Original Article

Role of Metformin in Reducing the Incidence of Gestational Diabetes Mellitus in Obese Women

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Abstract

Objective: To evaluate whether metformin administration reduces the incidence of gestational diabetes mellitus in obese women and to examine its impact on the incidence of preeclampsia, birth weight, and the APGAR scores of newborns.

Methods: This experimental study was done at Shalamar Hospital, affiliated with Shalamar Medical & Dental College, Lahore, Pakistan, from May1st 2022 to June 30, 2024. A total of 150 women with a BMI ≥ 30kg/m2, aged 18-40 years, between 11 to 14 weeks pregnant, were included. Those with contraindications to metformin, pre-existing diabetes, or any co-morbid medical disorder were excluded. The participants were divided into two groups with 75 in each: Group A the control group with only standard care. and Group B receiving metformin 250mg three times daily orally in addition to standard care. The oral glucose tolerance test was performed between 24 to 28 weeks and later at 32 weeks. The participants were followed till delivery to record preeclampsia, neonatal birth weight, and APGAR score.

Results: The mean age, gestational age, and BMI were similar between Group A (32.37 years, 11.37 weeks, 32.37 kg/m²) and Group B (31.35 years, 11.27 weeks, 32.3 kg/m²). The incidence of GDM (10% vs. 42%) and preeclampsia (13% vs. 74%) was significantly lower in the metformin group (p = 0.000). However, no significant differences were observed in birth weights or APGAR scores.

Conclusion: FMetformin reduces the incidence of GDM and preeclampsia in obese women when started at 11 to 14 weeks of gestation, without affecting birth weight and APGAR score of neonates.

Keywords: Gestational Diabetes Mellitus, Pre-eclampsia, Lifestyle changes, Metformin, Obesity.

Introduction

Gestational Diabetes Mellitus (GDM) is a metabolic condition that arises during pregnancy, affecting approximately 15% of pregnancies. It is linked to numerous adverse maternal and fetal outcomes, including preeclampsia, preterm delivery, cesarean section, macrosomia, stillbirth, low APGAR scores, neonatal hypoglycemia, respiratory distress, and neonatal jaundice.[1,2] Early treatment and good glycemic control have been evidenced to reduce these complications.[3] Similarly, there are many measures to prevent GDM, including lifestyle modification (diet management, exercise) and some pharmacological agents like metformin, myoinositol[4] As obesity is one of major risk factor to develop GDM, the women are at 1.9-2.69-fold increased risk to develop GDM when comparing obese and non-obese women and is associated with maternal and fetal complications.[5] Among the various pharmacological agents, metformin has been studied for its role in the prevention of GDM in pregnant patients with obesity and when it has been used in combination with lifestyle interventions, such as diet and exercise, may help reduce weight gain and prevent GDM in this population.[5] The International Federation of Gynecology and Obstetrics (FIGO) recommends metformin as a first-line medication for GDM patients who do not achieve ideal blood glucose levels through lifestyle interventions alone. Metformin targets insulin resistance and improves insulin action, making it a potential therapeutic option for managing hyperglycemia in pregnancy.[6] Studies have also shown that metformin treatment in early pregnancy may decrease the frequency of preeclampsia, a complication associated with GDM. The function of metformin in this population has been examined in a number of randomized clinical trials. The "Efficacy of Metformin in Pregnant Obese Women" (EMPOWaR) trial, which was conducted from February 3, 2011, to January 16, 2014, compared metformin to a placebo in pregnant women who were obese and did not have diabetes. The results showed that metformin decreased the incidence of preeclampsia but did not lower the frequency of large-for-gestational-age babies.[7] Metformin decreased maternal weight gain but had no effect on neonatal birth weight, according to a another study, the Fetal Medicine Foundation trial (2010–2015), which compared the medication with a placebo in pregnant women who were obese but not diabetic.[8] Metformin should not be advised to prevent unfavorable pregnancy outcomes in obese non-diabetic women, according to a meta-analysis of these trials.

Overall, metformin may have some benefits in reducing the risk of pre-eclampsia and maternal weight gain, its effectiveness in preventing gestational diabetes in obese pregnant patients is still uncertain because literature showed conflicting results.[7,8,9] We took up this study to evaluate the effect of metformin for preventing

GDM in pregnant women with obesity because more research is necessary to completely comprehend the drug's effectiveness in preventing GDM and its impact on maternal and newborn outcomes. So, the objective of this research is to evaluate the preventive role of metformin in obese women for the development of GDM, preeclampsia and its effect on neonatal birth weight and APGAR scores.

