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Original Research Article

Comparison study of metformin versus insulin in the treatment of gestational diabetes during pregnancy

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ABSTRACT

Background: Gestational diabetes was traditionally treated with insulin. Metformin is a peroral drug used worldwide in the treatment of type 2 diabetes and also in a few studies on patients with gestational diabetes. This study aimed to analyze and compare insulin and metformin in the treatment of gestational diabetes and to compare their effects on the pregnancy outcomes.
Method: This comparative prospective observational study was conducted at Deen Dayal Upadhyay Hospital, New Delhi, a tertiary care teaching hospital. The data was collected over a period of 15 months (April 2021 till June 2022). So pregnant females in the age group 18-45 years with 20-30 weeks period of gestation, are diagnosed with gestational diabetes as per the diabetes in pregnancy India (DIPSI). The study group was divided into 2 groups of 40 each, one receiving oral metformin and the other group receiving insulin for treatment.
Results: Metformin was found to be a better drug in controlling blood sugars vis a vis insulin in our study. GDM patients controlled on insulin were found to be associated with; higher weight gain, higher incidence of neonatal hypoglycemia, hyperinsulinemia and higher and longer ICU admission
Conclusions: Metformin was better in controlling blood sugar in GDM than insulin, with better neonatal outcome.

Keywords: Diabetes mellitus, Gestational diabetes mellitus, Metformin pregnancy

INTRODUCTION

Definition of pregestational diabetes mellitus is the occurrence of Type 1 and Type 2 diabetes before pregnancy, whereas gestational diabetes mellitus (GDM) defines as glucose intolerance for the first time during pregnancy.[1] During the last 30 years, the development of the treatment techniques enhances the prevention of diabetic complications during pregnancy, leading to a dramatic improvement in maternal and perinatal outcomes and that's need clinical efforts to maintain an excellent maternal glycemic control before conception and during pregnancy.[2] This definition of GDM applies to all patients controlled with pharmacologic therapy or controlled with diet modification and is irrespective of whether the condition persists after pregnancy .The definition includes the possibility that unrecognized glucose intolerance may have preceded the pregnancy .The primary mechanism of action of glucose tolerance seen in gestational diabetes are peripheral insulin resistance and decreased pancreatic insulin secretion. Insulin resistance worsens as the pregnancy progresses. It is postulated that insulin resistance in pregnancy is related to post receptor handling of glucose. Altered handling of glucose in pregnancy is attributed to impaired tyrosine kinase activity, decreased expression of insulin receptor substrate-1, decreased expression of the GLUT-4 glucose transport protein in adipose tissue. ACOG and USPSTF and most other groups call for screening all women's after 24 weeks of gestation by either medical history and risk factors or with universal

assessment by laboratory testing. Women at high risk of undiagnosed pre-existing diabetes may be offered laboratory testing in early pregnancy, including women with a history of gestational diabetes in previous pregnancy, known impaired glucose metabolism, obesity (BMI >30). Women who have normal testing in early pregnancy should have a repeat OGTT performed between 24-28 weeks of gestation. Most women are able to control their blood glucose levels with medical nutrition therapy or proper exercise, if not, insulin is the preferred agent for the management of GDM. However, insulin therapy has severe disadvantages like multiple injections, risk of hypoglycemia, excessive maternal weight gain and higher cost. These disadvantages could reduce a patient's will to use insulin. In contrast, metformin is an alternative which can improve hepatic and peripheral sensitivity to insulin with oral administration and decrease all the side effects of Insulin as narrated above.

METHODS

This study was conducted at Deen Dayal Upadhyay Hospital, New Delhi, n=80 patients were selected. 40 patients in each group on the basis of treatment with metformin and insulin. It was conducted from April 2021 till June 2022.

A total 80 women diagnosed with gestational diabetes mellitus according to the DIPSI criteria at booking and /or between 24-28 weeks of gestation. DIPSI criteria are 2 hours postprandial >140 mg/dl (following a loading dose of 75 grams glucose). Known cases of diabetes mellitus, mothers with liver or kidney diseases, patients with allergy to metformin and insulin were excluded from the study. Once they were diagnosed by the above DIPSI criteria, these women were divided alternately into 2 groups of 40 patients each. Patients were given either insulin or metformin, after taking informed consent. In group 1- Metformin was started at a dose of 500 mg/day to a maximum of 2000 mg/day based on a glycemic profile. If there's poor control after maximum dosage of Metformin in 2 weeks such patients were added with insulin (Mixtard, Regular, NPH). In group 2- The patients were started on the lowest dose of insulin and it was titrated based on plasma glucose values. All categorical variables have been compared across the 2 groups, using Chi square test for independence of attributes, while all continuous variables have been compared across those 2 groups using the student's t-test. Level of significance is taken as 5% i.e., if 'p' value i.e., if p value <0.005 there is significant difference between 2 groups.

RESULTS

In our study to compare the efficacy of metformin vs. insulin in GDM patients, age distribution, gravida and previous history of GDM between 2 groups were comparable (Table 1).

