreviations: E2, estradiol; AFC, antral follicle count; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone.
[a]All data are presented as mean ± standard deviation.
[b]Statistically significant difference.

Table 3. The Primary and Secondary Outcomes of the Study in Both Groups.

Variables	Metformin Group (n = 51)	Placebo Group (n = 51)	*P* Value
Number of retrieved oocytes[b]	9.06 ± 4.23	16.86 ± 8.3	<.01[a]
Number of fertilized (2pn) oocytes[b]	5.65 ± 2.66	9 ± 4.55	<.01[a]
Fertilization rate (%)	(288/462) 62.3	(459/860) 53.4	.10
CPR (%)	(17/51) 33	(14/51) 27.5	.52
Implantation rate (%)	(24/153) 15.7	(18/153) 11.8	.32
Miscarriage rate (%)	(4/17) 23.5	(5/14) 35.7	.46
Multiple pregnancy rate (%)	(7/51) 13.4	(2/51) 3.9	.08
LBR (%)	(13/51) 25.5	(9/51) 17.6	.34

Abbreviations: Pn, pronuclear; CPR, clinical pregnancy rate; LBR, live birth rate.
[a]Statistically significant difference.
[b]Data are presented as mean ± standard deviation.

central role in the pathology of PCOS. However, the effects of metformin on the IVF outcomes are still questionable.[25] Some investigators have recommended restricting the administration of metformin in PCOS to women with glucose intolerance, but many practicing clinicians do not agree with this recommendation.[4,26]

De Leo et al conducted a prospective trial using 1700 mg of metformin for 6 months and suggested that metformin improved ovulation and hyperandrogenic symptoms in the obese young women with PCOS.[27] In the present study, metformin was used as a co-treatment during COH and continues to cover the period of expected implantation, and the pregnant women were instructed to keep having the study medication for 12 weeks of gestation. We are aware of the differences and heterogeneity of women with PCOS. We restricted the study population to the overweight and obese women with PCOS. However, we did not determine the IR status of the study participants.

The findings of our study are in partial similarity with the study of Kjotrod et al[28] and Tso et al[29]; however, our study population is more homogenous as we only studied the metformin impact on the overweight and obese women with PCOS. Kjotrod et al used a dose of 1000 mg twice daily for 16 weeks prior to IVF to normalize the endocrinal changes with PCOS and demonstrated that the metformin did not improve the fertilization rate, implantation rate, CPR, or LBR; our study supports these results.[28] Tso et al conducted a systematic review of 9 RCTs with 816 women with PCOS and found metformin did not improve the LBR.[29]

In contrary to our findings, Tso et al concluded that metformin improved the CPR. We could not find any significant impact of metformin on the CPR in our study. In opposition to our results, Tang et al[30] in an RCT found that the short-term co-treatment with metformin did not affect the ovarian stimulation but significantly improved the CPR and the LBR. However, in Tang's trial,[30] the patients had average BMI 26.9 to 27.9 which does not correspond well with the overweight and obese patients in our study.

Our findings demonstrate that triggering estradiol level, the total number of retrieved oocytes, and the total number of embryos are significantly lower in the metformin-treated women. Metformin could decrease the triggering estradiol level through 2 ways: reducing the number of nonperiovulatory follicles and reducing the E2 secretion by periovulatory follicles. The lower E2 level could decrease the cancellation rates of IVF cycles as a result of OHSS. There were no differences of total gonadotropins used in COH in both groups. Palomba et al in a double-blinded RCT concluded that metformin co-treatment in women with PCOS was associated with significant decrease in the triggering estradiol level and the cancellation rates. However, Palomba's team did not find a significant difference in the total number of retrieved oocytes or the total number of embryos.[21]

In another RCT, Palomba et al aimed to evaluate the effect of metformin on the IVF outcome in PCOS women with poor ovarian reserve, and similar to our finding, they concluded that metformin worsens the ovarian response to COH in the expected poor ovarian reserve participants with PCOS. The working team decided to early terminate the study due to the unexpected reduction in the number of the retrieved oocytes in the metformin-treated group.[22] This is comparable to the significant decrease in the retrieved oocytes that we found in the present study.

Despite the significant decrease in the total retrieved oocytes in the metformin-treated group, there was no significant improvement in fertilization rate. In partial agreement with our results, several studies documented improved fertilization rate in the women with PCOS when treated with metformin for IVF indicating the impact of metformin on improving the oocyte quality and the fertilization.[16,28,31] We expected an increase in fertilization rate because of the better

quality oocytes; however, the improved fertilization rate in our study did not reach statistical significance.

We did not find significant improvement in the implantation rate, clinical pregnancy, or miscarriage rates in the metformin-treated group. Similar results were found by Costello et al in a systematic review that included 8 RCTs to evaluate the effects of metformin coadministration in patients with PCOS who underwent IVF cycles.[25] They did not find differences in the CPR in the women treated with metformin. A more recent systematic review, done by Palomba et al, found similar results regarding the pregnancy rate after they had included 10 RCTs. However, in contrary to our study, they found the miscarriage rate was reduced and the implantation rate was improved in the metformin-treated patients.[32] This could be related to the miscarriage rate that was positively affected by use of higher doses >1000 mg daily, a longer duration of pretreatment, and delaying the stopping time of metformin intake.

Reports on the efficacy of metformin coadministration in the obese women with PCOS are still conflicting and debatable. In the present study, we did not find significant improvement in the overweight and obese women with PCOS regarding the IVF outcomes. However, we can recommend metformin as an adjuvant drug during COH in the prospective hyperresponders, as it can reduce the number of retrieved oocytes, thus preventing the ovarian hyperresponse. In the future studies, data about IR and follicular fluid androgens should be collected to determine the specific woman with PCOS who will benefit from metformin as an adjuvant treatment.

In conclusion, short-term administration of metformin to overweight or obese women with PCOS undergoing IVF decreased the number of the retrieved oocytes but did not improve the LBR. Our study suggests that the prospective hyperresponsive overweight and obese women with PCOS will not benefit from short-term metformin administration regarding the IVF outcomes.

Authors' Note

S. Abdalmageed involved in protocol development, data management, and manuscript writing. TA. Farghaly, AA. Abdelaleem, AE. Abdelmagied, and MK. Ali participated in data collection and manuscript editing. AM Abbas contributed to data management and manuscript writing.

Acknowledgments

We thank the clinical and laboratory team in Assiut University IVF Center.

Declaration of Conflicting Interests

The author(s) declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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