Section: Obstetrics and Gynaecology

Original Research Article

MATERNAL AND FETAL OUTCOMES WITH METFORMIN VS INSULIN THERAPY IN GESTATIONAL DIABETES MELLITUS: A PROSPECTIVE OBSERVATIONAL STUDY

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Received *: 18/02/2025*
Received in revised form *: 08/04/2025*
Accepted *: 23/04/2025*

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DOI: 10.70034/ijmedph.2025.2.159

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (2); 881-887

ABSTRACT

Background: Gestational Diabetes Mellitus (GDM) is a common metabolic disorder in pregnancy. It is particularly prevalent in South Asian populations, including India. Although Insulin is commonly considered standard pharmacological treatment metformin has also gained attention as an oral alternative with promising results. The purpose of this study was to compare the efficacy and safety of metformin versus insulin in GDM management.

Materials and Methods: This was a prospective observational study conducted in the department of obstetrics and gynecology of a tertiary care hospital. 60 pregnant women between 20–30 weeks gestation diagnosed with GDM based on DIPSI criteria were included in this study. Patients were randomized into two groups: one received oral metformin (500–2000 mg/day), and the other received Mixtard insulin with dose titration as per glycaemic control. Maternal fasting and postprandial glucose levels and mode of delivery were compared between two groups. Neonatal outcomes such as birth weight, hypoglycaemia, hyperbilirubinemia and NICU admission were also assessed. SPSS version 23 was used for statistical analysis and p value less than 0.05 was considered statistically significant.

Results: Fasting blood glucose levels were significantly lower in the metformin group (102.4 ± 9.1 mg/dL) as compared to patients in insulin group ($p = 0.0098$). Postprandial blood sugar level was better controlled with insulin ($p < 0.0001$). No significant differences were found in mode of delivery or neonatal birth weight. Neonatal hypoglycaemia was more commonly seen in the insulin group (40.0%) as compared to metformin group (23.3%) although this difference was not statistically significant ($p = 0.266$). Metformin showed better compliance and was associated with fewer adverse neonatal outcomes.

Conclusion: Both metformin and insulin effectively manage GDM with metformin offering advantages in fasting glucose control, fewer neonatal complications and better patient compliance. Metformin is found to be first-line pharmacologic alternative to insulin particulalry in resource-limited settings.

Keywords: Gestational Diabetes, Metformin, Insulin, Glycaemic Control, Neonatal Outcomes.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance which is first recognised during pregnancy. It is usually identified in the second or third trimester of pregnancy and excludes diabetes diagnosed prior to pregnancy.[1] GDM is reported to be affecting 7%–14% of all pregnancies globally. Its incidence is affected by factors such as ethnicity, maternal age as well as body mass index (BMI). In South Asian population prevalence is comparatively higher and is reported to range from 10% to 18%.

This high incidence is largely due to increased insulin resistance and metabolic risk factors. With the rise in sedentary lifestyles GDM is rapidly becoming a growing public health concern.[2]

The pathophysiology of GDM depends upon progressive pancreatic β-cell dysfunction superimposed on chronic insulin resistance which is exacerbated during pregnancy. In early pregnancy insulin sensitivity increases slightly but as pregnancy progresses placental hormones such as human placental lactogen, progesterone, cortisol and prolactin contribute to a diabetogenic state.[3] This insulin resistance is physiologically intended to shunt glucose to the growing fetus but becomes pathological when maternal insulin secretion cannot compensate for the effects of these hormones. As a result, maternal hyperglycemia develops. Uncontrolled GDM poses risks such as preeclampsia, increased chances of caesarean section and polyhydramnios. For the fetus hyperglycemia leads to macrosomia, neonatal hypoglycaemia, respiratory distress syndrome and an increased predisposition to obesity and type 2 diabetes mellitus later in life.[4]

GDM is generally diagnosed between 24 and 28 weeks of gestation. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) and the American Diabetes Association (ADA) recommend the one-step method as a preferred method for the diagnosis of GDM. Once the diagnosis is confirmed management of patients diagnosed primarily aims to maintain normoglycemia throughout gestation and includes dietary counselling, physical activity and strict blood glucose monitoring. When non-pharmacological interventions fail to achieve target glucose levels (fasting <95 mg/dL, 1-hour postprandial <140 mg/dL) prompt pharmacologic therapy is indicated.[5]

