ORIGINAL ARTICLE

Efficacy of metformin and insulin in the management of gestational diabetes mellitus: A comparative study

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Abstract

Background: In Gestational Diabetes Mellitus (GDM), the insulin secretion is not adequate enough to compensate for the severity of hyperglycaemia and pregnancy is also a state of high insulin resistance which leads to ineffective glycaemic control. *Aim and Objectives:* To compare the efficacy of metformin and insulin in management of GDM; and to assess neonatal and maternal outcomes in the study group. *Material and Methods:* One hundred pregnant women visiting the Outpatient Department of Obstetrics and Gynecology, JSS Hospital, Mysuru were screened for GDM at first antenatal visit. If the first test results were negative, then second test was done at 24 - 28 weeks of gestation. One hundred pregnant women diagnosed as GDM after 20 weeks of gestation by Diabetes in Pregnancy Study Group of India (DIPSI) method were included for the study. They were randomly assigned into two groups with 50 patients each and were subjected to pharmacological treatment with either insulin or metformin. Optimum glycemic control between the two groups was studied along with the maternal and fetal outcome. *Results:* Our study showed no significant difference in GDM with the use of metformin or insulin. All patients (100%) from the insulin group achieved good glycemic control whereas in the metformin group, 98% achieved good glycemic control. Maternal and fetal outcomes were also not significant between the two groups. *Conclusion:* Our study showed no significant difference in the use of metformin or insulin and suggests that metformin is effective in controlling GDM without associated higher risk of maternal or neonatal complications compared with insulin.

Keywords: Gestational Diabetes Mellitus, Metformin, Insulin

Introduction

Gestational Diabetes Mellitus (GDM) is defined as 'any degree of glucose intolerance first detected during pregnancy'. GDM mainly occurs because there is inadequate insulin secretion to compensate for the rising insulin resistance in pregnancy [1]. Pregnancy is a diabetogenic state. Increased levels of glucogenic hormones like human placental lactogen, glucagon and prolactin are commonly seen in pregnancy. In cases of GDM, the insulin secretion is not adequate enough to compensate for the severity of hyperglycaemia. In addition, pregnancy is also a state of high insulin resistance which leads to ineffective glycaemic control even in cases of hyperinsulinemia. This mismatch in hormones is the cause of GDM. GDM is a disease that is gaining more and more attention around the world because it causes various problems including maternal, perinatal and foetal complications.

To reduce the risk of developing GDM, investigators had proposed three strategies:

1. Diet (medical nutrition therapy)
2. Exercises

3. Pharmacotherapeutic agents

The goal of treatment in GDM is to prevent complications caused by high blood sugars like still birth and macrosomia [1]. For years, insulin served as the primary and only treatment modality in managing GDM. However, insulin had many drawbacks. Patient compliance was low as the administration of insulin had to be through a parenteral route. Constant monitoring and vigilance were necessary to prevent and rapidly treat hypoglycaemia which was a dreaded complication. Finally, the high cost of insulin made the drug out of reach for the poverty stricken (many of whom suffer from this increasingly common condition). A logical alternative to insulin would have to be a drug that was cheap, safe, easy to use and long acting in addition to having efficient glycaemic control.

Metformin, a biguanide, reduces the insulin resistance and increases the peripheral utilization of glucose. Metformin also reduces hepatic gluconeogenesis and crosses the placental barrier to ensure sensitization of the foetus in insulin [2]. In addition, metformin also does not result in unnecessary weight gain. Finally, metformin has less incidence of hypoglycaemia. Metformin, is an oral hypoglycaemic, used as a convenient alternative to insulin in treating GDM. It is a near ideal drug for the treatment of GDM because it prevents the development of hyperglycaemia in every way [3]. GDM prevalence is increasing especially in South Asian countries [4]. Inadequately treated GDM leads to maternal and foetal complications and also offspring of women with GDM have higher chances of developing type 2 diabetes later [5]. Maternal risks of GDM include polyhydramnios, preeclampsia, uterine atony, postpartum haemorrhage, infection, prolonged labour, obstructed labour, caesarean section, and retinopathy and add to the leading global causes of maternal morbidity and mortality [10]. Fetal complications of GDM includes spontaneous abortion, shoulder dystocia, birth injuries, neonatal hypoglycaemia, respiratory distress syndrome, intrauterine death, still birth and congenital malformations [6]. Both maternal and foetal complications can be potentially reduced if maternal blood glucose levels are controlled during pregnancy. Keeping these points in perspective, we aimed to compare the effectiveness of metformin with insulin which is considered as an effective alternative in the treatment of GDM. The objectives of our study were to compare efficacy of metformin and insulin in regulating maternal blood glucose levels in GDM; and to assess neonatal and maternal outcomes in the study group.

