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EFFECTIVENESS OF METFORMIN IN PREVENTING EARLY PREGNANCY LOSS IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

Gynaecology

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ABSTRACT

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

MATERIALS AND METHODS : This is a prospective cohort study conducted in the Obstetric Department of Krishna Institute of Medical Sciences, Karad, Maharashtra, India for a period of 2 years. This study involved 100 nondiabetic pregnant women with PCOS. They were divided into two groups, namely, the group that received metformin throughout pregnancy (metformin group) and the group that got pregnant but, did not receive metformin (control group). 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 with free testosterone). Statistical analysis was performed using Chi-square test to compare the differences 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 10% (5/50) compared with 36% (18/50) in the control group ($p < 0.001$). For patients in the metformin group with a history of previous miscarriage, the rate of pregnancy loss was 45% (35 cases/50 pregnancies).

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

KEYWORDS

Early Pregnancy Loss, Insulin Resistance, Metformin, Polycystic Ovary Syndrome (PCOS)

INTRODUCTION

Although the first description of polycystic ovary syndrome (PCOS) is generally credited to Stein and Leventhal (1935), it may have been observed as early as 1721 when Italian scientist Antonio Vallinsneri observed larger-than-normal ovaries in young peasant women, who were moderately obese and infertile [1].

PCOS is the most common cause of anovulatory infertility worldwide. In addition to poor conception rate, early pregnancy loss rates are significantly higher (30–60%) than in the general population [2], [3]. The etiology of this condition is unknown.

Previous studies have suggested that women who hypersecrete LH, a frequent feature of the polycystic ovary syndrome, are at increased risk for miscarriage after either spontaneous or assisted conception (35, 36). However, it was recently reported that suppression of endogenous LH release before conception, in women with elevated circulating LH concentrations and a history of recurrent miscarriage, did not improve the live birth rate (37). Other reported risk factors for early pregnancy loss in the polycystic ovary syndrome include obesity (38) and elevated serum androgen concentrations (39, 40). Obesity is characterized by insulin resistance with compensatory hyperinsulinemia (*i.e. hyper*insulinemic insulin resistance), and a recent study implicates hyperinsulinemia as an independent risk factor for early pregnancy loss (38).

Hyperinsulinemic 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 [4], [5].

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 [6].

The beneficial effects of metformin have been reported in previous studies [7], [8], [9] 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 [6].

In patients with PCOS, metformin reduces fasting insulin, stimulating luteinizing hormone (LH), and free testosterone levels [10]. 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 [11]. 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 [12], [13], [14].

It is documented that metformin has beneficial metabolic, endocrine, vascular, and anti-inflammatory effects on the risk factors contributing to early pregnancy loss [15]. However, its use to reduce pregnancy complications in women with PCOS is still controversial [16].

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 is a prospective cohort study conducted in the Obstetric Department of Associate professor, Krishna Institute of Medical Sciences, Karad, Maharashtra, India between January 2016 and December 2018.

Participants in the study were 100 nondiabetic pregnant women of whom 50 conceived while taking metformin and the remaining 50 concieved without taking metformin. The patients were divided into two groups: The first group who became pregnant while receiving metformin and continued the treatment at a dose of 1500 mg/d (metformin group; $n = 50$) and the second group who became pregnant and were not on metformin therapy (control group; $n = 50$).

The complete history of the study patients and their clinical examination results were completely reviewed to determine their age, previous history of miscarriage, and body mass index (BMI).

Specific investigations of serum analysis were carried out for LH, thyroid function test, free testosterone level, and oral glucose tolerance test.

The inclusion criteria of the study were the diagnosis of PCOS before pregnancy, maternal age of 18–40 years, gestational age between 5 weeks and 12 weeks, normal serum thyroid-stimulating hormone and prolactin levels, and pregnancy with singleton fetus.

