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EFFECTS OF METFORMIN ON EARLY PREGNANCY LOSS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

OBJECTIVE: To evaluate the effectiveness of metformin therapy in reducing early pregnancy loss in pregnant women with polycystic ovary syndrome (PCOS).

MATERIALS AND METHODS: This prospective cohort study was conducted in the Department of obstetrics and gynaecology, government medical college srinagar for a period of 2 years. This study involved 100 pregnant women with PCOS who became pregnant while using metformin. They were divided into two groups, namely, the group that received metformin throughout pregnancy (metformin group, n=50) and the group that discontinued the drug during pregnancy (control group, n=50). A comparison was made between the two groups of patients with respect to certain basal characteristics (age, body mass index, previous obstetric outcome, serum glucose and serum free testosterone) and the differences in the rates of early pregnancy loss between the two groups.

RESULTS: There were 50 patients who received metformin during pregnancy (metformin group) compared with 50 patients who did not receive the treatment (control group). The rate of early pregnancy loss in the metformin group was 12% (6/50) compared with 38% (19/50) in the control group (p = 0.003). For patients in the metformin group with a history of previous miscarriage, the rate of pregnancy loss was 55.6% (30 cases/54 pregnancies).

CONCLUSION: Metformin therapy in pregnant women with PCOS was associated with a significant reduction in the rate of early pregnancy loss.

KEYWORDS :

INTRODUCTION

Polycystc ovarian syndrome(PCOS) is the most common form of female infertility in the United States, and it affects 5–10% of women of reproductive age (1, 2). In addition to difficulty conceiving, women with polycystic ovary syndrome are at increased risk of miscarriage after either spontaneous or assisted conception. Rates of early pregnancy loss, defined as miscarriage during the first trimester, are reported to be 30–50% in women with the polycystic ovary syndrome (3–7), which is 3-fold higher than the rate of 10–15% reported in retrospective studies for normal women (8, 9)

The etiology of this condition is unknown. Insulin resistance is implicated as an independent risk factor for early pregnancy loss due to its adverse effects on endometrial function and implantation environment. Hyperinsulinemic resistance also plays a key role in the disorder by increasing androgen concentration and impending ovulation (10,11). Administration of various insulin-sensitizing drugs such as metformin has been shown to reduce androgen concentration with restoration of ovarian cycles and reduction of early pregnancy loss (12). The beneficial effects of metformin have been reported in previous studies (13,14,15) but the question arises whether its use can be continued throughout pregnancy.

Metformin pharmacology

Metformin, a biguanide, is an antihyperglycemic drug, which improves glucose tolerance. It lowers the basal and postprandial plasma glucose concentrations. Metformin decreases hepatic glucose production and intestinal absorption of glucose and improves insulin sensitivity by increasing glucose uptake and utilization (12). In patients with PCOS, metformin reduces fasting insulin, stimulating luteinizing hormone (LH), and free testosterone levels (16). During pregnancy, the drug passes through the placenta to the fetus and the fetal serum level becomes comparable to the maternal level but it is generally considered a safe treatment during pregnancy (17). The United States Food and Drug Administration has classified the drug as a category B medication, suggesting that it does not appear to cause harm to the fetus in animal studies (18-20).

It is documented that metformin has beneficial metabolic, endocrine, vascular, and anti-inflammatory effects on the risk factors contributing to early pregnancy loss (21). However, its use to reduce pregnancy complications in women with PCOS is still controversial (22).

This study was undertaken to evaluate the effect of metformin therapy on pregnancy outcome by comparing the rate of early pregnancy loss between two groups of patients who received or did not receive it throughout the pregnancy period

MATERIALS AND METHODS

This was a prospective cohort study conducted in the Department of obstetrics and gynaecology, government medical college Srinagar, between January 2012 and January 2014. Participants in the study were 100 pregnant women who conceived while taking metformin. The patients were divided into two groups: The first group pregnant while receiving metformin and continued the treatment at a dose of 1000 mg/d (metformin group; n = 50) and the second group who discontinued the use of the drug once pregnant because they refused to continue its use (control group; n = 50).

The study was approved from ethical committee and verbal consent was obtained from the patients. The complete history of the study patients and their clinical examination was done as per proforma. Specific investigations of serum analysis were carried out for thyroid function test, serum-free testosterone and oral glucose tolerance test.

The inclusion criteria of the study were: the PCOS pregnant women, singleton pregnancy, maternal age of 18 - 40 years, gestational age between 5 weeks and 12 weeks, normal serum thyroid-stimulating hormone and GTT.

The exclusion criteria were other risk factors for miscarriage such as abnormal karyotyping for both parents; diagnosis of antiphospholipid syndrome, uterine anomalies and diabetes

mellitus.

The diagnosis of PCOS was based on the Rotterdam criteria(23) Pregnancy was detected by urinary or serum beta-human chorionic gonadotropin (24) with confirmation by transvaginal ultrasound. Early pregnancy loss was defined as spontaneous loss before 12 completed weeks of pregnancy (25), and was documented by the ultrasonography.

Statistical analysis : Continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. Student's independend t- test or Mann-Whitney U-test , whichever feasible , was employed for comparing continuous variables. Chi-square test or Fisher's exact test , whichever appropriate , was applied for comparing categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 demonstrates the basal clinical and biochemical characteristics of patients in the metformin and control groups. There were no significant differences with respect to maternal age, BMI, fasting glucose concentration, and serum-free testosterone level between the metformin and control groups (Table 1). In metformin group, the mean gestational age was 9.1 ± 0.95 weeks and 54% of the patients (27/50) became pregnant with the use of clomiphene citrates or human chorionic gonadotropin for induction of ovulation. Four patients (8 %) conceived after in vitro fertilization procedure. None of the women in the two groups had diabetes mellitus before conception and all had normal blood glucose level at a range of 5.42 ± 0.72 mmol/ L in the metformin group and 5.35 ± 0.58 mmol/L in the control group.

