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Original Article (Pages: 11383-11392)

Investigating the Impact of Metformin Consumption on the Incidence of Gestational Diabetes and Preeclampsia in Pregnant Women Suffering Polycystic Ovary Syndrome: A Clinical Trial Study

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Abstract

Background

Women with polycystic ovary syndrome (PCOS) are at higher risk of developing pregnancy complications including gestational diabetes and preeclampsia. This study was performed with the aim of examining the impact of metformin on incidence of gestational diabetes and preeclampsia in pregnant women with PCOS.

Materials and Methods: In this clinical trial, 88 pregnant women with PCOS with a history of taking metformin referring to Fatemieh hospital in Hamedan, Iran in 2017-18 were randomly assigned into two groups: metformin consumption (1000-2000 mg/day) continuing throughout the pregnancy and control (stopping metformin consumption immediately after detection of pregnancy). The pregnancy and fetal consequences and complications were compared in both groups. The data were analyzed by STATA software version 14.0.

Results: In both groups, no significant difference was observed in terms of mean age, duration of infertility, body mass index, and baseline variables ($p>0.05$). The relative risk (RR) of incidence of gestational diabetes (RR: 1.97, 95% CI: 1.63 -2.39), preeclampsia (RR: 2.65, 95% CI: 1.95- 3.59), and abortion (RR: 2.33, 95% CI: 1.69 -3.22) was higher in the control group who did not continue metformin consumption throughout the pregnancy ($p<0.05$). The frequency of C-section was lower in the intervention group than in the control group ($p<0.05$).

Conclusion: Based on the results of the present study, continuation of metformin consumption in women with PCOS during pregnancy may be associated with decreased adverse consequences of pregnancy including gestational diabetes and preeclampsia.

Key Words: Metformin, Polycystic ovarian syndrome, Pregnancy.

*Please, cite this article as Alimohammadi Sh, Ghasemi E, Mohsenpour Z, Mohsenpour F. Investigating the Impact of Metformin Consumption on the Incidence of Gestational Diabetes and Preeclampsia in Pregnant Women Suffering Polycystic Ovary Syndrome: A Clinical Trial Study. Int J Pediatr 2020; 8(6): 11383-392. DOI: **10.22038/ijp.2020.45710.3737**

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Received date: Mar.17, 2019; Accepted date: Feb.12, 2020

1- INTRODUCTION

In 1935, for the first time Stein and Leventhal introduced polycystic ovary syndrome (PCOS) (1). PCOS is one of the common endocrine system diseases in women during reproductive ages, whose prevalence has been reported to be 5-10% in different studies, and is one of the important causes of infertility in women. The prevalence of this disease in our country has been estimated to be 7.1-14.6% (2). The criteria for diagnosis include oligomenorrhea or amenorrhea, elevated androgen levels, presence of polycystic ovary in ultrasonography (3, 4). The etiology of PCOS is still poorly understood. Nevertheless, genetic predisposition, increased insulin secretion, insulin resistance, elevated body mass index, as well as chemical and environmental contaminations are the possible causes of this disease (5).

Increased insulin resistance in women with PCOS may be because these women have a larger BMI. Alternatively, it may be due to elevated LH hormone in these patients (3). In this syndrome, the balance of sexual hormones is impaired; For example, testosterone, DHEA-S, and prolactin levels increase (6). Pregnant women with PCOS are at risk of developing gestational diabetes, preeclampsia, birthing a premature child, increased risk of mortality for the fetus, and the need of NICU for the baby born from these women (7). Pregnant women with PCOS may experience different risks during pregnancy; in the first trimester, these risks are abortion and congenital abnormalities of the fetus. On the other hand, in the second and third trimesters, the complications include impaired glucose tolerance test, gestational diabetes, hypertension, and preeclampsia (8, 9). Gestational diabetes (GDM) is the most common metabolic disorder throughout pregnancy, which is diagnosed during pregnancy (10). Prevalence of GDM differs across different societies, ranging between 1 and 14%. Pregnancy is associated with extensive anatomical and physiological changes; healthy pregnancy necessitates metabolic and hormonal balance, which fulfills the fetal needs during pregnancy (11). Preeclampsia is a pregnancy-specific syndrome, which can influence almost all organs of the body. Although it is far beyond simple gestational hypertension and proteinuria, protein discharge is still one of the most important criteria (12). Preeclampsia is still known as the most important disease in late pregnancy and is the main cause of mortality of pregnant mothers. It increases both mortality and morbidity for the mother and fetus, and its effects are contingent upon duration and severity of disease (13, 14). The drugs that lower the insulin level, by increasing insulin sensitivity, have provided an effective therapeutic method for the treatment of PCOS (15, 16). Metformin is an effective glucose-lowering drug, which reduces hepatic synthesis of glucose as well as its intestinal absorption (17).

