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MATERNAL AND PERINATAL OUTCOMES IN WOMEN WITH PCOS RECEIVING METFORMIN DURING PREGNANCY: A CLINICAL OBSERVATIONAL STUDY

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder that affects women of reproductive age. It is often associated with infertility, insulin resistance, and pregnancy complications. Metformin, an insulin-sensitizing agent, is frequently used to manage PCOS and has shown potential benefits during pregnancy. This study evaluates the maternal and perinatal outcomes in pregnant women with PCOS.

Objective: The study compares the maternal and perinatal outcomes in pregnant women with PCOS receiving metformin pre-pregnancy and throughout pregnancy with those in low risk healthy pregnant women.

Methods: This is a comparative study conducted over two years on pregnant women with PCOS who conceived on Metformin and continued it throughout pregnancy. The study compares pregnant women having PCOS who conceived on metformin and continued it throughout their pregnancy. Those patients were compared with low risk healthy pregnant women. Maternal and perinatal outcomes were assessed.

Results: There was no statistically significant difference between the miscarriage rates among the PCOS group (4.9%) and controls (6.0%) (p=0.679). Maternal complications like GDM, PIH, and polyhydramnios showed no significant differences between the study groups as well. However, preterm delivery was found to be significantly lower in the Metformin-treated PCOS group (14.7%) compared to controls (24.1%) (p=0.048). Other outcomes, including IUD and maternal hypoglycemia, were comparable between the study groups.

Conclusion: Present study concludes that the use of metformin throughout pregnancy in women with PCOS lowers the rate of preterm delivery without increasing the risk of miscarriage or other maternal and neonatal complications. It suggests that it may be a safe and beneficial option for improving pregnancy outcomes in this population.

Keywords: PCOS, Metformin, Gestational Diabetes, Perinatal Outcomes, Maternal Complications.

INTRODUCTION

Among the most common hormonal disorders associated with women is the polycystic ovarian syndrome or PCOS. The disorder affects ovaries during reproductive age group, including

pregnancy as well as after childbirth. Women with this disorder face difficulties in conception. They experience many complications even under successful pregnancies that is achieved through medication, surgery or in vitro fertilization [1]. These complications include, gestational diabetes mellitus, hypertension induced by pregnancy, preterm birth, preeclampsia, miscarriage, malformation or retardation of intrauterine growth. Ovulation can be promoted and menstrual cycle can be regulated by the use of metformin n the above cases. However, metformin use is recommended from the early stages of pregnancies in cases with PCOS [2]. There is also a risk where fetus may get exposed to this drug as there is a possibility that this drug can enter placenta through organic cation transporters as well as plasma membrane monoamine transporters. The use of metformin continuously for its efficacy, safety and benefits still remains unclear as various studies report the effects of its use differently either in a positive or in a negative manner [3]. It is necessary to analyse the efficacy of metformin when it is continuously used for women with PCOS during pregnancy and after child birth for some time. The current study focuses on the impact of metformin use on the metabolic aspects as well as the post pregnancy outcomes in women with PCOS.

Treatment with metformin can reduce the risks associated with the complications in pregnancy and may have impact on the body mass index of the offspring in the long run and also the levels of sex hormone binding globulin or SHBG [4]. Metformin use during pregnancy is largely associated with neutral or positive maternal outcomes and it may not be effective in reducing the risk of development of gestational diabetes mellitus during pregnancy. There is also an increased likelihood of gasterointestinal side effects (5). Metformin use may have beneficial effect in the life of offspring as it reduces the risk of metabolic syndrome and obesity. In some studies it was shown that, prenatal metformin has improved glucose tolerance, reduction in the accumulation of body weight, and fat mass in the off spring's adulthood (6]. Metformin use did not demonstrate adverse outcomes. When it was administered on pregnant women with PCOS, there was no pre-eclampsia and was found to be safe to mother and fetus [7]. Research studies by Jorquera et.al.,[8] show that, when the risk benefit ratio estimated for metformin use, it is important to consider COS, hyperandrogenism, GDM, low adherence to insulin, risk of preeclampsia. Although metformin prevents ovarian developmental programming, it is associated with increased body weight and derangement of metabolic activities.