Methodology

This experimental study was conducted in the OBGYN Department of Shalamar Hospital, affiliated with Shalamar Medical & Dental College in Lahore, Pakistan, IRB SIHS (IRB-542), between May 1, 2022, and Nov 30, 2024, with two groups by lottery method as Group A: Control group. and Group B Intervention (Metformin) group: With a power of 80% and a 5% threshold of significance, the sample size was determined to be 128 (64 in each group). In obese women, the incidence of GDM was 4% when using metformin versus 20% when not.[7], so 64 women were assigned in each group.. Total of 150 women who were having BMI ≥ 30 kg/m^2 without preexisting diabetes, aged 18-40 years, between 11 to 14 weeks, having singleton pregnancy were included in the study, however women with contraindications to metformin, pre-existing diabetes, renal impairment, or other co-morbid medical disorder, previous history of GDM, history of macrocosmic baby and with multiple gestation or fetus with abnormalities were excluded. Preexisting diabetes was checked by glycosylated (HbA1C) level. The enrolled participants were divided in two groups; Group A (control) who were receiving standard care (Diet & exercise) and the other Group B who were receiving metformin in addition to the standard care (Diet & exercise) only. Gestational diabetes was diagnosed based on standardized criteria as Oral Glucose tolerance test to be done at between 24 to 28 weeks and then 32 weeks. Following WHO Criteria with 75 gm oral glucose, three levels performed with fasting blood glucose < 95 mg/dl, less than 140 mg/dl after 1 & 2 hours are the levels followed to label a patient as case of Gestational Diabetes [10] Whereas pre-eclampsia was labelled when there was more than 140/90 mmHg at 4 hours interval after 20 weeks of gestation and neonatal birth weight and APGAR scores were recorded as per standard criteria.

Data Collection

After getting approval the patients who fulfilled the inclusion criteria from were enrolled in the study. The demographic data (age, gestational age, parity, and BMI) was taken. Pregnant women who were fulfilling the inclusion criteria were enrolled in this research after taking informed consent and divided into two groups as Group A (Control) whereas the other was experimental Group B (metformin treated). In Group B metformin was initiated at a daily dose of 250mg orally three times a day. We followed the patients in antenatal clinic regularly following WHO standards as monthly till 28 weeks followed by fortnight visit till 36 weeks and weekly visit after 36 weeks till the plan of delivery. On all antenatal visit patients were checked for maternal weight gain, blood pressure and glucosuria. Both groups were assessed for the developmental of GDM by OGTT at 24 to 28 weeks and 32 weeks of gestation. The routine followed up by antenatal visits and antenatal ultrasound scans were the same as mentioned for the patients in group A & B. All information was entered into a pre-made proforma in accordance with the operational definition. As OGTT was repeated at between 24 to 28 weeks, 32 weeks, however If the results show positive for gestational diabetes, then no further tests were performed and the study for that patient was concluded and were managed in Maternal Fetal Medicine unit of Shalamar Hospital. All these patients were managed efficiently as per standard protocol. The data were analyzed using the statistical software program IBM SPSS version 23. Mean ±SD was presented for quantitative variables like age, gestational age, BMI. Parity was presented as frequency. Chi-square test was applied to compare efficacy in both groups, taken p ≤0.05 as significant.

Data Analysis

The primary analysis has involved the comparison of the incidence of gestational diabetes between the metformin control groups using appropriate statistical tests (e.g., chi- square test). The proper statistical techniques was applied to the analysis of secondary outcomes.

Results

A total of 200 patients were initially enrolled, with 100 in each group. However, 25 patients from the control group and 23 from the metformin group were lost to follow-up. Furthermore, 2 patients in the metformin group discontinued treatment due to gastric discomfort. The incidence of gestational diabetes mellitus and preeclampsia was significantly lower in the intervention group compared to the control group, as shown in Table 1. Neonatal birth weight and APGAR scores at 1 and 5 minutes did not show any significant difference between the two groups (Table 2). The Chi-square test was used to analyze categorical variables, such as the incidence of gestational diabetes mellitus and preeclampsia, in Table 1. For continuous variables, including neonatal birth weight and APGAR scores, the independent sample t-test was applied in Table 2.

Table 1: Comparison of Gestational Diabetes Mellitus and Preeclampsia Incidence between Control and Intervention Groups

Variable		Control group A	Intervention group B	p-value
GDM	No	37(57.8%)	57 (89.1%)	0.000
	Yes	27(42.2%)	7 (10.9%)	
Preeclampsia	Yes	47(74%)	9 (13%)	0.000
	No	17(24%)	55(87%)	

Table 2: Comparison of Neonatal Birth Weight and APGAR Scores between Control and Intervention Groups

Variables	Group A Mean± SD	Group B Mean± SD	p-value
Birth weight (kg)	3.250 ± 0.50	3.32 ± 0.150	>0.05
APGAR score (1min)	7.12 ± 0.52.	7.35 ± 0.15	>0.05

APGAR score (5min)	7.35 ± 0.15	8.35 ± 0.15	>0.05

Discussion

This experimental study assessed the effectiveness of metformin in lowering the incidence of gestational diabetes among obese women. A total of 150 women with a BMI ≥ 30 kg/m^2 without preexisting diabetes, aged 18-40 years, between 11 to 14 weeks of gestation, and having singleton pregnancy, were included in the study. A Metformin dose of 250 mg was given orally three times a day and showed statistically significant results for reducing the incidence of GDM (Table 1) and preeclampsia but it had no significant effect on neonatal birth weight and APGAR score (Table 2). This study gave a valuable insight about preventive role of metformin in obese women which in turn reduce the consequential complication of gestational diabetes, including polyhydramnios, preterm births, intrauterine death etc. and preeclampsia. Among different interventions to prevent GDM, metformin's role is still under research along with other measures, however the exact mechanism of action by which metformin can reduce weight gain during pregnancy and hence GDM prevention has not been fully understood especially in obese patients with pregnancy, however certain proteins involved in the metabolism of the body may have its role. [11,12,13]. The role of metformin in limiting weight gain has been supported by numerous studies. Additionally, incorporating exercise and nutritional control has proven to be an effective strategy for managing obesity.[14,15,16,17]

