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PREGNANCY OUTCOMES OF METFORMIN USE IN PREGNANT WOMEN WITH PCOS: A COMPARATIVE STUDY

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is a commonly occurring endocrine disorder among women of reproductive age, which often complicates pregnancy outcomes. Metformin, an insulin-sensitizing agent, is used in many cases to manage PCOS and its associated complications during pregnancy. However, it has not proven its effectiveness for its role in the improvement of pregnancy outcomes.
Objective: The present study was aimed at evaluating the impact of Metformin therapy on pregnancy outcomes in pregnant women with PCOS through a comparative prospective study.
Subjects and Methods: The study was a comparative study conducted over two years on pregnant women having PCOS who conceived on metformin and continued it throughout their pregnancy. Those patients were compared with low risk healthy pregnant women. Pregnancy outcomes including abortion, intrauterine death (IUD) and preterm delivery were compared between the two age matched groups. The metfomin group received varying doses (500–2000 mg), with a mean dose of 868.53 mg at delivery. Maternal age and BMI were also analyzed.
Results: A higher percentage of participants in the Metformin group were obese (43.36%) compared to the control group (41.33%). Preterm birth was significantly lower in the Metformin group (14.7%) compared to the control group (24.14%) ($p = 0.048$). No significant differences were observed in rates of abortion ($p = 0.679$) or IUD ($p = 0.971$). Metformin usage was observed to be associated with reduced incidence of preterm delivery without increasing adverse pregnancy events.
Conclusion: Metformin use in pregnant women with PCOS appears to be associated with a significant reduction in preterm births, suggesting that it has a potential role in improving certain pregnancy outcomes.

Keywords: Metformin, Polycystic Ovary Syndrome (PCOS), Pregnancy Outcomes, Preterm Delivery.

INTRODUCTION

Metformin drug is an insulin sensitizer that is used to lower glucose levels in blood and prescribed commonly to pregnant women for the gestational diabetes mellitus. Recommendations for the metformin use, as a first line agent, are due to the fact that it crosses placenta to fetus (1). Metformin is primarily used in settings with low resource, where there is a significant increase in gestational diabetes mellitus. Metformin regulates menstrual cycle and also promotes ovulation through improving insulin resistance, reduction in hyperinsulinemia, and

also weight loss (2). Thus there is an increase in the rate of pregnancy for women with pregnancy related polycystic ovary syndrome (PCOS) (3).

PCOS is characterized by ovulatory dysfunction, polycystic ovarian change and hyperandrogenism. In addition to this, PCOS is also associated with dyslipidemia, insulin resistance and obesity. The advantage associated with metformin is that, it is relatively in expensive, and its storage is easy (4). Metformin can also be used for other conditions of pregnancy such as pre-existing diabetes and polycystic ovarian syndrome. It is found from the studies that, women treated with PCOS have lower risks of miscarriages (4,5). Metformin reduces testosterone, increase adiponectin and increases pregnancy outcomes in women with PCOS.

This study was a comparative assessment on the effects of Metformin use during pregnancy in women with Polycystic Ovary Syndrome (PCOS). The study was aimed at evaluating the pregnancy outcomes by comparing PCOS women who conceived on metformin and continued it throughout their pregnancy. Those patients were compared with low risk healthy pregnant women. the women who received metformin with women who did not take metformin during their pregnancy. The outcomes assessed include preterm birth, abortion and intrauterine fetal death.

SUBJECTS AND METHODS

The present study was a single centered comparative study, conducted at Dr B.L. Kapur Memorial Hospital New Delhi over a period of two years. In the scheduled time period for the study, there were 2056 deliveries. All pregnant PCOS women (143) who conceived on metformin and continued it throughout the pregnancy were included in the study as per the inclusion-exclusion criteria and results were compared with 150 low risk healthy pregnant women of the same age group. PCOS criteria (2003 Rotterdam Consensus criteria) were followed.

After receiving written informed consent, patient's personal and demographic details were taken. Complete general and obstetrical history with examination was taken at regular intervals and routine investigations were performed. All patients underwent oral glucose tolerance test (OGTT) with 75 gm glucose during 1st visit, repeated at 24 to 28 weeks and 32-34 weeks. These patients were followed up for weight, BP charting, regular blood sugar charting at home and USG monitoring for Fetal growth and liquor at regular intervals were done.

A dose variation of 500 mg - 2000 mg of metformin was used. As our hospital is a tertiary care centre, so this variation in metformin doses was there because of antenatal mothers attending our OPD at different month of gestation and were referred from various hospitals. Dose was only increased when GDM was diagnosed in the patient; otherwise preconception dose was continued till term.