SUBJECTS AND METHODS

The present study was a prospective, single-center, comparative study conducted at Dr B.L. Kapur Memorial Hospital, New Delhi**,** over a 2-year period from July 2018 to June 2020**.**

A total of 2,056 deliveries were recorded during the study period. Of these, 150 pregnant women with PCOS who had conceived while on Metformin therapy were identified. Among those women, 7 women lost to follow-up, 143 women with PCOS between the age group of 21–35 years were included for the study. Inclusion criteria was pregnant women in the age group between 21–35 years, diagnosed with PCOS as per the 2003 Rotterdam criteria**,** conceived while on Metformin therapy and continued Metformin use throughout pregnancy. While the exclusion criteria included Type 1 or Type 2 Diabetes Mellitus, chronic hypertension, serum creatinine >1.5 mg/dL on glucocorticoid therapy and twin pregnancies. Those cases were compared with 150 women who were between the same age-group. These women were at low-risk and were healthy pregnant women without PCOS.

The administered dose of metformin ranged from 500 mg to 2000 mg daily, based on Indian guidelines and clinical needs. The Pre-conception dose was continued unless GDM was diagnosed, and under those conditions, the dose was increased. Patients who discontinued Metformin during pregnancy were excluded.

Statistical was done with quantitative variables, where mean ± SD; compared using unpaired t-test; while the qualitative variables include frequencies and they were compared using Chi-square test. Statistical significance was considered at $p < 0.05$ and the analysis was performed using IBM SPSS version 22.0.

RESULTS

In the current study, a total of f 293 participants were included, among which 143 women in the **case group** (PCOS patients treated with Metformin during pregnancy) and 150 in the control group **(low**-risk healthy pregnant women). The maternal and pregnancy outcomes were analyzed and compared between the two groups using appropriate statistical tests.

1. Maternal Complications

In the table 1, the percentages of maternal complications are presented. The gestational diabetes mellitus (GDM) was observed in 22.5% of the total study population which is 21.0% in the case group and 24.0% in the control group. The occurrence of Pregnancy-induced hypertension (PIH) was 21.2% overall, with similar distribution between cases (18.9%) and controls (23.3%). It was found that, the rates of polyhydramnios and maternal hypoglycemia were low in both groups (≤4.4% and <1%, respectively). None of the maternal outcomes showed a statistically significant difference between the groups (**$p > 0.05$** for all parameters), indicating that Metformin use in PCOS pregnancies did not significantly alter the risk of maternal complications when compared to low-risk controls.

Table 1: Frequency and percentage of different maternal complications

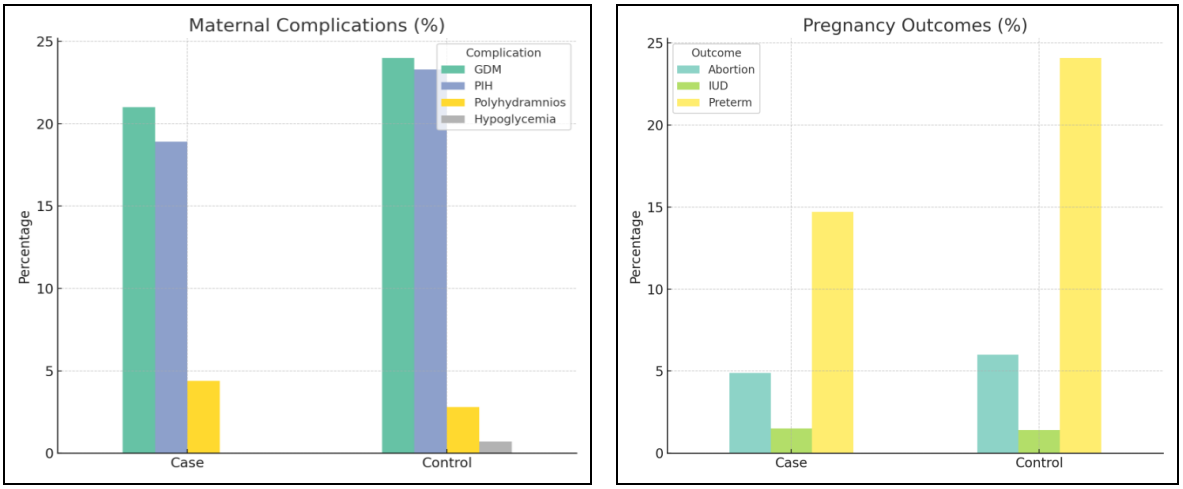
Parameters	Overall		Case		Control		P value
	N	%	N	%	N	%	
GDM	66	22.5	30	21.0	36	24.0	0.538
PIH	62	21.2	27	18.9	35	23.3	0.353
Polyhydramnios	10	3.6	6	4.4	4	2.8	0.484
Maternal hypoglycemia	1	0.4	0	0.00	1	0.7	0.327