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The exclusion criteria were other risk factors for miscarriage such as abnormal serum karyotyping for both parents; antiphospholipid syndrome, which was excluded by anticoagulant antibodies test; uterine anomalies as excluded by transvaginal ultrasound scanning; and diabetes mellitus by oral glucose tolerance test.

The diagnosis of PCOS was based on the Rotterdam criteria [17] implying that at least two of the following three criteria were fulfilled: presence of polycystic ovaries (≥ 9 subcapsular follicles of 10 mm by transvaginal ultrasonography), oligomenorrhea (length of menstrual cycles > 35 days or < 10 menstrual cycles/y), anovulation, and serum-free testosterone level > 2.5 nmol or clinical signs of hirsutism.

Pregnancy was detected by serum beta-human chorionic gonadotropin level > 50 IU/L [18] with confirmation of intrauterine pregnancy by transvaginal ultrasound scanning. Early pregnancy loss was defined as spontaneous loss before 12 completed weeks of pregnancy [19], and was documented as the absence of fetal viability that was confirmed by the ultrasonography.

For statistical analysis, Chi-square test was used to compare the differences in the rates of early pregnancy loss between the two groups and two-tailed test was used for independent samples. Results were reported as means ± standard deviation and $p < 0.05$ was considered 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).

Table 1. Basal clinical characteristics of patients with polycystic ovary syndrome before pregnancy who either received metformin (metformin group) or did not receive (control group) metformin throughout pregnancy.

Basal characteristics	Metformin group *N* = 50	Control group *N* = 50	*p*
Maternal age (y)	28.1 ± 1.6	28.6 ± 1.5	0.1
Body mass index (kg/m2)	28.4 ± 1.8	27.8 ± 1.3	0.4
Gestational age (wk)	8.6 ± 0.7	8.7 ± 0.5	0.2
Fasting serum glucose (mg/dl)	100.8 ± 10.8	93.6 ± 7.2	0.1
Number of criteria met (mean-+)	3.5 ± 1.6	3.6 ± 1.3	0.2
Serum-free testosterone (mmol/L)	4.8 ± 0.5	4.6 ± 1.4	0.2
Proportion of patients who received drugs for induction of ovulation (Clomid or gonadotropin)	25 (50)[a]	30 (60)[b]	0.4
Proportion of patients conceived after in vitro fertilization	4 (8)	3 (6)	0.2

a
Continuous variables are presented as mean ± standard deviation.
b
Categorical variables presented as *n* (%).

In the metformin group, 7 patients met all the five criteria of PCOS described in the *Materials and methods* section. A total of 15 patients and 18 patients, respectively, met two and three criteria; 10 patients met four of these criteria. In this group, the mean gestational age was 8.6 ± 0.2 weeks and 50% of the patients (25/50) 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 100.8 ± 10.8 mmol/L in the metformin group and 93.6 ± 7.2 mmol/L in the control group.

The rate of early pregnancy loss with the results of previous pregnancy outcome is described in Table 2. Among the 50 women who received metformin throughout the pregnancy period, there were five cases (10%) of early pregnancy loss, whereas there were 18 cases (36%) in the control group. The difference was significant ($p < 0.05$; Table 2).

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	5 (10)	18 (36)	<0.05
Positive history of early pregnancy loss in previous pregnancy	25 (50)	20 (40)	0.4
Negative history of early pregnancy loss in previous pregnancy	25 (50)	30 (60)	0.2
Rate of early pregnancy loss in previous pregnancy	35 (45)a	9 (36)b	<0.01

Data are presented as *n* (%).

a
Among the 25 women in the metformin group, there were 50 pregnancies with pregnancy loss in 35 cases (45%).
b
Among the 20 women in the control group, there were 25 pregnancies with a pregnancy loss in nine cases (36%).

The results of the previous pregnancy outcome in the patients studied showed that among the 50 women in the metformin group, there were 25 cases with a positive history of early pregnancy loss in previous pregnancies and 25 had a negative history. Patients with a negative history of early pregnancy loss were either primigravidas or cases with previous successful pregnancies. None of the patients had received metformin in the previous pregnancies.

