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Comparison of the Effect of Insulin with Metformin on Neonatal Outcome in Booked Patients with Gestational Diabetes Mellitus

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ABSTRACT

Insulin has long been used as a treatment for gestational diabetes that is not well managed with diet. Metformin has been shown in several trials conducted in recent years to produce perinatal and obstetric results that are comparable to those of insulin. Studies have reported conflicting results regarding both modalities, and not all clinical recommendations support its usage. **Objective:** To compare neonatal outcomes in patients with metformin-treated gestational diabetes mellitus versus those with insulin-treated gestational diabetes mellitus. **Methods:** An observational study took place at the Obstetrics and Gynaecology Unit-III of Lady Willingdon Hospital, Lahore, during the time period starting from January 1, 2023, until December 1, 2023. One hundred and eighty-eight patients (94 in each group) were included in the study. In Group A, metformin tablets were given, and patients in Group B were given insulin. Outcome variables were measured as per the operational definition, respectively. **Results:** Patients receiving insulin therapy developed macrosomia more frequently (10.6% in the Metformin group vs. 23.4% in the Insulin group, p=0.029), along with hypoglycaemia (19.2% for Metformin vs. 33% for Insulin, p=0.031) and respiratory distress (9.6% Metformin vs. 20.2% Insulin, p=0.041) statistically often. Research showed no meaningful differences in findings between study groups regarding jaundice occurrence, together with intrauterine growth restriction (IUGR) and amniotic fluid measurements. **Conclusions:** In comparison to insulin, metformin is equally effective in preventing neonatal complications such as macrosomia, hypoglycaemia, and respiratory distress in women with gestational diabetes.

INTRODUCTION

Insulin resistance is a characteristic of pregnancy, and insufficient insulin production to offset insulin resistance leads to gestational diabetes mellitus (GDM) [1]. Because of glucose intolerance, GDM is frequently discovered in the second trimester of pregnancy. Pregnancy-related obesity, autoimmune beta-cell dysfunction, modification of metabolism of carbohydrates, fats, proteins, decreased insulin production, and insulin resistance are important variables [2, 3]. When hyperglycemia is initially noticed with one or more abnormal readings on 75 g OGTT-fasting plasma glucose 5.1-6.9 mmol/l, 1-hour plasma glucose 10.0 mmol/l, or 2-hour plasma glucose 8.5-11.0 mmol/l, the World Health Organization advises labeling it as GDM [4]. In many parts of the world, GDM is a growing health issue [5]. Global occurrence of diabetes is 16.9 percent, with 80 percent residing in low- and middle-income countries. About 16.2% of live births are exposed in utero to hyperglycemia, 85.1% of which is due to gestational diabetes mellitus. In Southeast Asia, the prevalence of GDM is highest, estimated at approximately 24.2 percent, mainly

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in low or middle-income groups [6]. The survey within Pakistani healthcare facilities revealed that 11.8% of pregnant mothers received GDM diagnoses. The identification of gestational diabetes mellitus (GDM) occurred among 6.2% of women in their first trimester, and 51.1% during the third trimester, and 39.9% in the second trimester [7]. The goal of regulating high blood glucose levels in gestational diabetes mellitus patients makes insulin an established treatment option because of its proven effectiveness [8]. Research teams originally developed insulin as a life-saving medication for Type 1 diabetic patients before using it as the primary treatment for GDM because most oral hypoglycemic agents proved teratogenic [9]. The medical community considers insulin to be a dependable and secure treatment for diabetic pregnant women with diabetes. The use of insulin for managing gestational diabetes mellitus presents two main disadvantages due to its requirement for injections and potential risks for maternal hypoglycemia and excessive fetal growth, as well as increased costs [10]. The diabetes drug metformin, which entered clinical use in 1960 for type 2 diabetes patients, now serves as an acceptable option for the management of GDM. Medical professionals classify metformin as Category B because it does not cause congenital fetal malformations, maternal weight increases, or neonatal hypoglycemia during pregnancy [11]. The effect of metformin on insulin sensitivity, along with its ability to decrease gluconeogenesis, supports β-cell function according to studies [12, 13]. Medical science first employed metformin as an insulin resistance treatment for women, according to research available [14].

Although there is an increasing prevalence of gestational diabetes mellitus (GDM) and both insulin and metformin are available as treatment options, comparative evidence regarding their effect on neonatal outcomes, especially in low and middle-income countries such as Pakistan, is still scarce. This poses a clinical dilemma on the best treatment that leads to optimal efficacy, safety, and cost. Thus, the study aims to compare neonatal outcomes between patients who have undergone GDM treatment with metformin and those treated with insulin.

