Al-Azhar International Medical Journal

Volume 4 | Issue 10 Article 37

2023

Section: Obstetrics and Gynecology

First Trimester Metformin in Polycystic Ovary Syndrome Patients with History of Recurrent Early Pregnancy Loss: Randomized Controlled Trial

Farid Ibrahim Hassan
Department of Obstetrics and Gynecology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt.

Muhamed Ahmed Abdelmoaty
Department of Obstetrics and Gynecology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt.

Ahmed Hamdy Muhammed Saad
Department of Obstetrics and Gynecology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt., ahmedobg2019@gmail.com

How to Cite This Article

Hassan, Farid Ibrahim; Abdelmoaty, Muhamed Ahmed; and Saad, Ahmed Hamdy Muhammed (2023) "First Trimester Metformin in Polycystic Ovary Syndrome Patients with History of Recurrent Early Pregnancy Loss: Randomized Controlled Trial," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 10, Article 37.
DOI: https://doi.org/10.58675/2682-339X.1975

ORIGINAL ARTICLE

First-trimester Metformin in Polycystic Ovary Syndrome Patients with History of Recurrent Early Pregnancy Loss: Randomized Controlled Trial

Ahmed Hamdy Mohamed Saad*, Muhamed Ahmed Abdelmoaty, Farid Ibrahim Hassan

Department of Obstetrics and Gynecology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Background: **Women with polycystic ovarian syndrome (PCOS) who take metformin throughout their pregnancies have lower rates of miscarriage, labour, and foetal development restriction. Positive benefits of metformin on insulin sensitivity, plasma glucose concentration, and lipid profile have been shown in patients with polycystic ovary syndrome.**

Aim and objectives: **To the disparity in the occurrence of miscarriage between two patient cohorts who will get or not receive Metformin in the first trimester, to determine the efficacy of Metformin in preventing early pregnancy loss in pregnant patients with PCOs.**

Subjects and methods: **This was a randomised controlled trial that was conducted on 100 recently pregnant PCO patients at the Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, from January 2022 to November 2022.**

Result: **Group A had a much lower EPL rate than Group B.**

Conclusion: **In conclusion, Pregnant women with polycystic ovary syndrome who took metformin consistently during the first trimester had significantly lower rates of miscarriage. Patients accepted it well and experienced little negative effects. However, more research is needed to determine its impact on subsequent pregnancy problems and foetal outcomes.**

Keywords: Early pregnancy loss, Insulin resistance, Metformin, Polycystic ovary syndrome

1. Introduction

Depending on the criterion used, 1−2% of reproductive-aged women experience recurrent miscarriage. Nevertheless, accurate estimates are difficult to establish due to limited data availability.[1] Obesity, insulin resistance, and persistent inflammation have all been linked to polycystic ovarian syndrome (PCOS). Significant barriers to establishing a pregnancy in women with PCOS include poor endometrial receptivity and repeated implantation failure.[2]

Females of childbearing age are disproportionately affected by polycystic ovary syndrome (PCOS), this population's most common endocrine disorder.[3]

Type 2 diabetes mellitus may be managed by the biguanide metformin. It's been prescribed more often than any other antihyperglycemic drug. Mechanism of action involves lowering glucose synthesis within the body, especially in the liver.[4]

Metformin, one of several insulin-sensitizing medicines, has been proven to decrease testosterone levels, leading to normalised ovulation and decreased miscarriage. Previous studies have indicated metformin's positive effects, but it remains unclear if the drug can be safely used throughout pregnancy.[5]

By restoring ovulation, correcting infertility, preventing pregnancy loss, and lowering pregnancy-induced problems, metformin can improve

Accepted 25 May 2023.
Available online 22 January 2024

* Corresponding author at: Department of Obstetrics and Gynecology, Faculty of Medicine for Boys, Al-Azhar University, Resident of Obstetrics and Gynecology, Cairo, Egypt.
E-mail address: ahmedobg2019@gmail.com (A.H.M. Saad).