It has been reported that starting metformin in early pregnancy, around 12 to 18 weeks, effectively limits weight gain during pregnancy.[15,16,17,18] Previous studies have shown that metformin is not effective in preventing GDM in obese pregnant women, with one study reporting GDM incidence of 15.9% in the metformin group and 19.5% in the control group, showing no significant difference (p = 0.683).[7] Similarly, a meta-analysis of 11 randomized controlled trials reported a comparable risk of GDM between metformin users and controls (risk ratio 1.03).[9] While the study demonstrated limited weight gain with metformin use, it did not support its role in preventing GDM, which contrasts with the findings of our study. In the present study, GDM was observed in 57 (89.1%) patients in Group A compared to 37 (57.8%) patients in Group B (P = 0.000) (Table 1), which is consistent with the findings of previous studies which reported that metformin reduces the risk of GDM by 34%.[11,19]

In this research, metformin was initiated at a daily dose 250mg orally three time a day. This dose is different from Niroomanesh et al. (2010), who reported the use of metformin 500 to 2500 mg of metformin in 104 women and showed the effectiveness of metformin for good blood glucose levels control during pregnancy. They used 500mg twice daily to 2500mg daily and showed the effectiveness of metformin to prevent the GDM in metformin group.[20] Neola et al. (2024) reported the promising effect of metformin to reduce GDM, but the optimal dose is still inconclusive.[21] Another significant point is the level of BMI to be taken as to label as "obese". A multi-center, prospective research was reported from European world in which different strategies were compared to prevent GDM among women with BMI > 29kg/m^2 and the results found the development of GDM in 14% of the patients in their second trimester (24 to 28 weeks), regardless of type of approach or strategy used.[22] However, in this research BMI more than 30 mg kg/m^2 and WHO 2013 criteria was taken to label patient as GDM.[10] In 2022, Seshiah et al. reported that a 2-hour postprandial level of 110 mg/dl in early pregnancy, around 11 to 13 weeks, indicates the need for early intervention, such as metformin, to prevent gestational diabetes.[23] However, in this research WHO recommendation of OGTT at between 24 to 28 weeks and 32 weeks is followed.[10] Since metformin has demonstrated encouraging effects in preventing gestational diabetes in obese patients, this study also highlights the importance of early screening and intervention.

The incidence of preeclampsia as 13% of women in the metformin group compared to 74 % in the control group supports the preventative role of metformin for pre-eclampsia (Table 1). The potential of metformin to reduce the inflammatory response is believed to be the mechanism behind its ability to lower the incidence of pre-eclampsia, as reported by He et al. (2023).[24] However, Feig (2019) presented contradictory findings from randomized trials, with one trial indicating that metformin prevents pre-eclampsia, while another did not show the same result.[25]

The effect of metformin for preterm birth is still under investigations although it does affect the preterm birth by reducing the prevalence of pre-eclampsia as it is one of known etiology for preterm birth. However, this research showed (Table 3) the fetal birth weight, APGAR score at 1 min and 5 minutes are not significantly affected by both groups with and without metformin as evidenced by the EMPOWER trial.[7,11] This research provides insight regarding metformin's preventive role in obese women in the form of metformin in addition to other standard measures like diet control and exercise to be started in early pregnancy, however, metformin solely has not evidenced to prevent GDM in non-diabetic obese pregnant wome.[26]

Limitations

Although, the sample size is small but still have statistical power (80%), which made this study as pilot project to make foundation for future studies and gave insight to the preventive role of metformin. However, the recruitment of participants according to inclusion criteria, like obesity, 11 to 13 weeks' gestation, single fetus with no preexisting diabetes, no fetal abnormalities etc. was challenging. The recruitment constrains, reflect real world challenges, making these results valuable in our clinical practice. However, future studies at large scale research in collaboration with other centers is recommended to overcome recruitment challenges.

Conclusion

Metformin was found to be effective in preventing GDM and pre-eclampsia in obese pregnant women. The study highlights the need for early intervention and emphasizes the importance of lifestyle changes in conjunction with medication. These findings have significant implications for the management and prevention of GDM, and further research in this area is warranted to fully elucidate the safety and efficacy of metformin. **Author Contributions:** SR conceived the idea, designed the study, obtained IRB approval, analyzed, and interpreted the data, and drafted the manuscript; MFM assisted with IRB approval, data collection, analysis, interpretation, and drafting; ST contributed to data interpretation, drafting, and proofreading; and UFA was responsible for data collection and analysis.

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