METHODS

It was a prospective comparative study was conducted at the Department of Obstetrics and Gynaecology Unit-I, Lady Willingdon Hospital, Lahore, from 1st January 2023 to 1st December 2023. The ethical approval for this study was obtained from King Edward Medical University, Lahore (Ref No. 493/RC/KEMU; dated 23rd May 2022). Patients were randomized using a computer-generated simple randomization sequence. Group assignment was done using sealed, opaque envelopes to ensure allocation concealment. The outcome assessors were blinded to the treatment groups during data collection and outcome evaluation to reduce bias. A total sample size of 188 patients (94 in each group) is estimated by using 95% confidence interval level, 10% absolute precision, with expected percentage of neonatal hypoglycaemia associated with insulin as 28.2% and metformin as 4.4% [15]. All patients aged 18-36 years, having singleton pregnancies, who at 24-28 weeks of gestation, confirmed to have GDM (on the basis of oral glucose challenge test and oral glucose tolerance test) were included. The pre-gestational diabetes mellitus and multiple pregnancies were excluded. Patients were thoroughly assessed for study criteria and investigated during an outdoor appointment. Patients were assessed every 1-2 weeks throughout pregnancy for glycaemic control with HbA1C. Tests are advised at 24 and 32 weeks of gestation, and fetal outcome was monitored by ultrasound. at these visits. Advise women with gestational diabetes mellitus to maintain their plasma glucose below the target levels: Fasting 5.3 mg/dl, 1 hour after meal 7.8 mg/dl, and 2 hours after meal 6.4 mg/dl. Informed consent was obtained, patients were randomly assigned by parallel assignment with 94 in each group (in the second trimester, after confirmation of gestational diabetes mellitus with an oral glucose challenge test Metformin tablets with a 500 mg strength three times daily were provided to Group A patients (a total of 94 patients). The dosage increased from a single morning dose to three times daily based on blood sugar management. The patients whose numbers ended in even received subcutaneous insulin (Group B=94). Each insulin type was prescribed separately: short-acting insulin before meals (4–6 units), and intermediate or long-acting insulin (10–12 units) once daily, with doses adjusted based on glucose levels. The calculation of insulin dosage for the second trimester used 0.8 units per kilogram of body weight, and the amount was increased to 0.9 units per kilogram for the third trimester. Insulin was prescribed twice daily: short-acting insulin before meals and intermediate-acting insulin at bedtime, with doses adjusted according to blood glucose levels. Patients were advised through diet charts to strict diet control (1800-2000kcal/day. and were also prescribed at least thrice weekly for 30 minutes' walk. If a patient on metformin was not controlled during treatment, they were excluded from the study. Fetal outcome was monitored by using ultrasound scans at these visits in terms of macrosomia and polyhydramnios. Outcomes were measured with reference to the neonate regarding preterm, birth weight, Respiratory Distress Syndrome RDS, Jaundice, and polyhydramnios. It was a convenient sampling, including neonatal heart rate, neonatal blood sugar levels were assessed, and values below 2.6 mmol/l were labelled as hypoglycaemia. The sample size of 188 patients (94 in each

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group) was calculated using a 95% confidence level, 10% absolute precision, and the expected percentage of neonatal hypoglycaemia of 28.2% in the insulin group and 4.4% in the metformin group, based on the findings reported by Akinyemi *et al.* [16].

Data was entered and analysed with SPSS-26. Quantitative variable outcome was compared between groups with the help of an independent sample t-test, and qualitative outcome variables were compared between groups with the help of the chi-square test. Data were entered and analysed using SPSS version 26. The quantitative variables included maternal age, amniotic fluid index (AFI), neonatal birth weight, and neonatal heart rate. These were compared between the metformin and insulin groups using the Independent Sample t-test. The qualitative variables included the presence or absence of jaundice, macrosomia, neonatal hypoglycaemia, respiratory distress syndrome (RDS), and intrauterine growth restriction (IUGR). These categorical outcomes were compared between the two groups using the Chi-square test. A p-value of less than 0.05 was considered statistically significant. The p-value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of women in Group A was 27.47 ± 4.77 and 27.90 ± 4.92 years in Group B. There was statistically significant difference was noted between groups. The mean amniotic fluid was 16.16 ± 5.86 in group A, and 16.04 ± 5.88 in group B. No significant difference was seen for amniotic fluid between groups. The mean heart rate of neonates in Groups A and B was 142 ± 8.56 and 142.41 ± 8.45, and the mean weight of neonates in Groups A and B was 3.37 ± 0.30 and 3.39 ± 0.28 kg, respectively. There was a statistically significant difference between heart rate and weight between the groups (Table 1).