https://doi.org/10.58675/2682-339X.1975

reproductive abnormalities amongst females afflicted with PCOS. It was reported that continuing metformin during pregnancy is healthy and decreases first-trimester miscarriage from 64% to 5% without teratogenicity. Metformin usage may decrease the risk for early pregnancy loss by decreasing estrogen concentration and improving insulin sensitivity[6]

2. The study's overarching objective

To Determine Whether Metformin Has Any Effect on Reducing Pregnancy loss in pregnant PCO patients via a contrast of two patient cohorts who will or will not get it in the first trimester.

3. Patients and methods

This research was a randomized controlled study and included 100 pregnant women who were already diagnosed to have polycystic ovary syndrome and complained of recurrent early pregnancy loss. The participants were categorized in half, the first group (A) included 50 women who were on metformin treatment in a daily dose of 1000 mg, and treatment continued till 12 weeks of gestation, and women in the second group (B) 50 women serve as a control group. Women were selected from those who attended the outpatient clinic or inpatient ward of the Department of Obstetrics and Gynecology, at Al-Hussein university Hospital. From January 2022 to November 2022.

3.1. Inclusion criteria

Maternal age of 25–30, Patients who have had recurrent early pregnancy loss which is defined as loss of two or more consecutive pregnancies, Women with polycystic ovary syndrome who become pregnant, Diagnosis of PCOS before pregnancy and treatment with metformin based on Rotterdam criteria with at least two of the following three criteria will be fulfilled, Recently positive pregnancy test (Pregnancy is verified by a transvaginal ultrasound scan and a serum beta human chorionic gonadotropin level of 50 IU/l. Pregnancy occurred while on metformin therapy in group (A).

3.2. Exclusion criteria

Other type of abnormal pregnancy. (Blighted ovum, Ectopic pregnancy, vesicular mole), Other medical disorders like D.M, thyroid, Heart disease, systemic lupus erythematosus, rheumatoid arthritis, amyloidosis, atherosclerosis and antiphospholipid syndrome, Any uterine anomaly as excluded by transvaginal ultrasound scanning (unicornuate or bicornuate, submucous fibroid), Pregnant women after IVF, Uses of anticoagulant drugs, Not only do aberrant parental blood karyotypes increase the likelihood of a miscarriage, but so do other risk factors.

3.3. A standard set of tests was administered to every patient

Detailed history: including personal history and past history, obstetric history, history of last menstrual period (LMP), medical and surgical history, and previous history of miscarriage. **Clinical examination:** including (Maternal Body Maa Index (BMI) was calculated and Hyperandrogenism signs).

Routine investigation in the first trimester: Complete blood count (CBC, ABO and Rh typing). **Randomization and allocation**: 100 Patients who met the needs were randomly divided into two categories using a computer-generated random sequence list (1:1). After that, we split everyone up into two groups: **Group A (Metformin group):** It contains 50 pcos women who became pregnant while on metformin (Cedophage ® 500 mg, CID pharma, Egypt) in a daily dose 1000 mg per day during the first trimester together with folic acid. **Group B (Placebo group):** it contains 50 pcos women who became pregnant and receive only folic acid.

Follow-up: Follow-up of both groups was carried out at 8th and 12th week gestation and thereafter routine ANC visits until delivery.

4. Results

Table 1.

Based on the data in the table, we can conclude that there is no statistically significant difference in age parity or body mass index between the groups (Table 2, Fig. 1).

Table 1. Demographic characteristics distribution between the two groups.

Variables	Group A ($n = 50$)	Group B ($n = 50$)	t	P
Age (years) Mean ± SD	28.52 ± 3.6	29.88 ± 5.35	1.49	0.139
Parity Mean ± SD	2.08 ± 0.976	2.17 ± 1.03	MU 249	0.622
BMI (kg/m^2) Mean ± SD	27.03 ± 2.68	26.45 ± 2.29	0.543	0.592

Table 2. Primary outcome distribution between the two groups.