Material and Methods

Source of data and method of collection of data: Pregnant women visiting the Outpatient Department of Obstetrics and Gynecology, JSS Hospital, Mysuru were recruited for this comparative study conducted for a period of 24 months from November 2019 to October 2021.

Study design: Study was initiated after obtaining approvals from the Institutional Scientific Committee and the Institutional Ethics Committee of JSS Hospital, Mysuru. A preformed written consent form was taken from all patients before the start of the study. The sample size was calculated using the below formula by purposive sampling:

Sample size (n) = Z^2pq / d^2, where n = sample size

p = prevalence of gestational diabetes in Mysuru (6.2%) and hence p was taken as 6.

q = 100-6 = 94

d = Absolute error = 5

Sample size was taken considering the dropout rates and dropout subjects were compensated by recruiting extra cases. Based on the above calculations, the sample size was found to be 100 *i.e.,* Metformin group = 50 patients and Insulin group = 50 patients.

Methodology

One hundred pregnant women visiting the Outpatient Department of Obstetrics and Gynecology, JSS Hospital, Mysuru were screened at first antenatal visit for GDM. Second test was done at 24 - 28 weeks of gestation, if the first test results were negative. A single step test recommended by Diabetes in Pregnancy Study Group of India (DIPSI) method was used. DIPSI recommends one step procedure with 75-gram oral glucose through Oral Glucose Challenge Test (OGCT) irrespective of the last meal. A venous plasma glucose value of more than 140 mg/dl, after 2 hours, was diagnosed as GDM. Counselling on diet and regular physical exercise were given to all pregnant women diagnosed as GDM. Initially GDM patients were placed on dietary instruction from a nutritionist and an exercise program of 30 min walk or exercise per day. Those women in our study who were still not maintaining normal blood glucose levels on medical nutritional therapy and regular physical exercise and those who did not maintain the desired blood glucose levels within 2 weeks of intervention, satisfied the inclusion and exclusion criteria, and gave informed consent, were included in the study. They were then randomly assigned for treatment with metformin or insulin along with dietary advice and exercise. Irrespective of body weight and OGCT values, randomization was done with odd number assigned to metformin treatment and even number for insulin treatment.

Pregnant women with single foetus who were diagnosed as GDM after 20 weeks of gestation by DIPSI method were included in the study while any patient with overt diabetes, recognized foetal anomaly and/or risks factors for lactic acidosis (severe chronic pulmonary disease, coronary insufficiency, history of thromboembolic phenomena, renal failure, heart failure, chronic liver disease) were excluded.

Metformin group

Tablet metformin was started with a dose of 500 mg twice daily and increased up to 2000 mg in 3 divided doses as tolerated until we achieved glycaemic control. If blood sugar was not controlled with the maximum dose of metformin along with dietary advice and exercise, insulin was added.

Insulin group

Injection human premix insulin 30/70 is a mixture of 30% regular human insulin + 70% NPH, human insulin isophane suspension. Regular human insulin (trade names: Humulin, Novolin, Actrapid) is a type of short acting insulin. Onset of action is typically in 30 minutes and lasts for 8 hours. NPH insulin also known as isophane insulin is an intermediate acting insulin. Onset of action is typically in 90 minutes and lasts for 24 hours. Fasting Blood Sugar (FBS) and Post Prandial Blood Sugar (PPBS) were tested every third day to assess the blood sugar levels till dose of insulin was adjusted. If PPBS was raised, 2 units pre-breakfast was added and if FBS was raised, 2 units pre-dinner was added. The insulin was continued till the levels of 95 mg/dl and 120 mg/dl were achieved for FBS and PPBS, respectively. Insulin syringe 40 IU was used and administered through subcutaneous injection only.

Results

Majority of the study subjects in both the groups were in the age group of 26 - 35 years. Patients in age group more than 35 comprised 10% of total population. Majority of the study subjects were multigravida, both in metformin and insulin groups. Three patients had polyhydramnios in metformin group while 4 patients in the insulin group had polyhydramnios, which indicated that glycaemic control was better with metformin (Table 1).

Mean gestational weeks at treatment initiation in metformin group was 26.94 ± 4.033 and 26.80 ± 3.123 in insulin group. OGCT at the time of diagnosis of GDM in metformin group was 177.94 ± 23.696 and in insulin group was 187.50 ± 27.610. The mean difference between the groups was 9.560 with *p* value of 0.066 which was not significant between the two groups. In metformin group, 2 antenatal women were started on insulin during the course of treatment since blood sugar levels were not under control and continued insulin along with metformin till the time of delivery. In insulin group, all antenatal women were continued on insulin till the time of delivery (Table 2).