Table 1: Comparison of Age and Amniotic Fluid of Patients in Both Groups

Variables	Group A	Group B	p-value[(t)]
Age (Years)	27.47 ± 4.77	27.90 ± 4.92	0.528
Amniotic fluid	16.16 ± 5.86	16.04 ± 5.88	0.911
Heart rate (bpm)	142.00 ± 8.56	142.41 ± 8.45	0.662
Weight (kg)	3.37 ± 0.30	3.39 ± 0.28	0.708

[(t):] Independent sample t-test

The frequency of jaundice showed no significant difference between groups, Group A 7.4% vs Group B 13.8%, with p-value=0.156. Macrosomia was significantly higher in group B as compared to group A, 10.6% vs. 23.4%, with a p-value of 0.020. Hypoglycaemia was significantly higher in group B as compared to group A, 19.2% vs. 33%, with a p-value of 0.031. Respiratory distress was significantly higher in group B as compared to group B 9.6% vs 20.2%, with a p-value of 0.041. IUGR was seen in 3 (3.2%) neonates in Group A and 3 (3.2%) neonates in Group B, respectively (Table 2).

Table 2: Comparison of Jaundice, Macrosomia, Hypoglycaemia, and Respiratory Distress in Both Groups

Variables	Group A	Group B	X^2 value	p-value
Jaundice				
Yes	7 (7.4%)	13 (13.8%)	2.01	0.156
No	87 (92.6%)	81 (86.2%)		
Macrosomia				
Yes	10 (10.6%)	22 (23.4%)	5.423	0.020*
No	84 (89.4%)	72 (76.6%)		
Hypoglycaemia				
Yes	18 (19.2%)	31 (33%)	4.66	0031*
No	76 (80.9%)	63 (67%)		
Respiratory distress				
Yes	9 (9.6%)	19 (20.2%)	4.196	0.041*
No	85 (90.4%)	75 (79.8%)		
IUGR				
Yes	3 (3.2%)	3 (3.2%)	0.000	-p < 0.001
No	91 (96.8%)	91 (96.8%)		

Chi-Square test, (*) p-value <0.05

DISCUSSION

It is essential to control diabetes throughout pregnancy to reduce negative consequences on the mother and fetus. Two frequently used treatment options for managing GDM are metformin and insulin. Although the goal of both drugs is to manage blood sugar levels, their modes of action and possible effects on the health of newborns are different. In this trial, we have examined the comparison of newborn outcomes linked to metformin vs insulin usage for the treatment of GDM. The mean age of women in Groups A and B was calculated to be 27.47 years and 27.90 years, respectively, and the age range in both groups was 20-36 years. Comparison of neonatal outcomes was done among the study groups. Some outcomes have not shown any difference among comparison drugs, i.e., neonatal HR, amniotic fluid mean, and IUGR development. In both groups, the mean of neonatal HR calculated was similar, showing no significant difference, i.e., 142.00 (group A) and 142.41 (group B) bpm, respectively, p=0.662. Both study groups also have similar mean neonatal weights calculated, 3.37 kg in group A and 3.39 kg in group B, p=0.708. In both groups, 3.2% newborns developed intrauterine growth restriction. The mean of amniotic fluid calculated in both groups was also nearly equal, metformin group mean calculated was 16.16, and in the insulin group, 16.04, p=0.91. Fetal development may also be linked to diabetes during pregnancy. Type 1 diabetes that has been uncontrolled encompasses a variety of clinical problems, like diabetic vasculopathy leading to placental malfunction and consequent fetal growth limitation since the placenta