The mechanism of action of metformin in enhancing insulin sensitivity is not fully understood. Nevertheless, it may increase the activity of adenosine monophosphate enzyme at the molecular level. Because of the high prevalence and complications resulting from this syndrome including impaired ovulation and menstruation, infertility, hirsutism, and metabolic disorders, PCOS has a special healthcare significance and incurs staggering financial costs to the healthcare system of the country. Nevertheless, there are disagreements over the cause and therapeutic measures for PCOS patients (18). The results of studies have shown that PCOS is associated with pregnancy complications such as gestational diabetes and possibly preeclampsia (7-9). The studies by Thatcher and Koren et al. indicated that metformin has considerable effects on treating PCOS patients as rate of

pregnancy increases. In addition, sustained consumption of metformin during pregnancy in the above studies revealed better pregnancy outcomes without any increase in fetal abnormalities (19, 20). Thus, investigation of pregnancy consequences during metformin treatment and comparison of its results with those who have stopped metformin consumption upon initiation of pregnancy seems to be essential. Also, demonstration of risk-freeness of metformin in terms of teratogenicity and complications during pregnancy can be an effective factor in creating assurance for both the physician and patient in using its considerable benefits. Since there is sparse information about the duration of metformin consumption during pregnancy and its possible impact on the fetus and course of pregnancy, this study was performed with the aim of examining the impact of metformin on incidence of gestational diabetes and preeclampsia in pregnant women with PCOS.

2- MATERIALS AND METHODS

2-1. Study design and population

This study is of clinical trial type. The sampling method in this study was consecutive sampling on pregnant women with PCOS referring to Fatemieh hospital, Hamedan from December 2018 to May 2019, who were also eligible to be included in the study. The sample size was based on previous studies (21) at confidence interval of 95% and statistical power of 80% using the following sample size formula for each of the studied groups (one control group and two intervention groups) was estimated as 44 and totally 88 subjects. The patients were randomly assigned into the two groups. Block randomization was used to randomize the assignment.

$$\overline{P} = \frac{P_1 + P_2}{2} = \frac{0.08 + 0.23}{2} = 0.155$$

$$n = \frac{\left[Z_{1-\alpha/2}\sqrt{2\overline{P}(1-\overline{P})} + Z_{1-\beta}\sqrt{P_1(1-P_1) + P_2(1-P_2)}\right]^2}{(P_1 - P_2)^2}$$

$$= \frac{[1.96\sqrt{2 \times 0.155 \times 0.845} + 0.842\sqrt{0.03 \times 0.97 + 0.23 \times 0.78}]^2}{(0.03 - 0.23)^2} = 44$$

2-2. Inclusion criteria

Inclusion criteria: diagnosis of PCOS before pregnancy based on Rotterdam 2003 criteria and confirmed by a physician, age over 18 and younger than 40 years, positive β-human chorionic gonadotrophin (β-hCG) with a live fetus. Rotterdam criterion includes presence of two out of three symptoms of no ovulation and oligoovulation, chemical or clinical symptoms of hyperandrogenism, and PCOS symptoms for diagnosing PCOS (22).

2-3. Exclusion criteria

Patients who previously had diabetes and received insulin, history of frequent abortion, uterus abnormalities, high parity, and age > 40 years, a history of chronic diseases such as lupus and kidney failure, and the patients' unwillingness to continue drug consumption during pregnancy constituted the exclusion criteria.

2-4. Intervention

A nursing specialist in the unit measured height, weight, body mass index (BMI), and waist-to-hip ratio of patients. The weight was measured by a digital balance made in Iran with an accuracy of 0.1 kg, while the height was measured by a tape meter in a standing position whereby the

heels and shoulders of the patient were fixed against the wall. BMI was calculated through the following formula: weight (kg) divided by height squared (m); the patients were categorized based on the BMI obtained. Note that all of the subjects in this study consumed metformin 3-6 months before pregnancy. The metformin receiving patients (Osveh Metformin, Company Name: Osveh, Iran) received it on a daily basis with a dose of 1000-2000 mg (one or two tablets) based on BMI until the end of pregnancy. However, in the other group, metformin consumption was stopped after becoming pregnant or eight weeks post pregnancy. The patients were recommended to take the drug with food to reduce its digestive side effects.