Table 1: Demographic profile between metformin and insulin groups (n=40).

Parameters	Metformin group	Insulin group	P value
Age distribution	26.98±4.2	28.9±4.8	0.62
Parity N (%)			
Primi	28 (70)	28 (70)	0.99
Multi	12 (30)	12 (30)	
Previous h/o GDM			
Yes	6 (50)	3 (25)	0.28
No	6 (50)	9 (75)	

Table 2: Weight gain during pregnancy between insulin and metformin groups (n=40).

Parameters	Metformin group	Insulin group	P value
Mean weight gain	9.98±3.84	12.95±5.32	<0.05
<10 kgs	19 (47.50)	15 (37.5)	
>10 kgs	21 (52.50)	25 (62.5)	

Table 3: OGTT.

Parameters	Metformin group	Insulin group	P value
Before breakfast	99.90±4.54	109.73±7.80	<0.05
After breakfast	122.38±16.58	152.23±15.13	<0.05
After lunch	82.05±5.30	101.60±6.13	<0.05
After dinner	107.78±8.91	110.40±12.90	0.29

In our study, it was observed that the mean weight gain was significantly higher among patients in the insulin group as compared to metformin groups (p<0.005) (Table 2). It is clear from (Table 3), that the mean blood sugar levels before breakfast, after breakfast and after lunch were found to be significantly higher in the insulin group as compared to the metformin group respectively while mean blood sugar levels after dinner were found to be statistically similar between the 2 study groups. In our study (Table 4), there was no statistical difference between mode of delivery between the 2 groups and the gestational age at which the patients delivered were similar and statistically insignificant between the 2 groups. The mean birth weight of the babies born to mothers in the two groups were statistically insignificant. Although the incidence of neonatal hypoglycemia (S. glucose <100 mg/100 ml) was significantly higher in insulin treated patients as compared to those treated with metformin. The incidence of hyperbilirubinemia found to be higher in insulin treated patients. Neonates requiring NICU were significantly higher in patients on Insulin. In our study, there were no cases of intrauterine death, APGAR<7 or RDS in either group (Table 5-6).

Table 4: Distribution based on mode of delivery and gestational age (n=40).

Parameters	Metformin group	Insulin group	P value
Mode of delivery			
NVD	28 (70)	26 (65)	0.63
LSCS	12 (30)	14 (35)	
Gestational age at delivery (weeks)			
<37	4 (10)	5 (12.50)	0.72
>37	36 (90)	35 (87.50)	

Table 5: Neonatal data.

Parameter	Metformin group	Insulin group	P value
Birth weight	2.98±0.41	2.89±0.44	0.36

Table 6: Complications.

Parameters	Metformin group	Insulin group	P value
Neonatal hypoglycemia			
Yes	28 (70)	26 (65)	<0.01
No	12 (30)	14 (35)	
Neonatal hyperbilirubinemia			
Yes	4 (10)	5 (12.50)	<0.05
No	36 (90)	35 (87.50)	
NICU admissons			
Till 24 hours	38 (95)	33 (82.50)	<0.05
24 hours-1 week	1 (2.50)	4 (10)	
>1 week	1 (2.50)	3 (7.50)	

