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Original Research Article

Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective study

Neeta Bansal*, Priyanka Chaudhary, Monika Ramola, Namrata Saxena

Department of Obstetrics and Gynecology, Sri Guru Ram Rai institute of Medical and Health Sciences, Patel Nagar, Dehradun, India

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***Correspondence:**
Dr. Neeta Bansal,
E-mail: neetanbansal@gmail.com

ABSTRACT

Background: As various data are available on treatment of gestational diabetes mellitus (GDM), our aim is to compare the effect of treatment of metformin, insulin and diet control in GDM on maternal and neonatal outcomes.
Methods: A retrospective study was conducted and it includes 50 women of GDM treated with Metformin, 50 women with insulin and 50 with only diet control without any drug.
Results: The outcome was not much different in all groups studied. Maternal outcomes were similar in all three groups. The difference was: post prandial glucose values after 2 hour of oral glucose were slightly high in the insulin group than in the metformin group ($p < 0.003$). Neonatal outcome was also not different in all groups. But the incidence of neonatal hypoglycemia was higher in the insulin group ($p = 0.03$).
Conclusions: The study suggests that metformin is effective for GDM and maternal or neonatal outcomes were similar as compared with insulin.

Keywords: Gestational diabetes, Hypoglycemia, Insulin, Metformin

INTRODUCTION

Insulin resistant is present in pregnancy and increases with advancement of the pregnancy. This predisposes to the development of gestational diabetes mellitus (GDM). Obesity is other condition of insulin resistance. Insufficient insulin secretion leads to development of GDM.[1]

Incidence of GDM is about 3-7% of pregnancies and it increases with advancement of age and weight increase in pregnant women.[2-4] Complications are high in GDM like pregnancy-induced hypertension and adverse perinatal outcome. There are also increase chances of development of type 2 diabetes mellitus (T2DM) after pregnancy.[1,2,4,5] Other studies also support that effective treatment of hyperglycemia in women with GDM can reduce adverse perinatal out comes.[6] Fetal hyperinsulinemia and fetal macrosomia also associated with GDM and by reducing maternal glucose levels, these complication can be prevented.[7] Treatment of GDM started with traditional approach that is with exercise and diet control. Pharmacology treatment is also required and insulin is started traditionally.[2] 20% to 60% of GDM patients require additional treatment.[8] Multiple injections, hypoglycemia and weight gain are disadvantage of insulin therapy.[8,9] Metformin reduces hepatic gluconeogenesis and improves peripheral glucose uptake with causing hypoglycemia and weight gain.[10] Metformin in pregnancy is used in patients with polycystic ovary syndrome (PCOS). Infertility secondary to PCOS is also treated with Metformin.[4,11] It has no adverse effect on foetus as it crosses placenta.[12-14] Reduction in spontaneous abortion by treatment with metformin is reported in the first trimester.[15-17]

There are few studies which suggest use of metformin in women with type 2 diabetes or GDM. One retrospective

study concluded increased rates of pre-eclampsia and perinatal loss women with GDM or type 2 diabetes treated with Metformin when compared with insulin treatment.[18] But in this study patients were of older age and more obese.[1]

One study comparing insulin and Metformin in the treatment of GDM has a small number of patients and it suggests that Metformin is an effective alternative to insulin.[19] Another multinational non inferiority study compared outcomes in terms of a composite of neonatal complications. It turned out that treatment with Metformin is better and Metformin treatment is less than 10% worse than treatment with insulin.[20] So, we compared GDM patients with various modalities of treatment in our controlled study using parameters like pre-pregnancy body mass index (BMI) and age. Maternal and neonatal outcomes are evaluated to get more data that Metformin can be considered to be an alternative pharmacologic treatment to insulin in GDM.