2. Perinatal Outcomes

As can be observed in Table 2, the rate of abortion was found to be 5.5% in the overall population, with comparable rates in both case (4.9%) and control (6.0%) groups ($p = 0.679$). In a similar manner, the incidence of intrauterine death (IUD) was low and nearly identical between groups (1.5% vs. 1.4%, $p = 0.971$). However, a statistically significant difference was observed in the rate of preterm delivery, which was notably lower in the Metformin-treated group (14.7%) compared to the control group (24.1%), with a p-value of 0.048. these results suggests that Metformin may have a protective effect in reducing the risk of preterm birth in PCOS pregnancies.

Table 2: Frequency and percentage of perinatal outcome

Parameters	Overall		Case		Control		P value
	N	Percent	N	Percent	N	Percent	
Abortion	16	5.5	7	4.9	9	6.0	0.679
IUD	4	1.4	2	1.5	2	1.4	0.971
Preterm	55	19.86	20	14.7	35	24.14	**0.048**



DISCUSSION

Polycystic Ovary Syndrome (PCOS), an endocrine disorder, is commonly found in women and is associated with adverse reproductive outcomes, such as increased risks of miscarriage, gestational diabetes mellitus (GDM), preterm birth, and hypertensive disorders in pregnancy. The use of Metformin in PCOS has been recommended to improve these outcomes by addressing underlying insulin resistance, a key pathophysiological feature of the syndrome.

In our study, we found that the miscarriage rate was comparable between PCOS women treated with Metformin (4.9%) and low-risk healthy pregnant women (6.0%), with no statistically significant difference. This aligns with previous research studies [9] suggesting that Metformin may help reducing pregnancy loss at early stages in PCOS patients in a significant manner by improving endometrial receptivity and reduced hyperinsulinemia.

A significant finding in our study was that there is a lower rate of preterm delivery in a significant way in the Metformin-treated group (14.7%) in comparison to the control group (24.1%). This supports the hypothesis that Metformin may exert a protective effect on pregnancy duration, possibly through better glycemic control and reduction in systemic inflammation. This assumption was similar to that obtained from some research studies. [10,11]

Rates of GDM and PIH were slightly lower in the Metformin group but did not reach statistical significance. This may be due to the limited sample size or the fact that both groups received regular antenatal care and monitoring. Nevertheless, the findings are consistent with the studies that reported [12] the known benefits of Metformin in improving insulin sensitivity, which may contribute to better metabolic outcomes during pregnancy.

Other maternal complications such as polyhydramnios and maternal hypoglycemia were rare and not significantly different between groups, indicating that Metformin use did not increase maternal risks.

From our study, it is important to highlight that Metformin dosage was based on individual clinical needs, with doses ranging from 500 mg to 2000 mg daily. All patients received continued Metformin throughout pregnancy, which is a common clinical practice in some centers despite ongoing debate regarding its use beyond the first trimester.

One of the limitations of this study is its single-center design, which may limit the generalizability of results. It would be beneficial to confirm findings with larger, multicentric randomized controlled trials would establish more definitive guidelines.

CONCLUSION

A continued use of Metformin during pregnancy in women with Polycystic Ovary Syndrome (PCOS) is associated with positive maternal and perinatal outcomes. Women with PCOS who are treated with Metformin- has lower miscarriage rate when compared to healthy pregnant women. A significantly fewer cases of preterm delivery were observed in the Metformin group. There were no significant differences in rates of gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), polyhydramnios, or neonatal complications such as hypoglycemia, low birth weight, macrosomia, or growth abnormalities between the two groups. These findings support the safety and potential protective effect of Metformin in reducing preterm births among PCOS pregnancies without increasing the risk of adverse outcomes. Further large-scale studies may help to reinforce these findings and guide standardized recommendations for Metformin use in pregnancy among women with PCOS.

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