DISCUSSION

In this study, it was observed that the mean age of the patients was 28.9±4.8 and 26.98±4.2 years in the insulin and metformin group respectively (p value=0.62). In a similar study by Hamid et al, mean age of the mothers in insulin group was 31.4 years and 31.9 years in the metformin group which is nearly similar to the mean age obtained in our study. Mean maternal age in the study by Ghomian et al was 28.3 and 28.4 years in the insulin group and metformin group respectively (p value = 0.87) keeping up with our results.[3,4] Khan et al observed that the mean age of the cases was 24.92±2.57 years and 28.01±2.53 years in the metformin and insulin group respectively.[5] In the study,70% of the patients were primipara. The 2 groups were respect to the distribution of patients according to parity (p value=0.99). Hamid and colleagues found 6.7% of the insulin group to be primiparous and 8.3% of the metformin group to be primiparous.[3] In our study among multiparous patients, 25% of the insulin group and 50% of the metformin group had a history of GDM. Ghomian et al found that past history of GDM was present in 20% in the insulin group and in 24% in the metformin group (p value =0.39).[4] We observed that mean weight gain during pregnancy was significantly higher among patients in the insulin group compared to the metformin group. Tertti et al found similar weight gain between metformin and insulin group 8±5.3 vs 7.9±5.3 kgs (p value =0.82).The weight gain after starting medication was slightly, on average 0.5 kg, lower in the metformin group than in the insulin group, as expected, but this difference did not reach statistical significance. We also observed that mean blood sugar levels before breakfast, after breakfast and after lunch were found to be significantly higher in the insulin group as compared to the metformin group respectively after 1 week of therapy. However, there is no statistical difference in the post dinner values. Similar to our findings, Picon-Cesar et al found that greater postprandial glucose control was observed after some meals (lunch or dinner) in the metformin- treated group vs. the insulin treated group (2 weeks after inclusion: glycemia after lunch, 116.76±14.41 mg/dl (6.48±0.80 mmol/l) vs. 123.78±15.68 mg/dl (6.87±0.87 mmol/l); p<0.003; after dinner, 121.44±13.87 mg/dl (6.74±0.77 mmol/l) vs. 125.95±15.32 mg/dl (6.99±0.85 mmol/l); p<0.041).[6] Khan et al observed significant differences for FBS at entry (p=0.000), FBS after treatment (p=0.000), HBA1c at entry (p=0.000) and HBA1c after treatment (p=0.000), with significantly between sugar control with metformin as compared to insulin.[5] We observed that 35% and 30% in the insulin and metformin group respectively had LSCS, while the rest had NVD. There was no statistical difference between the two groups with respect to mode of delivery (p value=0.63). Similarly, in the study by Hamid et al, no significant difference was observed between insulin and metformin group with respect to mode of delivery.[3] Ghomian et al observed that eighty-seven (60.8%) pregnant women in the metformin group and 78 (54.5%) pregnant women in insulin group experienced vaginal delivery (X2=1.160; p=0.281).[4] On the other hand, 25 (42.9%) and 24 (38.5%) of the patients from the metformin and insulin groups, respectively, underwent cesarean section due to delay in dilatation or arrest of descent. Picon-Cesar et al found that labor inductions; 45.7% (metformin) vs. 62.5% (insulin); OR,0.506; 95% CI, 0.283-0.903; p=0.029 and cesarean deliveries (27.6% (metformin) vs. 52.6% (insulin); OR, 0.345; 95% CI, 0.187-0.625; p=0.001) were significantly lower for the metformin -treated group.[6] The lower cesarean delivery rate for women treated with metformin was not associated with macrosomia, LGA or SGA, or other complications of pregnancy. We observed that 11.25% of the cases had gestational age of less than 37 weeks, 12.5% in the insulin group and 10% in the metformin group. There was no statistical difference between the two groups with respect to gestational age at delivery (p value = 0.72). In the study by Hamid et al, preterm delivery occurred in 7.5% and 10.8% in the insulin and metformin group respectively, with no significant difference between them (p value 0.37).[3] Ghomian and colleagues observed that 13.9% and 13.2% of the cases in metformin and insulin group had gestational age at birth of less than 37 weeks (p value = 0.86).[4] We observed that mean birth weight was 2.89 ± 0.44 vs 2.98 ± 0.41 kg, with no significant difference

between them, p value = 0.36. In addition, neonates born to mothers in the insulin group had significantly higher incidence of hypoglycemia as compared to the metformin group(15% vs 0%), p value < 0.01. It was observed that neonates born to mothers in the insulin group had significantly higher incidence of hyperbilirubinemia as compared to metformin group (15% vs. 2.5%), p value <0.05. It was observed that 10% of the neonates born to mothers in the insulin group had NICU admission for 24 hours to 1 week and 7.5% for more than 1 week. This was significantly higher as compared to neonates born to mothers in the metformin group as 95% of these were in NICU for 24 hours, one case was admitted for 24 hours to 1 week and one case for more than 1 week, p value <0.05. In addition, there were no cases of intrauterine death, APGAR less than 7 or respiratory distress syndrome.In the study by Ghomian et al, APGAR less than 7 (13.2% vs. 11.8%, p value=0.58), hypoglycemia (8.3% vs. 11.8%, p value=0.32) and NICU admission rate (20.2% vs. 18.8%, p value=0.76) were found to be statistically significant between metformin and insulin group respectively.[4] In another study, Hamid et al found that no significant differences were found between the studied groups according to neonatal outcome in terms of neonatal hypoglycemia, macrosomia, 5 min APGAR score less than 7, respiratory distress syndrome, admission to neonatal intensive unit, or need for phototherapy.[3] Similarly, Picon-Cesar et al found no differences were observed between groups regarding perinatal outcomes (stay in NICU, respiratory distress syndrome, neonatal hypoglycemia, and jaundice requiring phototherapy).[6,7]

Limitations

Even though metformin is an oral drug and is proven to be beneficial in the treatment of GDM much similar to insulin but Insulin should be considered as the first-line treatment in women with GDM who are at high risk of failing on OAD therapy, including some of the following factors : Diagnosis of diabetes <20 weeks of gestation, need for pharmacologic therapy >30 weeks, fasting plasma glucose levels >110 mg/dl, 1-hour postprandial glucose >140 mg/dl, Pregnancy weight gain >12 kg.

CONCLUSION

In current study we realized that metformin is equally effective in the treatment of GDM patients and with lower risks of maternal and neonatal complications compared with insulin. Due to certain advantages of metformin being more convenient because of peroral administration as compared to insulin which requires parenteral administration. Hence metformin can be recommended as a favourable substitute for insulin the treatment of GDM. Also, it would be of great interest to evaluate glycemic profiles with subcutaneous continuous monitoring devices and also to compare new long-acting formulations of insulin among them and with metformin.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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