For decades insulin has been considered the gold standard for pharmacologic management of GDM. It does not cross the placenta and allows for precise titration.[6] However insulin therapy has several limitations including the need for subcutaneous injections, increased risk of maternal hypoglycaemia, refrigeration requirements and chances of lower patient compliance. Metformin is an oral biguanide agent which acts by reducing hepatic glucose production and increasing peripheral insulin sensitivity. Several studies have demonstrated its efficacy in achieving glycaemic control comparable to insulin with the added advantages of oral administration. It has also advantage of improved compliance, lower risk of maternal weight gain and potential cardiometabolic benefits. However, metformin does cross the placenta which raises concerns about its long-term fetal safety.[7]

The comparative efficacy and safety of metformin versus insulin in the treatment of GDM remains subject of ongoing debate. While randomized controlled trials (RCTs) and meta-analyses have attempted to evaluate this question existing literature demonstrates significant differences in outcomes. Some studies suggest that metformin is as effective as insulin in glycaemic control and results in lower maternal weight gain and fewer episodes of neonatal hypoglycaemia. Others raise concerns about increased rates of supplemental insulin requirements in metformin-treated women and potential unknown effects on fetal metabolic programming.[8]

This study aims to address some of these limitations by conducting a hospital-based observational study evaluating the efficacy and safety of metformin versus insulin in pregnant women diagnosed with GDM.

MATERIALS AND METHODS

This was a prospective observational study conducted In the Department of Obstetrics and Gynecology of a tertiary care hospital. 60 pregnant women between 20-30 weeks of pregnancy and diagnosed to be having gestational diabetes were included in this study on the basis of a predefined inclusion and exclusion criteria. The diagnosis of gestational diabetes was made on the basis of according to Diabetes in Pregnancy Study Group India (DIPSI) criteria (2-hour postprandial blood glucose ≥140 mg/dL following a 75 g glucose load).9 The patients were divided in to 2 groups on the basis of whether they were prescribed metformin or insulin. Participants were allocated into the metformin or insulin groups using simple randomization by employing computer-generated random numbers.

Demographic details were collected in all cases. Age, parity, obstetric history, family history, and history of GDM in prior pregnancies were also noted. Once diagnosed with GDM patients were divided into 2 groups on the basis of either they were prescribed metformin or insulin

Metformin Group: Participants started on oral metformin at a dose of 500 mg/day, titrated to a maximum dose of 2000 mg/day based on glycaemic response and tolerance. Patients who failed to achieve adequate glycaemic control.

Insulin Group: Participants started on insulin therapy (Mixtard insulin), with dosing individualized and titrated based on regular monitoring of blood glucose levels.

Maternal glycaemic control was assessed by monitoring fasting and postprandial blood glucose values. Maternal weight gain during pregnancy was recorded, and patients were followed up until delivery. Obstetric outcomes recorded included mode of delivery (normal vaginal delivery or caesarean section) and gestational age at the time of delivery. Neonatal outcome assessment included birth weight, neonatal hypoglycaemia (defined as serum glucose level <40 mg/dL), neonatal hyperbilirubinemia, and requirement for neonatal intensive care unit (NICU) admission along with the duration of NICU stay.

Statistical analysis was done using SPSS software (version 23.0). Continuous variables were expressed as mean±standard deviation (SD) whereas categorical variables were presented as numbers and percentages. Comparison between the insulin and metformin treatment groups was done using the independent student's t-test for continuous data and Chi-square test for categorical data. A p-value of less than 0.05 was considered statistically significant.

Inclusion Criteria

- Pregnant women aged between 18-45 years.
- Gestational age between 20-30 weeks at the time of GDM diagnosis.
- Diagnosed as GDM based on DIPSI criteria.
- Singleton pregnancy.
- Willingness to participate and provide informed written consent.

Exclusion Criteria

- Pre-existing diabetes mellitus (Type 1 or Type 2).
- Known hepatic or renal dysfunction.
- Known allergy to insulin or metformin.
- Multiple pregnancy or major obstetric complications.
- Refusal to provide informed written consent.
- Major psychiatric illness.

RESULTS

The analysis of the age group of the studied cases showed that the most common age group in both the insulin (40.0%) and metformin (36.7%) groups was 26–30 years. This was followed by the 18–25 years group, with 23.3% in the insulin group and a slightly higher (30.0%) in the metformin group. The mean age of patients receiving insulin was 28.9 ± 4.8 years, which was slightly higher compared to 26.98 ± 4.2 years in the metformin group. There was no statistically significant difference in age distribution of both the groups (P = 0.1046) [Table 1].