The quantitative variables in both groups were expressed as mean ± SD and compared using Student's unpaired t-test between the groups. The qualitative variables were expressed as frequencies/percentages and compared using Chi-square test. As discussed in protocol p- value < 0.05 was taken to be considered as statistically significant. Statistical Package for Social Sciences (SPSS by IBM) version 22.0 was used for statistical analysis.

RESULTS

In the current study, a total of 293 pregnant women with PCOS participated and the study population was divided into two groups: a Metformin group (A) and a non-Metformin group (C-control).

1. **Age:**
Mean age of the whole study population was 30.93 ± 3.46 years. Group A had a mean age of 30.56 ± 3.34 years, while the group C had a slightly higher mean age of 31.29 ± 3.54 years. However, no statistically significant difference in the age was observed between the two groups (p value = 0.07), i.e., the two groups were comparable or age matched.

Table 1: Mean age of the study participants among the study groups

Parameter	Overall	Group A (n=143)	Group C (N=150)	P value
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	
Mother age (yrs.)	30.93 ± 3.46	30.56 ± 3.34	31.29 ± 3.54	0.07 (NS)

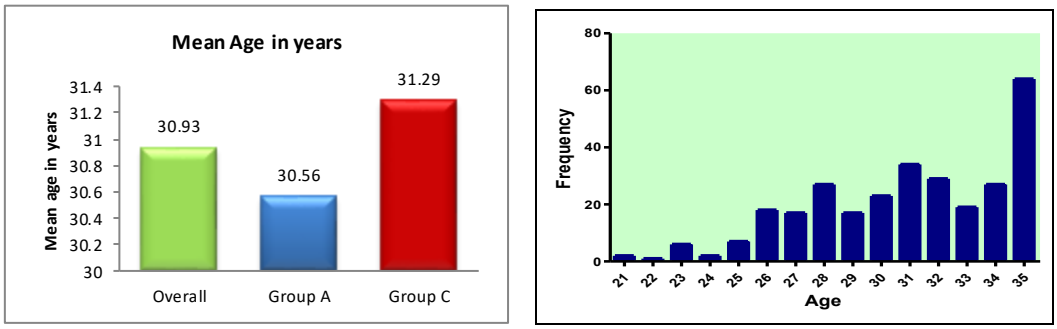

Figure 1: Mean age and Distribution of study participants according to age

2. **Body Mass Index (BMI):**
According to the Asia Pacific BMI Classification, the distribution of BMI categories among the participants was as follows:

- Normal BMI (18.5 – 22.9): on whole, 22.53% of participants had BMI with 19.58% in the A and 25.33% in the C group respectively.
- Overweight (23.0 – 24.9): among the 35.15% of participants 37.06% were of A group and 33.34% were of the C group.
- Obese (>25.0): of the 42.32% of participants in the category, 43.36% were in the A group, while 41.33% were in the C group.
- Underweight (<18.5): No participants were categorized as underweight.

The observations of the study reveal that, majority of women in both groups were either overweight or obese, which is consistent with the higher prevalence of obesity among women with PCOS.

Table 2: Frequency and percentage of mothers' BMI (Asia Pacific Classification)

Parameters	Overall		Case (Group A)		Control (Group C)	
	N	Percent	N	Percent	N	Percent
Underweight (<18.5)	0	0.00	0	0.00	0	0.00
Normal (18.5 – 22.9)	66	22.53	28	19.58	38	25.33
Overweight (23.0 - 24.9)	103	35.15	53	37.06	50	33.34
Obese (>25.0)	124	42.32	62	43.36	62	41.33

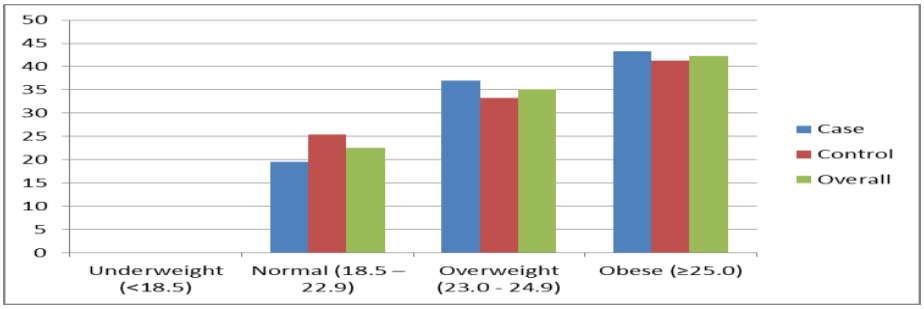

Figure 2: Bar graph showing distribution of BMI across groups

3. **Metformin Dosage:**

The mean Metformin dose in A group was 703.15 mg. The distribution of Metformin doses in the A group was as follows:

- 500 mg: 46.2% of participants,
- 850 mg: 44.1%,
- 1000 mg: 9.7%.