Variables	Group A ($n = 50$)	Group B ($n = 50$)	χ^2	P
EPL	5 (10%)	13 (26%)	**4.34**	**0.037**

The table above demonstrate that the EPL rate was significantly lower in group A compared to group B (Table 3).

This table shows that gestational diabetes, gestational hypertension, and preeclampsia incidences were lower in group A compared to group B, but statistically significant was found only in gestational diabetes (Table 4, Fig. 2).

This table shows that neonatal outcomes Group A had lower levels, on average, than Group B, but the difference was not statistically significant (Fig. 3 Table 5).

This table shows that the most common side effects were nausea & vomiting (40%) followed by heartburn (34%).

5. Discussion

Polycystic ovarian syndrome is the leading reason for female infertility in the United States, affecting 5-10percentage of reproductive-age women. Patients who suffer from polycystic ovary syndrome have a higher chance of miscarriage following both natural and medicallyassisted conception. Women with polycystic ovaries or polycystic ovarian syndrome, the risk of miscarriage in the first trimester was three times higher, defined as miscarriage during the first trimester, compared to the rate of 10–15% observed in retrospective studies for normal women.[7]

Type 2 diabetes mellitus can be treated with the biguanide metformin. It's been prescribed more often than any other antihyperglycemic drug. The reduction of liver glucose synthesis is crucial to its mechanism of action. Women of childbearing age who have polycystic ovary syndrome and have not

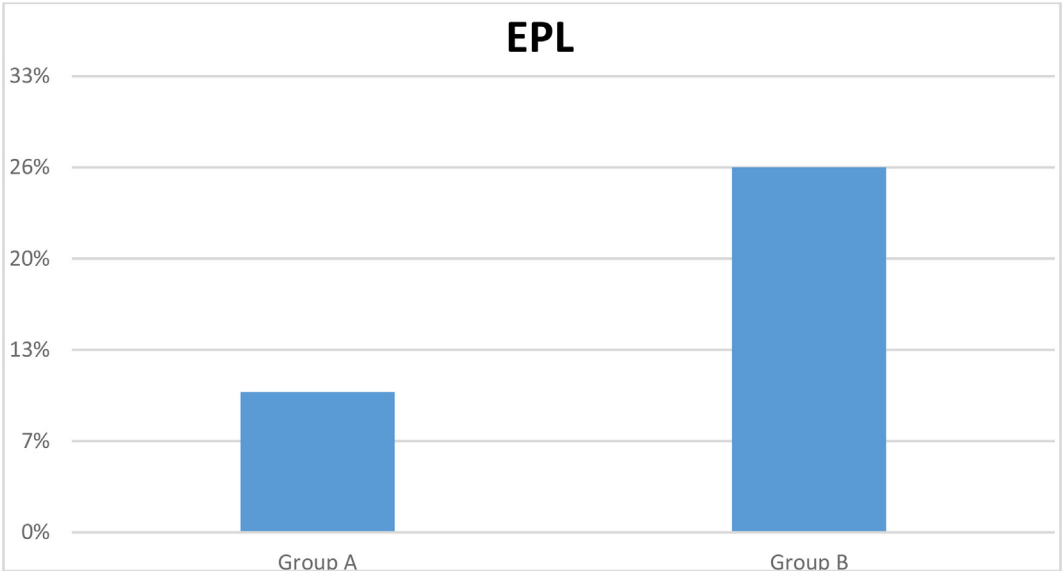

Fig. 1. Rate of early pregnancy loss between the two groups.

Table 3. Secondary outcome distribution between the two groups.

Variables	Group A ($n = 50$)	Group B ($n = 50$)	χ^2	P
Gestational diabetes	6 (12%)	14 (28%)	4	0.046
Gestational Hypertension	5 (10%)	8 (16%)	0.796	0.372
Preeclampsia	2 (4%)	5 (10%)	1.38	0.240

Table 4. Neonatal outcome distribution between the two groups.