Table 1: Comparison of Age distribution of studied cases.

Group	Age Group (years)	Number of Patients	Percentage (%)	Mean Age ± SD (years)
Insulin	18–25	7	23.3%	28.9 ± 4.8
	26–30	12	40.0%	
	31–35	8	26.7%	
	>35	3	10.0%	
Metformin	18–25	9	30.0%	26.98 ± 4.2
	26–30	11	36.7%	
	31–35	7	23.3%	
	>35	3	10.0%	
P =0.1046 (Not Significant)				

The analysis of the parity distribution of the studied cases showed that primigravida patients were more frequent in both groups, accounting for 66.7% in the insulin group and 73.3% in the metformin group. Multigravida patients made up 33.3% of the insulin group and 26.7% of the metformin group. There was no statistically significant difference in parity distribution of both the groups (P = 0.7787) [Table 2].

Table 2: Comparison of parity distribution of studied cases.

Group	Parity	Number of Patients	Percentage (%)
Insulin	Primigravida	20	66.7%
	Multigravida	10	33.3%
Metformin	Primigravida	22	73.3%
	Multigravida	8	26.7%
P=0.7787 (Not Significant)			

The analysis of previous GDM history among the multigravida patients showed that the majority of patients in the insulin group had no prior history of gestational diabetes mellitus (70%). 3 (30.0%) reported presence of previous GDM. In the metformin group, an equal distribution was observed, with 50.0% having a history of GDM and 50.0% not having it. There was no statistically significant difference in previous GDM history of both the groups (P = 0.6305) [Table 3].

Table 3: Previous history of GDM in multiparous women.

Group	Previous GDM History	Number of Patients	Percentage (%)
Insulin	Present	3	30.0%
	Absent	7	70.0%
Metformin	Present	4	50.0%
	Absent	4	50.0%
P = 0.6305 (Not Significant)			

The analysis of fasting blood glucose levels of the studied cases showed that in the insulin group the most common range was 100–109 mg/dL (43.3%) followed closely by levels ≥110 mg/dL (40.0%). In comparison the metformin group had a higher proportion of patients with fasting glucose levels

<100 mg/dL (33.3%) and within the 100–109 mg/dL range (46.7%). Only 20.0% showed levels ≥110 mg/dL. The mean fasting blood glucose was notably higher in the insulin group (109.2 ± 10.6 mg/dL) than in the metformin group (102.4 ± 9.1 mg/dL). There was statistically significant difference in fasting blood glucose levels in both the groups and metformin group showed relatively low fasting blood glucose levels as compared to insulin group (P = 0.0098) [Table 4].

Table 4: Comparison of Fasting Blood Glucose level in studied cases.

Fasting Blood Glucose Level	Blood Glucose Range (mg/dL)	Number of Patients	Percentage (%)	P Value
Insulin Group	<100	5	16.7%	P = 0.0098 (Significant)
	100–109	13	43.3%	
	≥110	12	40.0%	
	Mean ± SD (mg/dL)= 109.2 ± 10.6			
Metformin Group	<100	10	33.3%	
	100–109	14	46.7%	
	≥110	6	20.0%	
	Mean ± SD (mg/dL)= 102.4 ± 9.1			

The analysis of post prandial blood glucose levels of the studied cases showed that in the insulin group, the majority of patients had glucose levels below 140 mg/dL (46.7). In contrast, the metformin group had half of the patients (50.0%) with post prandial glucose levels ≥160 mg/dL. The mean post prandial glucose level was lower in the insulin group (142.3 ± 11.2 mg/dL) compared to the metformin group (158.9 ± 12.5 mg/dL). There was statistically significant difference in post-prandial blood glucose levels in both the groups and lower levels were found to be more frequent in the insulin group (P < 0.0001) [Table 5].

Table 5: Comparison of Post-prandial Blood Glucose level in studied cases.