Table 1: Demographic profile and maternal data between metformin and insulin groups

Parameter	**Metformin (n=50)**	**Insulin (n=50)**	***p***
Age (years)	**Frequency**	**Frequency**	
18-25 **26-35** **> 35**	10 (20%) 36 (72%) 4 (8%)	15 (30%) 29 (58%) 6 (12%	0.253
Primigravida	19 (38%)	23 (46%)	0.418
Multigravida	31 (62%)	27 (54%)	
History of GDM in previous pregnancy	6 (12%)	5 (10%)	0.749
History of preeclampsia	10 (20%)	10 (20%)	1
History of diabetes mellitus in family	22 (44%)	17 (34%)	0.305
Polyhydramnios	3 (6%)	4 (8%)	1
LSCS	42 (84%)	44 (88%)	0.687
FTND	8 (16%)	6 (12%)	0.766

GDM: Gestational Diabetes Mellitus, LSCS: Lower segment cesarean section, FTND: Full term normal delivery

Table 2: Control of mean blood sugar between metformin and insulin groups

Variable	Groups	N	Mean ± SD	Mean Difference	*p*
Gestational week at treatment initiation	**Metformin**	50	26.94 ± 4.033	-0.140	0.847
	Insulin	50	26.80 ± 3.123		
OGCT at diagnosis of GDM	**Metformin**	50	177.94 ± 23.696	-9.560	0.066
	Insulin	50	187.50 ± 27.610		
BMI(Kg/m^2)	**Metformin**	50	26.32 ± 1.99	-1.041	0.02
	Insulin	50	27.36 ± 1.19		
Control of blood sugar levels	**Groups**	**N**	**Control**		1.66
	Metformin	50	48		
	Insulin	50	50		

GDM: Gestational diabetes mellitus, OGCT: Oral glucose challenge test, BMI: Body mass index

Three (6%) babies with macrosomia were observed in each of the 2 groups. Majority *i.e.,* 27 (54%), of the newborns in metformin group were in birth weight range between 3.1 - 3.9 kg, while, in the insulin group, majority i.e., 24 (48%), were in birth weight range 2.5 - 3 kg. Eleven newborns in metformin group and 17 newborns in insulin group were diagnosed to have neonatal jaundice. The incidence of neonatal hypoglycaemia was statistically significant between metformin and insulin groups. Neonatal hypoglycemia was the most common indicator for Neonatal Intensive Care Unit (NICU) admission in both metformin and insulin groups i.e., 5 (10%) in metformin and 15(30%) in insulin group (Table 3).

When given an option to choose medication in next pregnancy, in metformin group, 37 study subjects would choose metformin and 13 patients were not sure as to what they would choose (Table 4).

Table 3: Neonatal outcome between metformin and insulin groups

Parameter	Metformin (n=50)	Insulin (n=50)	*p*
Preterm	7 (14%)	12 (24%)	0.202
Term	43 (86%)	38 (76%)	
Macrosomia	3 (6%)	3 (6%)	1
Birth weight (kg)			
< 1.5	1 (2%)	0	
1.5-1.99	1 (2%)	0	
2-2.499	1 (2%)	4 (8%)	
2.5-3	17 (34%)	24 (48%)	
3.1-3.9	27 (54%)	19 (38%)	
> 4	3 (6%)	3 (6%)	
RDS	4 (8%)	4 (8%)	1
Neonatal hypoglycaemia	5 (10%)	15 (30%)	0.012
Neonatal jaundice	11 (22%)	17 (34%)	0.181
NICU admission	14 (28%)	16 (32%)	0.663

RDS: Respiratory distress syndrome, NICU: Neonatal intensive care unit

Table 4: Distribution of study subjects in metformin and insulin groups based on the choice of medication

Which medication would you choose in next pregnancy?	Groups		Total
	Metformin	Insulin	
Insulin	0	13 (26%)	13 (13%)
Metformin	37 (74%)	22 (44%)	59 (59%)
Not sure	13 (26%)	15 (30%)	28 (28%)
Total	50 (100%)	50 (100%)	100 (100%)

Discussion

GDM prevalence is increasing in developing countries including the South Asian Nations. The present study was conducted to know the effect of metformin in the treatment of GDM and to compare metformin to the conventional gold standard treatment of GDM with insulin. In our population, which is predisposed to GDM, and also with emerging high insulin resistance, there is an increasing incidence of GDM. We hypothesized that women who have been treated with metformin would have similar perinatal and maternal outcomes as women treated with insulin and better treatment acceptability. Our study findings have been compared with those by Landi (Table 5) [7].