Variables	Group A ($n = 50$)	Group B ($n = 50$)	χ^2	P
Prematurity	3 (6%)	4 (8%)	0.154	0.695
Macrosomia	2 (4%)	3 (6%)	0.211	0.646
IUGR	3 (6%)	5 (10%)	0.544	0.461
APGAR at 5 min < 7	4 (8%)	5 (10%)	0.122	0.727
Anomalies	0	1 (2%)	1.01	0.317

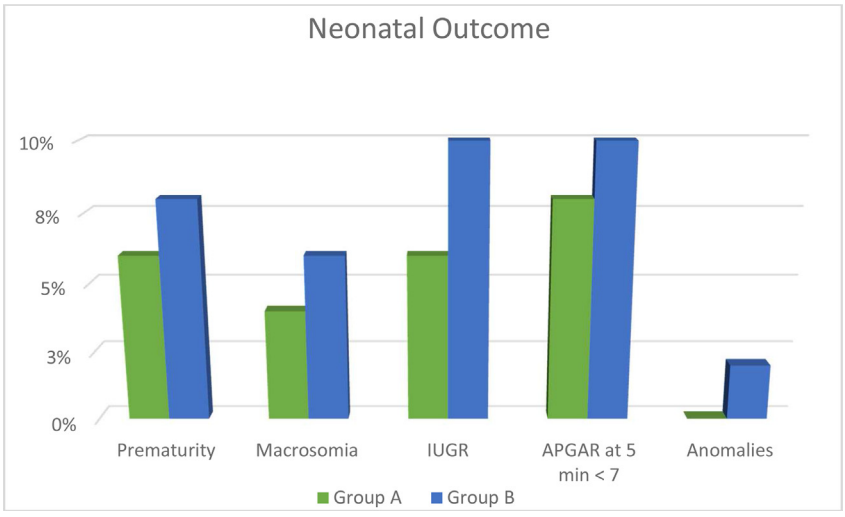

Fig. 2. Neonatal outcome distribution between the two groups.

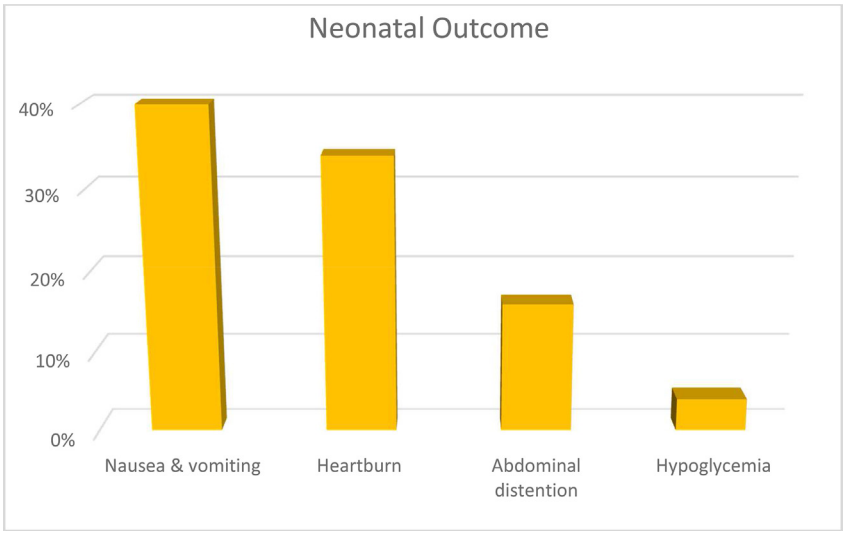

Fig. 3. Side effects distribution among the metformim group.

responded to ovulation-inducing medications like clomiphene may benefit greatly from taking metformin[8].

By statistical analysis, we determined that neither group differed significantly from the other in terms of age, parity, or body mass index (BMI), and that the mean SD for group A was 28.52 3.6 years and for group B it was 29.88 5.35 years.