Post Prandial Blood Glucose levels	Blood Glucose Range (mg/dL)	Number of Patients	Percentage (%)	P Value
Insulin Group	<140	14	46.7%	P < 0.0001 (Significant)
	140–159	12	40.0%	
	≥160	4	13.3%	
	Mean ± SD (mg/dL): 142.3 ± 11.2			
Metformin Group	<140	5	16.7%	
	140–159	10	33.3%	
	≥160	15	50.0%	
	Mean ± SD (mg/dL)=158.9 ± 12.5			

The analysis of the type of delivery among the studied cases showed that normal vaginal delivery (NVD) was the most common mode in both groups, accounting for 22 cases in the metformin group and 20 cases in the insulin group. Caesarean section (LSCS) was observed in 5 patients from the metformin group and slightly more, 8 patients, from the insulin group. Assisted vaginal delivery was the least common and was seen in 3 patients from the metformin group and 2 from the insulin group. There was no statistically significant difference in the type of delivery of both the groups (P = 0.778) [Figure 1].

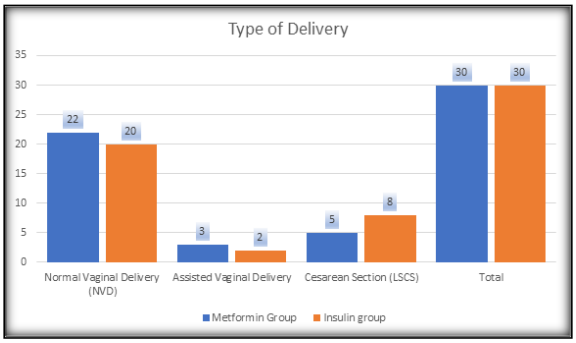

Figure 1: Comparison of type of delivery in both the groups.

The analysis of birth weight among the studied cases showed that most newborns in both groups had normal birth weight (2500–3999 g), with 21 cases in the metformin group and 19 in the insulin group. Low birth weight (1500–2499 g) was observed in 2 babies from the metformin group and 4 from the insulin group. Very low birth weight (1000–1499 g) was seen in 2 cases in the insulin group and none in the metformin group, while extremely low birth weight (<1000 g) occurred in only 1 case from the insulin group. Large for gestational age (≥4000 g) was more frequent in the metformin group with 7 cases, compared to 4 in the insulin group. There was no statistically significant difference in birth weight distribution of both the groups (P = 0.332) [Figure 2].

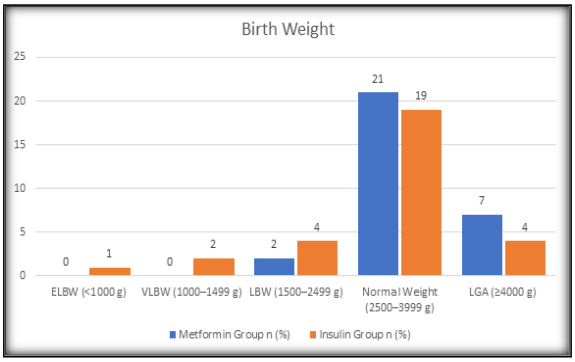

Figure 2:- Comparison of birth weight in both the groups.

The analysis of neonatal outcomes among the studied cases showed that neonatal hypoglycaemia was more common in the insulin group (40.0%) compared to the metformin group (23.3%). Neonatal hyperbilirubinemia was observed in 10.0% of the metformin group and 16.7% of the insulin group. NICU admissions for up to 24 hours were highest in both groups—86.7% in the metformin group and 73.3% in the insulin group. Birth asphyxia was reported in 6.7% of the metformin group and 13.3% of the insulin group while neonatal seizures were noted in 3.3% of the metformin group and 10.0% of the insulin group. There was no statistically significant difference in any of these neonatal outcomes between both the groups (P>0.05) [Table 6].

Table 6:- Comparison of neonatal outcomes in studied groups.

Parameters	Metformin Group n (%)	Insulin Group n (%)	p-value
Neonatal hypoglycaemia			0.266
Yes	7 (23.3%)	12 (40.0%)	
No	23 (76.7%)	18 (60.0%)	
Neonatal hyperbilirubinemia			0.706
Yes	3 (10.0%)	5 (16.7%)	
No	27 (90.0%)	25 (83.3%)	
NICU admissions			0.333
Till 24 hours	26 (86.7%)	22 (73.3%)	
24 hours – 1 week	2 (6.7%)	5 (16.7%)	
>1 week	2 (6.7%)	3 (10.0%)	
Birth asphyxia			0.6707
Yes	2 (6.7%)	4 (13.3%)	
No	28 (93.3%)	26 (86.7%)	
Neonatal seizures			0.6120
Yes	1 (3.3%)	3 (10.0%)	
No	29 (96.7%)	27 (90.0%)	