Next, the groups were investigated in terms of pregnancy complications and consequences including examination of gestational diabetes (through measuring blood glucose every three months as a laboratory diagnostic test) and preeclampsia (through clinical examination once every two weeks).

Preeclampsia was diagnosed after 20th week of pregnancy based on systolic pressure 140 mmHg or diastolic pressure 90 mmHg, proteinuria (protein equal to or higher than 300 mg in the 24-h urine or equal to 2+ and greater in urine test strip) (23), and gestational diabetes was diagnosed based on the American diabetes Association criteria, fasting blood sugar equal to or greater than 92 mg/dl, postprandial one-hour blood sugar equal to or greater than 180, and postprandial two-hour blood sugar level of 153 mg/dl (24).

2-5. Ethical consideration

Written informed consent form was taken from all subjects before participation. The data of the study were collected anonymously and the results were reported in general. The participants were free to quit the study at any time they desired. This study followed the standards of Declaration of Helsinki, and was registered in the website of clinical trial studies under the code of IRCT20120215009014N252.

2-6. Data Analyses

In this study, for data analysis, STATA 14 was used. Data description was performed using descriptive statistics through expressing the mean and standard deviation for quantitative variables as well as RATIO and percentage for qualitative variables. In order to compare the relationship between qualitative variables, chi-square test was employed to compare the incidence of GDM and preeclampsia in the two intervention groups through Poisson regression test. In addition, underlying variables in the two groups were analyzed through chi-square test. In order to compare the quantitative variables between the two groups, student t-test was employed. The statistical significance level was considered as less than 0.05.

3- RESULTS

In this study, 88 women with PCOS qualifying the inclusion criteria were enrolled in two 44-subject groups: one group (case) continued metformin consumption during pregnancy, while the second (control) stopped taking this drug from the first trimester, and they were compared with each other. Both groups were comparable to each other in terms of age, BMI, and duration of infertility, and were not significantly different ($p>0.05$).

The mean age of pregnancy in the intervention group was significantly higher in the metformin taking group than in the control (**Table.1 and Figure.1**). Out of the 44 patients in the control group, 39 (88.6%) had a pregnancy age of longer than 37 weeks, and out of 44 subjects in the intervention group, 41 had a pregnancy age longer than 37 weeks (**Figure.2**).

Table 1: Comparison of mean age, body mass index, gestational age and duration of infertility in case and control groups (n=88).

Variables	Metformin group	Control group	P-value (T-test)
Age, year, Mean± SD	31.4±4.4	30.5±4.6	0.380
BMI, (kg/m^2), Mean± SD	29.6±1.9	30.1±2.4	0.421
Duration of infertility, year, Mean± SD	4.7±1.1	4.91±0.8	0.200
Pregnancy age, week, Mean± SD	37.8±2.5	36.6±2.7	0.027

SD: standard deviation.

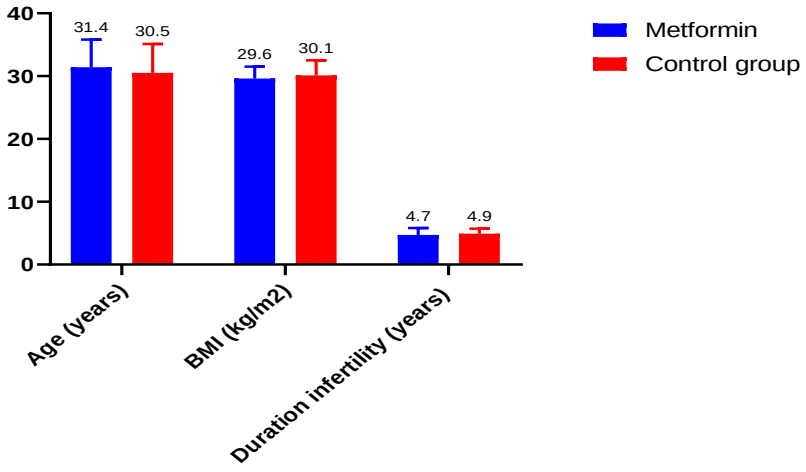

Fig.1: Comparison of mean baseline variables in case and control groups.