Table 5. Metformin side effects distribution among Metformin group.

Variables	Group A (n = 50)
Nausea & vomiting	20 (40%)
Gastric irritation (heartburn, discomfort, … …)	17 (34%)
Abdominal distention	8 (16%)
Hypoglycemia	2 (4%)

In line with our findingsAccording to the research by Jakubowicz et al.,[9] 48 of the 65 women who took metformin had already given birth at least once, whereas 17 were unable to have children. Age, parity, and BMI were not statistically different across groups, and none of the women had taken metformin during their prior pregnancies.

Liu et al.[10] found that of the 65 women who used metformin, 48 had a history of at least one past pregnancy and 17 were nulliparous. Metformin was not used by any of the women in any of their prior pregnancies. Sixty-two live births and fifty-three miscarriages were recorded among the seventy-five pregnancies had by the 48 Metformin-treated females who had previously given birth. Twenty-one of the thirty-one women in the groups of the control

condition had a record of at least one previous pregnanc, whereas ten were nulliparous. There were a total of 24 pregnancies among the 21 women in the control group, 11 of which led to successful pregnancies and healthy babies, for a miscarriage rate of 54.2%. Within that study, age had also been supplied, with a mean SD of 29.5 3.7 years for group A and 30.1 1.9 years for group B.

Patient PCOS is associated with a higher risk of having an unfavourable pregnancy outcome, however, there is now incongruity in the research on the mechanisms that contribute to this. Age, weight, and use of IVF are all examples of potential dangers.[11] The clinical manifestations of polycystic ovary syndrome (PCOS) in patients are quite variable.

In the study on our hands, we found that the incidence of EPL was 5 (10%) in group A, and was 13 (26%) in the control group.

The percentage of EPLs was much lower in Group A than in Group B.

Researchers **Hussein** et al.[4] showed that giving Metformin to pregnant women in the first trimester significantly lowered the miscarriage rate. Pregnancy losses as a percentage of the total that started using Metformin dropped to 10.8%, but it was 42.2% in the group that stopped taking Metformin (p 0.05). Significantly more people in the Metformin group experienced adverse effects like nausea, vomiting, gastric irritation, and flatulence than in the other group (15.1% vs. 38.1%), but no serious side effects were reported (i.e.: lactic acidosis).

Sohrabvand et al.[12] conducted a similar trial with three groups totaling 75 pregnant women with PCOS. When pregnancy was detected, Group A patients immediately stopped using metformin (500 mg TDS) (5–6 weeks gestation) Metformin was given to Group B till 8 weeks gestation and Group C until 12 weeks. Miscarriage rates decreased from 40% in Group B to 8% in Group C, and from 32% to 4% in Group C, indicating a statistically significant difference between prior and current pregnancies. Although Group A had a far lower miscarriage rate (from 20% to 4%), The size of the sample was insufficient to draw any firm conclusions.

Although all three conditions were shown to be less common in group A than in group B, the difference was only statistically significant for gestational diabetes.

Women in Group A had a somewhat lower risk of developing gestational hypertension than women in Group B, according to the results of this study (p value: 0.372). **Abd El Hameed** et al.[13] found a similar result, albeit without statistical significance, reporting that metformin users had a decreased rate of developing gestational hypertension than those who did not take the drug. Preeclampsia occurred in fewer women in the metformin group than in the placebo group (3.0% vs. 11.3%; odds ratio, 0.24; 95% confidence range, 0.10 to 0.61; $P = 0.001$).

Conclusions of the incidence of GDM was nearly twice as high in the group B of women who stopped taking metformin compared to the group A of women who maintained metformin medication, 14 (28%) versus 6 (12%) with a p value of 0.046. **Ainuddin** et al.[14] revealed that while just 1 patient in the metformin group (4.6%) acquired GDM, 9 patients in the no metformin group (40.9%, 0.004) did. Those who did not take metformin were found to have a fourfold higher risk of developing GDM compared to those who did.