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is an organ made almost entirely of vessels [17]. It was observed previously that there was no change in newborn length or IUGR, but metformin usage was linked to lower birth weights and decreased likelihood of macrosomia (OR 0.59) [2]. Jaundice was detected in 7.4% neonates in the metformin group and 13.8% in the insulin group. The total number of cases with jaundice was 20, accounting for 10.6% of the total sample size of 188 neonates. However, the difference between groups was not statistically significant (p=0.156). In women with GDM, metformin along with insulin has been demonstrated to reduce newborn jaundice. 10.71% neonates developed jaundice on combined treatment as compared to 26.79% using insulin alone [18]. Incidence of neonatal jaundice (13.6 vs. 33.6%, p<0.000), in combination therapy, was noted to be low versus when insulin was used alone in another RCT [19]. 10.6% newborns in the metformin group and 23.4% in the insulin group had macrosomia; the p-value of 0.020 indicated statistically significant differences in the occurrence of macrosomia between comparison groups. Another trial has supported our findings in which 3 groups were compared, i.e., diet, metformin, and insulin groups, and it was observed that compared to the diet (29.5%) and insulin (21.7%) groups, fewer macrosomic newborns were seen in the metformin group (12.5%) [19]. In contrast to what we and this study experienced, the proportion of LGA babies in the metformin (8.2%) vs insulin (14.3%) groups did not differ significantly from each other in the MiG9 experiment, p>0.05. It might be because the metformin group in the aforementioned research received more insulin. Similar findings to ours were reported in the Gandhi *et al.* investigation [19]. In group A, hypoglycaemia occurred in 19.2%, but in group B, it was noted to be high, 33%, p-value of 0.031 indicated statistically significant differences. According to earlier research, the metformin group experienced a lower rate of newborn hypoglycaemia than the insulin group. There was no difference in infant morbidity between the groups receiving oral treatment and those receiving insulin; moreover, the oral treatment groups did not exhibit any occurrences of severe hypoglycaemia or jaundice [20, 21]. One study discovered that preterm births and glyburide use for gestational diabetes mellitus increased the incidence of hypoglycaemia in neonates. There was no discernible difference in risk of neonatal hypoglycaemia between pregnancies that were insulin-dependent and those that were controlled only with dietary changes. This study has also emphasized how crucial it is to check all newborns for hypoglycaemia during pregnancies involving GDM. Even those who were regarded as "lower risk" had a rather high chance of newborn hypoglycaemia, with hypoglycaemia seen in 39% of GDM-affected women's neonates, 35% of whom had hypoglycaemia treated with diet alone, and 33% of whom had it treated with medication [22]. 9.6% newborns in the metformin group and 20.2% in the insulin group had the incidence of RDS, p-value of 0.041 indicated statistically significant variances among comparison groups. The pooled OR calculated was 1.47 for the relationship between maternal DM and risk of newborn RDS. For both GDM and pre-gestational diabetes mellitus, the pooled OR for the risk of newborn RDS was 1.57 and 2.66, respectively. So, it means GDM is a cause of RDS, not the treatment modalities [23]. It was concluded in one study that, when compared to insulin treatment for GDM, metformin may lower the risk of certain outcomes for mothers and newborns [24]. Insulin has several drawbacks, including daily injections, the possibility of hypoglycaemia, and weight gain in mothers. On the other hand, metformin is less expensive, safe, and has no appreciable effects on the mother or newborn, making it more acceptable to women with GDM [25]. More iatrogenic preterm births would occur if metformin had any unforeseen negative effects on fetal development or well-being. Furthermore, compared to insulin, metformin therapy produced better glycaemic control and better outcomes for newborns [2]. It was evaluated that the long-term effects of metformin on offspring occur due to its placental crossing. They demonstrated that over the first 18 months of life, growth, motor, and social development of children whose mothers were on metformin did not vary from those of control newborns. Thus, metformin is a good option for GDM, particularly for patients who are overweight but not obese [26].

Although the primary goal of our study was to compare the newborn outcomes using either metformin or insulin, it is essential to recognize that some limitations exist. First off, the relationship between maternal glycaemic management and newborn outcomes was not specifically examined in our study. Although it wasn't expressly included in our study, the effectiveness of metformin and insulin in lowering maternal blood glucose levels may have an impact on the outcomes of newborns. Furthermore, the primary focus of our research was the assessment of short-term newborn outcomes; there was no assessment of long-term neonatal outcomes. Further investigation is necessary to thoroughly assess these connections and the long-term results on the newborn.

CONCLUSIONS

The efficacy of metformin is as high as that of insulin in terms of neonatal outcome (macrosomia, hypoglycaemia, and respiratory distress) in women with gestational diabetes.

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Authors' Contribution

Conceptualization: MI
Methodology: MI, MJ
Formal analysis: NA, SC, NA
Writing and Drafting: MI, TA
Review and Editing: MI, MJ, NA, SC, TA, NA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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