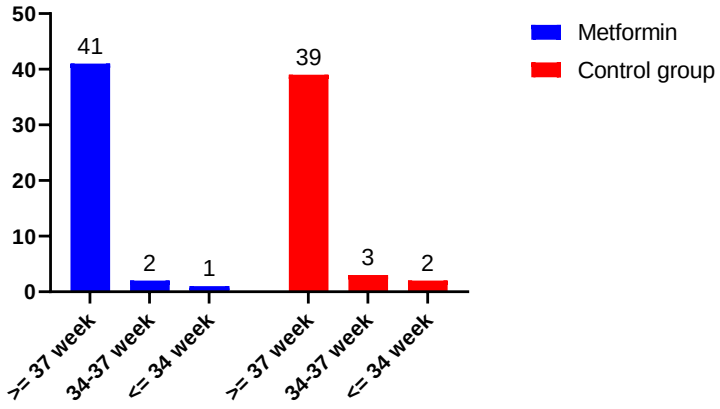

Fig.2: Comparison of gestational age in case and control groups.

Considering the pregnancy complications, the patients who did not continue metformin had less favorable situation, such that they developed GDM twice more frequently compared to the other group. Preeclampsia occurred three times more in the patients who stopped metformin as compared to the case group, the patients with preeclampsia all had grade 1. In terms of incidence of abortion, it was 7% more

in the patients who stopped metformin. Cesarean section was significantly higher in the control group than in the intervention group (**Table.2 and Figure.3**). The risk of developing GDM, preeclampsia, and abortion was 1.97, 2.65, and 2.33 times greater respectively in the patients who stopped metformin, where all of the three variables were statistically significant (P<0.05) (**Table.3**).

Table-2: Comparison of gestational diabetes, abortion and cesarean section and preeclampsia in two groups.

Variables	Metformin group	Control group	P-value (Chi-square)
Gestational diabetes, number (%)	5(11.4)	11(25)	0.097
Preeclampsia, number (%)	2(4.5)	6(13.6)	0.138
Abortion, number (%)	2(4.5)	5(11.4)	0.237
Cesarean section, number (%)	20(45.4)	30(68.2)	0.031

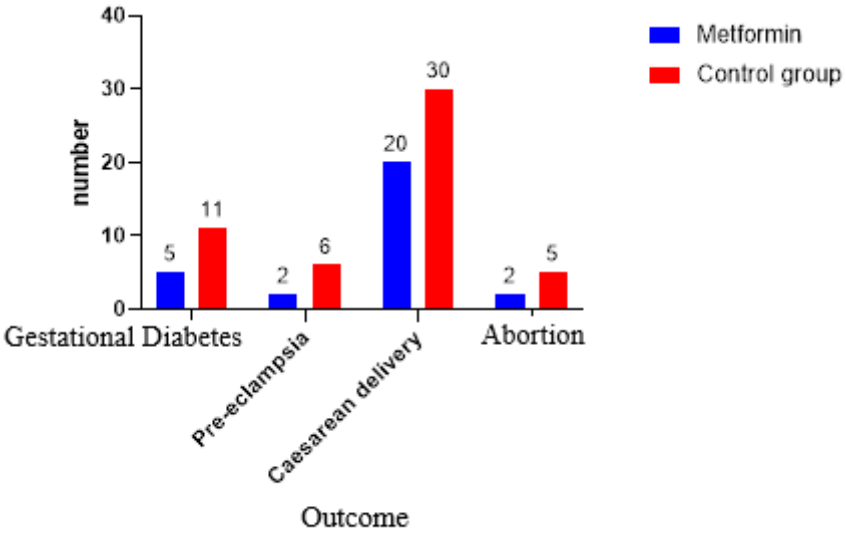

Fig.3: Frequency of pregnancy outcome in case and control groups.

Table-3: Comparison of relative risk of gestational diabetes, abortion and preeclampsia using Poisson regression model.

Outcomes	Relative Risk	95% CI	P-value
Gestational diabetes	1.97	1.63-2.39	0.001
Preeclampsia	2.65	1.95-3.59	0.001
Abortion	2.33	1.69-3.22	0.001

CI: Confidence Interval.

4- DISCUSSION

The present clinical trial study was performed to investigate the impact of continuing metformin consumption on pregnancy outcomes in women with PCOS and among those with this condition who stopped metformin during pregnancy. The findings of this research briefly indicated that not consuming metformin during pregnancy is associated with increased risk of incidence of GDM, preeclampsia, abortion, prematurity, and cesarean delivery. PCOS is one of the most common diseases of the endocrine system of women during reproductive ages whose etiology is still not fully understood (8, 25). Patients with PCOS suffer a lower rate of pregnancy as compared to the normal population because of improper ovulation. Therefore, these patients usually suffer long-term infertility.