DISCUSSION

The present study was done to compare the efficacy and safety of metformin as compared to insulin in the management of gestational diabetes mellitus (GDM). Metformin is associated with better fasting blood glucose control and reduced rates of neonatal hypoglycaemia whereas insulin demonstrated better control of postprandial blood glucose levels. These results are similar to the outcome of previous studies on same topic. Rowan et al reported that metformin was not associated with an increased risk of perinatal complications compared to insulin and its use for management of GDM led to less maternal weight gain and higher patient satisfaction.10 Similarly, Hyer S et al reported that metformin was effective in controlling fasting glucose with minimal maternal side effects. These findings are similar to observations of our study.[11]

In contrast, our results showed better postprandial glucose control in the insulin group, which supports the observations by Spaulonci et al who reported that while both drugs are effective insulin may be more precise in controlling postprandial hyperglycemia.[12] Moreover the study also reported that gestational age at the time of diagnosis as well as mean pretreatment blood glucose level were predictors of the need for supplemental insulin therapy in cases initially treated with metformin. This distinction may be clinically significant, given that postprandial hyperglycemia has a stronger association with macrosomia and other neonatal complications. Nonetheless, our findings did not show significant differences in neonatal birth weights or incidence of macrosomia between groups, aligning with the findings of Niromanesh et al who reported no significant differences in neonatal anthropometric outcomes between metformin and insulin treatment groups.[13] On the basis of these findings the authors concluded that metformin is an effective and safe alternative treatment to insulin for women with GDM.

Regarding delivery outcomes we found a comparable rate of normal vaginal deliveries and caesarean sections across both treatment groups, which suggests that glycaemic control with either therapy does not markedly alter the mode of delivery. This corroborates the findings of Butalia et al who in a meta-analysis concluded that the route of delivery was unaffected by the type of pharmacological treatment for GDM.[14] Additionally Tertti et al observed similar caesarean section rates in women treated with insulin and metformin thereby pointing out that obstetric decisions are multifactorial and not solely dependent on the type of glucose-lowering therapy.[15] Additionally the authors reported that there were no significant differences in neonatal as well as maternal data between the insulin and metformin groups.

With respect to neonatal outcomes, we found fewer adverse neonatal events in the metformin group, however this difference was not statistically significant. In this study neonatal hypoglycaemia was more common in the insulin group (40.0%) as compared to the metformin group (23.3%). This finding is consistent with the results of a meta-analysis by Balsells et al which showed a significantly lower risk of neonatal hypoglycaemia in pregnancies treated with metformin as compared to those patients who were treated by insulin.[16] Similarly, Nachum et al demonstrated that insulin

therapy often necessitated tighter glucose targets which might increase the risk of neonatal hypoglycaemia due to stricter intrauterine glycaemic control.[17] However, concerns remain regarding the long-term safety of metformin-exposed offspring, as highlighted by Newman C et al who called for further investigation long term follow up to find out whether metformin in GDM is associated with obesity during childhood.[18]

The general acceptability and compliance to metformin is usually higher likely due to the oral route of administration and reduced cost burden factors particularly relevant in resource-limited settings such as India. This aspect is echoed by the work of Liang HL et al who emphasized improved patient compliance and satisfaction with oral antidiabetic agents compared to injectable therapies.[19] Similarly, Balani et al observed greater adherence and quality of life in metformin users.[20] The study concluded that women with GDM treated with metformin and with similar baseline risk factors for adverse pregnancy outcomes had less weight gain and improved neonatal outcomes compared with those treated with insulin.

CONCLUSION

Metformin as well as insulin were found to be effective in the management of gestational diabetes mellitus (GDM). However, Metformin showed better control of fasting blood glucose levels and relatively less cases of neonatal hypoglycaemia. Obstetric outcomes and neonatal birth weight were comparable in both the groups. Slightly higher rates of neonatal complications were observed with insulin however this difference was not statistically significant. Given its oral use, affordability, and better compliance metformin can be considered a promising first-line option, particularly in low-resource settings. However, due to individual variations and limited long-term data its use should be individualised with respect to maternal glycaemic profile, tolerance to oral therapy and risk factors requiring insulin initiation.

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