Metformin may reduce the incidence of preeclampsia by reducing the maternal inflammatory response and by reducing the insulin resistance. This fact was supported by Gui *et al*. who found that lower the weight gain with metformin, lower was the risk of preeclampsia [8]. Viollet *et al*. also reported that metformin significantly reduced preeclampsia by eliminating the endothelial dysfunction [9]. Forty-two patients underwent Lower Segment Caesarean Section (LSCS) in metformin group while 44 patients underwent LSCS in insulin group. This was comparable to Rowan *et al*. who reported that caesarean section rates were lower in the metformin treatment group when compared to the insulin treated group [10]. They also reported that eight (8%) patients underwent Full Term Normal Delivery (FTND) in metformin group while 6 patients underwent FTND in

Table 5: Comparison between data of our study and study by Landi

Parameters	Our study		Study by Landi [7]	
	Metformin	Insulin	Metformin	Insulin
Multigravida	62%	54%	14.4%	11.9%
Mean gestational weeks at treatment initiation	26.94 ± 4.033	26.80 ± 3.123	32.0 ± 2.9	31.6 ± 2.9
Body Mass Index	26.32 ± 1.99	27.36 ± 1.19	29.4 ± 7.6	29.2 ± 8.4
History of GDM in previous pregnancy	12%	10%	8.3%	9.3%
History of preeclampsia in previous pregnancy	10%	10%	3.6%	3.5%
Macrosomia	3%	3%	10.7%	12.2%
Mean birthweight (kg)	3.1-3.9	2.5-3	3.3	3.3
Neonatal hypoglycemia	10%	30%	14.3%	22%
NICU admission	28%	32%	12.1%	28.1%

GDM: Gestational Diabetes Mellitus, NICU: Neonatal Intensive Care Unit

insulin group which is in agreement with our study. According to the MiG study, metformin group was associated with significantly less weight gain when compared with insulin [11]. According to Rowen *et al*. [10] there was no statistical significance between the metformin and insulin group which was comparable with our study. There was no statistical significance between the NICU admissions between our study group and study by Landi, as shown in Table 6 [7]. This was again comparable with the MiG study [11] and Masoodi *et al*. [12]. In a study by Rowen *et al*., 92.6% continued to receive metformin until delivery and 46.3% received supplemental insulin while 76.6% women in the metformin group would choose metformin over insulin which was similar to our study [10]. In a study by Dhulkotia *et al*. [13], metformin was not associated with risk of neonatal hypoglycemia, increased birthweight, incidence of caesarean section, or incidence of large-for-gestational-age babies which was also the same with our study. In a study by Bansal *et al*. [14], neonatal outcome was not different between metformin and insulin groups but the incidence of neonatal hypoglycemia was higher in the insulin group. In a study by Huhtala *et al*. [15], there were no clinically evident differences between two groups in terms of pregnancy outcome.

In a study by Balsells *et al*. [16], metformin versus insulin, significance was reached for maternal weight gain (mean difference -1.14 kg (-2.22 to -0.06), gestational age at delivery (mean difference -0.16 weeks (-0.30 to -0.02), and preterm birth (risk ratio 1.50 (1.04 to 2.16), with a trend for neonatal hypoglycemia (risk ratio 0.78 (0.60 to 1.01).In a study by Gante *et al*. [17], 35% of women did not achieve adequate glycemic control with metformin, but insulin supplementation was not associated with poor neonatal outcomes. In a study by Mahmood *et al*. [18], the number of cesarean section in the insulin treatment group (60%) was higher than in the metformin treatment group (46%). The number of neonates admitted to the NICU was higher in the insulin-treated group (58%) than in the metformin-treated group (6%) which was also true in our study.

In the present study, the patients' adherence to treatment was good in both groups. However, mothers who were on metformin found it very easy to take a tablet. They found it more acceptable and the monitoring of blood sugar levels was easy. However, with insulin, since the incidence of hypoglycaemia was much higher, an ideal four-point monitoring was indicated. So, almost every day, they had their fingers pricked for blood which proved painful. Considering the cost, each tablet of metformin costs around one rupee per tablet (whole strip of ten tablet- Rs. 10/-) while one vial of insulin Humalog (40 u) costs around 172 rupees. In addition, daily subcutaneous injections were painful. Hence most of our study subjects preferred metformin over insulin.

Conclusion

Our study findings show that overall metformin treatment in GDM had advantages such as it being easily acceptable and cost-effective with lesser incidence of maternal hypoglycaemia and good adherence. Additionally there were lesser incidences of neonatal hypoglycaemia and fewer NICU admissions, thereby suggesting that, metformin could be a reasonable alternative to insulin in the management of GDM.

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