While it's true that women with PCOS are at a higher risk for developing GDM than healthy women, metformin was linked to a reduction in the incidence of GDM in women with PCOS that was roughly 10 times greater than that seen in women without PCOS.[15]

Metformin has been shown in numerous trials to decrease the occurrence of gestational diabetes, preeclampsia, and foetal macrosomia.

According to Khattab et al.,[16] Metformin's effectiveness in reducing the occurrence of type 2 diabetes and preeclampsia in women with PCOS is encouraging.

Metformin use during pregnancy was linked to and perhaps responsible for a decline that is nine times greater (30–3.44%) in GDM in women with PCOS.[17]

In keeping with previous studies, **Zeng** et al.[18] found a precipitous drop in the frequency of negative pregnancy complications such gestational diabetes and hypertension.

According to the results of this study, newborn outcomes were reported to be poorer in group A compared to group B, despite the fact that no statistically significant difference existed between the two groups.

The risk of preterm birth, macrosomia, IUGR, foetal hypoxia (Apgar score 7), and congenital anomalies was slightly reduced in women who continued metformin therapy throughout the first trimester of pregnancy compared to women who discontinued taking metformin during the first trimester.

The incidence of neonatal growth deficits, congenital abnormalities, and admission to the neonatal critical care unit compared to the control group were lower in the metformin group, or lower in the metformin-treated group, according to a study by **Diamanti-Kandarakis** et al.[19] **Gilbert** et al.[20] agreed that there was no proof that using metformin in the first trimester increased the

incidence of serious abnormalities. Metformin is beneficial for both the mother and the developing child when taken before pregnancy in women with PCOS and continued until term. This includes a decrease in maternal complications such as type 2 diabetes, hypertension, and premature labour (lowering rates of miscarriage and foetal development restriction). Exposure to metformin during pregnancy has lasting consequences for the child's brain development, which remain mostly unknown. At 9 years, there appeared to be no significant difference between the metformin and insulin groups with regard to body fat, visceral adipose tissue, or liver fat, suggesting that the MiG TOFU had no effect.

Body-mass-index increases in metformin-exposed kids may, on the other hand, be indicative of an elevated risk of childhood obesity. However, the results are not easily interpreted due to the low follow-up rate. Long-term investigations that begin with the children of women participating in the obesity trials will help shed light on this question.[21]

The metformin group had 62 live births, as shown by **Daniela** et al.[9] There were 53 full-term births and 8 preterm births (37 weeks). All of the newborns were healthy and of suitable size for their gestational ages. Achondrodysplasia was the only foetal anomaly seen in a single full-term delivery. Eighteen live births occurred among the non-experimental group. Twelve were full-term births, and six were premature. In the group given the placebo, there were no birth defects.

Based on the results of this study, dizziness and headache were the least prevalent adverse effects, with nausea and vomiting (40%) and heartburn (34%).

According to **Lord** et al.,[22] the results were consistent across studies. Most participants dropped out of one study due to stomach pain. No severe adverse events were reported during the trials.

5.1. Conclusion

Conclusion Continued use of metformin in the first trimester of pregnancy by women with polycystic ovary syndrome was linked with a significantly lower incidence of early pregnancy loss. Patients reported minimal, manageable adverse effects. In order to fully understand its impact on future pregnancy problems and foetal outcomes, however, larger research are necessary Fig. 2.

Authorship

Ll authors have a substantial contribution to the article.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Conflicts of interest

The authors declared that there were NO conflicts of Interest.