METHODS

This study was conducted at Sri Guru Ram Rai Institute of Medical and Health Sciences, Patel Nagar, Dehradun. 150 (n) patients are selected. 50 patients in each group on the basis of treatment with metformin, insulin or diet control and exercise. It was conducted from 01 June 2015 to 31 May 2016. OGTT was performed in all patients in study. Pregnancy body mass index (BMI, kg/m^2) and age were matched. Five BMI groups (<25, 25-29, 30-34, 35-39, >40 kg/m^2) were made. Three age groups (<25, 25-34 and >35 years). The groups were matched. Data were collected retrospectively from the maternal and neonatal patient records. Only primary para patients were included. The standard 2 hour 75 gm OGTT was performed at 11-32 weeks because of high risk duration.[21] GDM diagnosis is made on the basis of at least two out of three abnormally high plasma glucose value measurements in the 75 gm OGTT (fasting >120, 1 hours >180, 2 hours >160 mg/100 ml). All patients were evaluated on OPD basis. Dietary and exercise counseling were done. Self-monitoring of plasma glucose was taught. Blood glucose levels were measured at fasting state and postprandial values at 90 minutes after main meals at least four times a day during three consecutive days.

Metformin was given if fasting is >120 and postprandial blood glucose level is >160. Informed written consents were taken. Metformin was started from 500 mg once a day to 750 mg twice a day (500 mg to 2gm per day). Regular insulin thrice daily was given. Ultrasound was performed in all patients in third trimester.

The outcomes were recorded: preeclampsia (increased blood pressure >140/90 mmHg accompanied by proteinuria >0.3g/24 hours), pregnancy-induced hypertension (PIH; blood pressure elevation detected for the first time during pregnancy without proteinuria), macrosomia (birth weight > 4500 g and/or >2 SD), birth weight (grams and SD for gestational weeks), the incidence of small for gestational age (SGA; birth weight <2 SD), prematurity (birth < 37 weeks of gestation), Apgar score at the age of 5 min, umbilical artery pH <7.05 and base excess, hypoglycemia (s-gluc <2.6 mmol/l, measured during the first two hours post-partum), hyperbilirubinemia (need for phototherapy), need for intensive care treatment, respiratory distress syndrome (RDS), the mode of delivery (spontaneous, assisted or caesarean section) and shoulder dystocia.[22]

Statistical analysis

SAS software for Windows, version 9.1 (SAS Institute Inc., Cary, NC) was used for statistical analysis. The comparisons were made between all three groups (overall test) and pair-wise comparisons were made between mothers treated with metformin and insulin and mothers treated with metformin and diet. We considered p-values lower than 0.05 to be statistically significant.

RESULTS

The dose of Metformin varied from 500 mg to 2 g a day. Insulin was added in 10 out of 50 (20%) patients on metformin eight out of 45 patients (18 %) to main proper blood glucose level (fasting glucose <100 mg /100 ml, postprandial glucose <126 mg /100 ml). Huminsulin (30/70) was given in insulin-treated group (n = 50).

Table 1: Maternal parameter.

Parameter	Metformin (n=50)	Insulin (n=50)	Diet (n=50)	p-value
Age (years)	30.0±5.0	30.2±5.1	30.3±4.9	NS
BMI (kg/m^2)	32.0±5.2	31.2±5.0	31.4±5.3	NS
Total weight gain (kg)	10.0±5.3	9.8±6.2	8.6±4.2	NS
Weight gain GDM (kg)	2.9±3.0	3.2±5.0	3.1±2.2	NS

Table 1 shows maternal data. Average age was 30 years in all three groups and weight gain during gestation was 8.6 to 10 kg which was not much different from other groups. It is clear from table 2 that there were significantly higher Glucose values (at 0, 1, 2 hours) in OGTT (respective p-values 0.005, 0.006 and 0.003). HbAIc values and OGTT levels were higher in Metformin group in comparison to diet only group

(respective p-values 0.0005, 0.03 and 0.02); whereas gestational weeks at OGTT were significantly lower (p-values 0.004 and 0.02). It was found that there were no statistically significant differences between groups with respect to maternal age, pre-pregnancy BMI, total weight gain during pregnancy or after the diagnosis of GDM, pre-existence of hypertension, PIH or pre-eclampsia. Gestational weeks at birth and the incidence of induction of labor were also similar (Table 3).