At the time of delivery, the distribution of Metformin doses between A group and C groups showed significant differences:

- 0 mg: 78.7% in C group was only 1.4% in the A group, it is p = 0.002
- 500 mg: 34.3% in the A group and 3.3% in the C group.
- 850 mg: 35.0% in the A group and 2.0% in the C group.
- 1000 mg: 14.7% in the A and 8.0% in the C group.
- 1500 mg: 5.6% in the A group and 2.7% in the C group.
- 2000 mg: 4.9% in the A group and 1.3% in the C group.

The mean Metformin dose at delivery was found to be significantly higher in the A group (868.53 mg) compared to C (248.33 mg), with a p-value of 0.002, indicating that Metformin was more commonly continued throughout the pregnancy in A group.

Table 3: Pre-pregnancy dosage of metformin

Metformin dose (mg)	Cases (Group A)	
	N	Percent
500	66	46.2
850	63	44.1
1000	14	9.7
Mean ± S.D.	703.15 ± 193.49	

4. **Pregnancy Outcomes:**

- **Abortion**: A total of 5.5% of pregnancies ended in abortion across both groups, while 4.9% in the A group and 6.0% in the C group. The difference was not statistically significant (p = 0.679).
- **Intrauterine Death (IUD)**: 1.4% in the A group and 1.5% in the C group, with no statistically significant difference (p = 0.971).
- **Preterm Delivery**: The rate of preterm delivery was significantly lower in the case group (14.7%) compared to the control group (24.14%), with a p-value of 0.048, indicating a potential benefit of Metformin in reducing preterm birth rates.

Table 4: Pregnancy outcomes among the study groups

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

DISCUSSION

This study aimed to evaluate the pregnancy outcomes associated with Metformin use during pregnancy among the women diagnosed with Polycystic Ovary Syndrome (PCOS). It is known that, PCOS increases the risk of various adverse pregnancy outcomes such as miscarriage, preeclampsia, gestational diabetes, and preterm delivery (6). Metformin, has an insulin-sensitizing as well as anti-inflammatory properties, and it has been considered a supportive therapeutic agent during pregnancy in such women. Similar studies were conducted by various researchers (7).

In our study, we found that incidence of preterm delivery was significantly lower in the Metformin group compared to the control group (14.7% vs. 24.14%, p = 0.048). This suggests that Metformin may play a protective role in completing the gestation, potentially by improving insulin sensitivity and reducing inflammatory markers known to trigger preterm labor. Similar findings have been reported in other studies (8) reinforces the hypothesis that Metformin can reduce the risk of early delivery in PCOS pregnancies.

However, no significant differences were observed in the abortion rates (4.9% in Metformin group vs. 6.0% in C group, p = 0.679) or intrauterine death (1.5% vs. 1.4%, p = 0.971). These findings suggest that Metformin may positively influence some pregnancy outcomes, while it may not significantly impact early pregnancy loss or late fetal demise. Similar findings (9) were observed and support the results of our study.

A high prevalence of overweight and obesity across both groups, which aligns with the known metabolic challenges associated with PCOS. Despite this, the favorable outcome in terms of reduced preterm births in the Metformin group highlights the drug's potential benefit even among women with elevated BMI. Results obtained from some research studies (10) coincide with our results.

Furthermore, Metformin dosing varied widely among patients, with a mean dose of approximately 868 mg at the time of delivery in the case group. This suggests that a scheduled dosing approach may have been applied based on individual risk profiles and tolerance. However, one study (11) underscores the need for personalized treatment strategies.

Overall, the findings support the continued use of Metformin in managing PCOS pregnancies, particularly for reducing the risk of preterm birth (9). However, its lack of impact on miscarriage and IUD indicates the need for adjunct strategies to improve all aspects of pregnancy outcomes in this population. Larger multicentric trials with long-term follow-up are warranted to further validate the efficacy and safety of Metformin during pregnancy.

CONCLUSION

The study demonstrates that Metformin use during pregnancy in women with PCOS is associated with a significant reduction in preterm births, suggesting a protective effect on pregnancy outcomes. While no significant differences were observed in miscarriage or intrauterine death, the study and research trends supports the beneficial role of Metformin in improving pregnancy duration without increasing adverse events. These findings highlight the importance of individualized treatment strategies in PCOS pregnancies and underscore the need for larger, multicentric studies to further establish the safety and efficacy of Metformin as a routine therapeutic intervention during pregnancy.

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