Among the 25 women in the metformin group with a history of previous pregnancies, there were 50 pregnancies (15 live births and 35 miscarriages), with a miscarriage rate of 45%.

In the control group, 20 (40%) of the 50 women had a history of previous pregnancy loss, whereas 30 cases were primigravidas. Among the 20 women with previous pregnancy loss, there were 25 pregnancies, which resulted in 16 live births and 9 miscarriages, yielding a miscarriage rate of 36%. 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 45% in the previous pregnancies to 10% in the present pregnancies. In the control group, however, there were no significant differences between the rates in the previous and present pregnancies (36% vs. 36%), respectively.

The analysis of the effect of metformin on the maternal androgen and BMI shows that there was a significant reduction in the level of free testosterone in the serum of patients in the metformin group compared with those in the control group (1.6 ± 0.5 nmol/L vs. 4.2 ± 0.7 nmol/L). However there were no significant differences of BMI in the two groups. In addition, it was observed that most cases of pregnancy loss in the metformin and control groups were associated with elevated serum-free testosterone level (> 4 nmol/L) and higher BMI (> 29 kg/m^2; Table 3).

Table 3. Maternal serum androgen level and body mass index in pregnant women with polycystic ovary syndrome in the two study groups.

Maternal serum androgen (free testosterone) level and BMI	Metformin group (*n* = 50)	Control group (*n* = 50)	*p*
Serum-free testosterone (nmol/L)	1.56 ± 0.6	4.2 ± 0.7	<0.05
BMI (kg/m2)	29.4 ± 2.3	29.6 ± 1.2	0.3

BMI = body mass index.

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 hyperins ulinemia, PCOS, and hyperandrogenism [4], [5]. They are also at risk of reduced fertility due to ovulatory dysfunction and suboptimal hormonal milieu that may impair conception and implantation [20]. 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 [6]. 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 [14].

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 [20], [21], [22], [23]. 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 10% is comparable to the rate of 8.8 reported by Jakubowicz et al [9] and to the rate of 11% reported by Glueck et al [23] 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 [15], [24], [25], [26], [27]. 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 [28], [29]. In addition to the effect of immunoglobulin G-binding protein, which seems to facilitate the adhesion process at the endometrial interface [30].

In addition, mechanisms other than androgen reduction may also have played a role in metformin's apparent effects to protect against miscarriage. For example, metformin's salutary effects may have been related directly to its action to improve insulin sensitivity in the polycystic ovary syndrome. A recent study implicates insulin resistance as an independent risk factor for early pregnancy loss in women with polycystic ovary syndrome , and a report suggests that hyperinsulinemia adversely affects endometrial function and the periimplantation environment by decreasing expression of glycodelin and IGF binding protein-1. Glycodelin may play a role in inhibiting the endometrial immune response to the embryo, and IGF binding protein-1 seems to facilitate adhesion processes at the fetomaternal interface.

Furthermore, plasma plasminogen activator inhibitor-1 concentrations are increased in insulin-resistant states, including the polycystic ovary syndrome. Increased plasminogen activator inhibitor-1 activity is an independent risk factor for miscarriage in the polycystic ovary syndrome, presumably because it induces a hypofibrinolytic state. Metformin administration has been reported to decrease circulating plasminogen activator inhibitor-1 in women with polycystic ovary syndrome.

This study showed that maternal serum androgen level was reduced significantly after metformin treatment. This is in agreement with the studies of Sarlis et al [31] and Glueck et al [21]; however, our results are in contrast to those of Vanky et al [32], who reported that the maternal androgen level was more or less unaltered during pregnancy or it had no major effect on pregnancy.

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 [33].

Nausea and mild gastrointestinal symptoms are the most frequent side effects of metformin treatment [34]. 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.

CONCLUSION

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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