References

1. Woolner AM, Raja EA, Bhattacharya S, Danielian P, Bhattacharya S. Inherited susceptibility to miscarriage: a nested case-control study of 31,565 women from an intergenerational cohort. *Am J Obstet Gynecol*. 2020;222, 168–e1.
2. Albaghdadi AJ, Kan FW. Therapeutic potentials of low-dose tacrolimus for aberrant endometrial features in polycystic ovary syndrome. *Int J Mol Sci*. 2021;22:2872.
3. Kalyanaraman R, Pal L. A narrative review of current understanding of the pathophysiology of polycystic ovary syndrome: focus on plausible relevance of vitamin D. *Int J Mol Sci*. 2021;22:4905.
4. Hussein I, Abdel Shafy AH, Awwad H. The role of metformin for prevention of first trimesteric miscarriage in women with polycystic ovary syndrome: a randomized controlled trial. *Evidence Based Women's Health J*. 2020;10:72–78.
5. Al-Biate MA. Effect of metformin on early pregnancy loss in women with polycystic ovary syndrome. *Taiwan J Obstet Gynecol*. 2015;54:266–269.
6. Ibrahem BS, El Syokar AA, Ossman AM, El-Saba TM. Incidence of early pregnancy loss in poly cystic ovary syndrome patients with/without metformin therapy: a comparative study. *J Adv Med Med Res*. 2020;32(24):55–62.
7. Clowse M, Fischer-Betz R, Nelson-Piercy C, et al. Pharmacovigilance pregnancy data in a large population of patients with chronic inflammatory disease exposed to certolizumab pegol. *Ther Adv Musculoskelet Dis*. 2022;14, 1759720X221087650.
8. Johnson NP. Metformin use in women with polycystic ovary syndrome. *Ann Transl Med*. 2014;2:6.
9. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metabol*. 2002;87:524–529.
10. Liu X, Han Y, Wang X, et al. Serum anti-Müllerian hormone levels are associated with early miscarriage in the IVF/ICSI fresh cycle. *BMC Pregnancy Childbirth*. 2022;22:279.
11. Helvaci N, Yildiz BO. Polycystic ovary syndrome and aging: health implications after menopause. *Maturitas*. 2020;139:12–19.
12. Sohrabvand F, Shariat M, Haghollahi F, Bagheri B. Effect of metformin on miscarriage in pregnant patients with polycystic ovary syndrome. *W Indian Med J*. 2009;58:433.
13. Abd El Hameed AA, Shreif HE, Mowafy HE. The role of continuing metformin therapy during pregnancy in the reduction of gestational diabetes and improving pregnancy outcomes in women with polycystic ovary syndrome. *Middle East Fertil Soc J*. 2011;16:204–208.
14. Ainuddin JA, Kazi S, Aftab S, Kamran A. Metformin for preventing gestational diabetes in women with polycystic ovarian syndrome. *J Coll Phys Surg Pak*. 2015;25:23741.
15. Glueck CJ, Wang P, Kobayashi S. Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. *Fertil Steril*. 2002;77:520–525.
16. Khattab S, Mohsen IA, Aboul Foutouh I, et al. Can metformin reduce the incidence of gestational diabetes mellitus in pregnant women with polycystic ovary syndrome? Prospective cohort study. *Gynecol Endocrinol*. 2011;27:789–793.
17. Begum MR, Khanam NN, Quadir E, et al. Prevention of gestational diabetes mellitus by continuing metformin

therapy throughout pregnancy in women with polycystic ovary syndrome. *J Obstet Gynaecol Res*. 2009;35:282–286.
18. Zeng XL, Zhang YF, Tian Q, Xue Y, An RF. Effects of metformin on pregnancy outcomes in women with polycystic ovary syndrome: a meta-analysis. *Medicine*. 2016;95:36.
19. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. *Eur J Endocrinol*. 2010;162: 193–212.
20. Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertil Steril*. 2006;86:658–663.
21. Abdelhameid AA, Helal KF, Abohashem MF, Minshawy A, Abdel-Moneim M. Effects of metformin on pregnancy outcomes in women with polycystic ovary syndrome during first trimester. *The Egyptian J Hosp Med*. 2021;82:558–564.
22. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ*. 2003; 327:951.