In the present study, the patients had five years of infertility on average, causing pregnancy with more costs and complications. Hence, for these patients, loss of pregnancy and pregnancy complications can be more problematic as compared to normal women. Hence, taking measures for reducing the loss of pregnancy and the complications that may threaten the life of the fetus and mother in these women is crucial. Studies have reported PCOS as a risk factor for increased incidence of pregnancy complications such as gestational hypertension, gestational diabetes, abortion, IUGR, cesarean, preeclampsia, eclampsia, premature delivery, and increased risk of hospitalization in NICU for the neonate (8, 9, 26, 27).

One of the concerns regarding consumption of drugs during pregnancy including metformin is that they may cross the placenta and exert adverse effects on the fetus and thus congenital abnormalities (28). The results of clinical trial studies show that metformin consumption during pregnancy is not associated with complications or abnormalities on the fetus or mother (29). Animal studies have also shown that metformin has no detrimental effect on the fetus (30). Nevertheless, some studies have reported that this drug has teratogenic effects in animals, and causes increased risk of hypoglycemia in the human fetus (31). Metformin relatively crosses the placental barrier. Most studies have shown that metformin consumption during pregnancy can be sustained and no robust evidence has been reported on its detrimental effects on the fetus (28, 32, 33). Metformin is also secreted in the mother's milk in trace amounts, but this level cannot cause serious complications on the fetus (34).

Although it has been more than three decades that metformin has been in use for treating diabetic patients, its mechanism of action is still not fully understood. The main effect of metformin is reducing the hepatic glucose output by inhibiting glucogenesis. In addition, metformin results in increased glucose uptake through insulin in peripheral tissues such as the muscle and liver especially after food ingestion. It also has lipolytic effects causing reduced concentrations of free fatty acids, thereby decreasing substrate availability for glucogenesis. Because of improving blood sugar control, serum concentrations of insulin drop to some extent. Metformin can also lead to decreased food consumption and body weight (21, 35).

Different studies have dealt with examining the effect of metformin in women with PCOS, and have reported different results. In a prospective study with a large sample size by Khattab et al. (36) in 2011 in Egypt, it was found that metformin consumption was associated with decreased risk of developing GDM and preeclampsia, confirming the findings of the present study. In a meta-analysis performed by Zheng et al. (37) in 2013, it

was observed that the patients who did not risk of premature abortion, GDM, premature birth, and preeclampsia, which is congruent with the results of the present study. In another study in Pakistan in 2008, it was observed that if pregnant patients with PCOS do not stop metformin consumption, they would have better pregnancy outcomes (38). In a clinical trial study by Ainuddin et al. (17) in 2014, metformin consumption in women with PCOS was associated with beneficial fetal, neonatal, and maternal outcomes.

In contrast, in a prospective study by Vanky et al. in 2012 (39), it was observed that metformin consumption from the first trimester until delivery is not associated with decreased risk of pregnancy complications such as GDM and preeclampsia in the patients. One reason for the support of metformin by most studies is that those that did not find a positive outcome may not have been published, which signals publication bias. In another study by Legro et al., the patients who consumed metformin, as compared to clomiphene, had worse outcomes in terms of pregnancy (40).

In the present study, the patients tolerated metformin well and no significant side effects causing avoidance of metformin were observed in the patients. The most common side effects of metformin include digestive complications such as metal taste in the mouth, mild anorexia, abdominal discomfort, and soft stool or diarrhea. These symptoms are usually mild and transient, and are reversible after reducing the drug dose or stopping it (39, 40).

At the end, it should be noted that most studies suggest that metformin consumption during pregnancy in patients with PCOS is associated with decreased risks of pregnancy consequences such as premature abortion, prematurity, mothers' weight loss, prevention of IUGR, and lack of teratogenic effects. Since this drug is stop metformin during pregnancy had less fairly safe and inexpensive, therefore it can be stated that most probably the patients who consume this drug would have better outcomes in pregnancy. Nevertheless, there is still no specific guideline for use of metformin in these patients; as such, further studies are warranted in this regard.

4-1. Study Limitations

The patients that did not participate in this study may have been different with the subjects. Relatively small sample size was another limitation. On the other hand, since lifestyle and dietary habits may affect the disease outcomes, they have not been examined in this study. It is also suggested that a study with a larger sample size be conducted. Another suggestion is to examine the long-term effect of metformin on neonates.

5- CONCLUSION

Based on the results of the present study, metformin consumption throughout the entire course of pregnancy in patients with PCOS is associated with beneficial results, as it causes diminished pregnancy complications including GDM, prematurity, preeclampsia, and abortion. Nevertheless, clinical trial studies with a larger sample size are suggested for further investigation.

6- CONFLICT OF INTEREST: None.

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