Table 1 Basal clinical and laboratory characteristics of patients with polycystic ovary syndrome

Basal characteristics	Metformin group N = 50(%)	Control group N = 50(%)	P
Maternal age (y)	27.8 ± 2.19	28.1 ± 1.89	0.463
Body mass index (kg/m2)	28.1 ± 1.76	27.6 ± 2.57	0.259
Gestational age (wk)	9.1 ± 0.95	8.9 ± 0.86	0.273
Fasting serum glucose (mmol/L)	5.42 ± 0.72	5.35 ± 0.58	0.594
Serum-free testosterone (mmol/L)	4.51 ± 0.97	4.74 ± 1.19	0.292
Proportion of patients who received drugs for induction of ovulation (Clomid or gonadotropin)	27 (54)	31 (62)	0.418
Proportion of patients conceived after in vitro fertilization	4 (8)	5 (10)	0.726

Among the 50 women who received metformin throughout the pregnancy period, there were six cases (12 %) of early pregnancy loss, whereas there were 19 cases (38%) in the control group. The difference was significant (p =0.003) Table 2

The results of the previous pregnancy outcome in the patients studied showed that among the 50 women in the metformin group, there were 23 cases with a positive history of early pregnancy loss in previous pregnancies. None of the patients had received metformin in the previous pregnancies.

Among the 23 women in the metformin group with a history of previous pregnancies, there were 54 pregnancies (24 live births and 30 miscarriages), with a miscarriage rate of 55.6%. In the control group, 20 (40%) of the 50 women had a history of previous pregnancy loss. Among the 20 women with previous pregnancy loss, there were 26 pregnancies, which resulted in 18 live births and 8 miscarriages, yielding a miscarriage rate of 30.7%.

For the patients in the metformin group with a previous history of early pregnancy loss, there was a reduction in the rate of pregnancy loss from 55.6 % in the previous pregnancies to 12 % in the present pregnancies. In the control group, however, there were no significant differences between the rates in the previous and present pregnancies (30% vs. 38%), respectively. Table 2

Rate of early pregnancy loss in the metformin and control groups with previous pregnancy outcome.

Cohort	Metformin group N = 50 (%)	Control group N = 50 (%)	P
Rate of pregnancy loss in the present pregnancy	6 (12)	19 (38)*	0.003*
Positive history of early pregnancy loss in previous pregnancy	23 (46)	20 (40)	0.544
Rate of early pregnancy loss in previous pregnancy	30 (55.6) [a]	8 (30.7) [b]	0.038*

- Statistically significant (P- value <0.05)
- a: among the 28 women in metformin group, there were 54 pregnancies with pregnancy loss in30 cases (55.6%)
- b: among the 23 women in control group, there were 26 pregnancies with pregnancy loss in 8 cases (30.7%)

Metformin was well tolerated in all patients. None of the patients required cessation or reduction in the treatment dose. No side effects or serious complications were observed.

DISCUSSION

Women with insulin resistance are at increased risk of hyperinsulinemia, PCOS, and hyperandrogenism [10,11] .They are also at risk of reduced fertility due to ovulatory dysfunction and suboptimal hormonal milieu that may impair conception and implantation [26].This emphasizes the need for a treatment using drugs such as metformin, which will actively reduce insulin resistance, and will restore ovulatory cycles and reduce early pregnancy loss (12).In addition to this there is accumulating evidence suggesting that this drug is probably safe in the first trimester of pregnancy despite the traditional response that all oral hypoglycemic agents are contraindicated in pregnancy (20).

The findings of this study support the previous reports that stated that decreasing insulin resistance with metformin in women with PCOS decreases the rate of early pregnancy loss (26-30). In our analysis, it is observed that there was a dramatic reduction in the rates of early pregnancy loss in the metformin group compared with the control group.

The early pregnancy loss rate of 12% is comparable to the rate of 8.8 reported by Jakubowicz et al (15), to the rate of 8.9% reported by (27) and to the rate of 11% reported by Glueck et al (30) in another pilot study. It is observed in this analysis that the rate of cumulative early pregnancy loss in all previous pregnancies was high in the metformin group; however, the heterogeneity of individuals should also be considered in this condition. It is reported that the beneficial role of metformin is independent of its hypoglycemic activity but occurs through the effect on lipid, inflammation, hemostasis, endothelial cells, and platelet function (21,31-34). In addition to these, there are several mechanisms for the action of this drug in patients with PCOS. One major effect is brought about by the reduction of the hyperandrogenization of the embryo (35,36). In addition to the effect of immunoglobulin G-binding protein,

this seems to facilitate the adhesion process at the endometrial interface (37).

An analysis of the effects of BMI in both groups of patients shows that although the mean BMI was not significantly different, high BMI was associated with a higher rate of early pregnancy loss. These observations may be explained by the adverse effect of high insulin resistance, which is more prominent with high BMI (38). Nausea and mild gastrointestinal symptoms are the most frequent side effects of metformin treatment (39). It is anticipated that this treatment might exaggerate the morning sickness of pregnancy. However, it was well tolerated in all patients, with no serious complications.

In conclusion, the use of metformin in pregnant women with PCOS during pregnancy was associated with a significant reduction in the rates of early pregnancy loss. It was well tolerated by patients with a minimum of side effects. However, extended studies are required to evaluate its effect on further pregnancy complications

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