Table 2: OGTT.

Parameter	Metformin (n=50)	Insulin (n=50)	Diet (n=50)	p-value
OGTT (0 hour)	105.0±12.0	110±14.0	100±6.0	<0.0001
OGTT (1 hour)	210±28	228±34.0	190±14	<0.0001
OGTT (2 hours)	140±30	170±32.0	130±18.0	<0.0001
HbAIc	5.4±0.3	5.3±0.4	5.2±0.3	0.001

Table 3: Gestational age.

Parameter	Metformin (n=50)	Insulin (n=50)	Diet (n=50)	p-value
Gestational week at OGTT	23.2±5.2	23.3±5.4	26.1±2.1	0.0002
Gestational week at delivery	38±1.2	37.9±1.4	38.2±2.0	0.015

Table 4: Complications.

Parameter	Metformin (n=50)	Insulin (n=50)	Diet (n=50)	p-value
PPH, n (%)	1 (2)	2 (4)	1 (2)	NS
PIH, n (%)	0 (0)	1 (2)	2 (4)	NS
Pre-eclampsia, n (%)	2 (4)	2 (4)	1 (2)	NS
Induction of laor, n (%)	20 (40)	27 (54)	30 (60)	NS

Table 5: Neonatal data.

Parameter	Metformin (n=50)	Insulin (n=50)	Diet (n=50)	p-value
Birth weight	2762±300	2758±350	2661±400	NS
Apgar score at 5 min	8.2±0.8	8.4±1.0	8.6±0.7	NS
UA pH	7.2±0.1	7.2±0.1	7.2±1	NS
Neonate at NICU (days)	2.0±2.0	3.0±1.0	2.0±0	NS
Macrosomia, n (%)	8 (16)	11 (22)	7(14)	NS
Hyperbilirubinemia, n (%)	13 (26)	11 (22)	12 (24)	NS
Hypoglycemia, n (%)	15 (30)	24 (48)	10 (20)	NS
Spontaneous delivery, n (%)	25 (50)	30 (60)	38 (76)	NS
Assisted delivery, n (%)	4 (8)	4 (8)	3 (6)	NS
Caesarean section, n (%)	15 (30)	10 (20)	10 (20)	NS
Pre-mature, n (%)	2 (4)	5 (10)	4 (8)	NS

Study also inferred from Table 4 that complications of pregnancy were also not different among groups. The incidence of neonatal hypoglycemia (S-glucose <100 mg/100 ml) treated with intravenous glucose was significantly higher in insulin-treated patients (p= 0.03) compared with those treated with metformin. The incidence of neonates requiring NICU care was not much different. NICU stay was also not different. There were also no statistically significant differences between the groups in relation to birth weight (grams), incidence of macrosomia, Apgar score at 5 min, asphyxia (umbilical artery pH <7.05) and neonatal hyperbilirubinemia. No shoulder dystocia was detected in this study, but there were two clavicle fractures of the newborn, one in the metformin group and one in the insulin group, and one Erb's paresis in the insulin group. Different modes of delivery (spontaneous, assisted or caesarean section) were also not different in all three groups. No significant differences were found in other neonatal outcome data. There was one child in the metformin group, who had trisomy. This child died at the age of two months. No intrauterine deaths occurred. Eleven patients gave birth prematurely (<37 weeks of gestational age): two in the metformin group (4.0 %, gestational ages 35 and 36

weeks), five in insulin group (10.0%, gestational ages 34, 35 and 36 weeks), and 4 in the diet only group (8.0%, gestational ages 30 to 36 weeks).

DISCUSSION

In this study, there was significantly fewer neonates with hypoglycemia during the first two hours post-partum in the Metformin-treated group compared with the insulin treated group (p= 0.03). There was no difference in incidence of hypoglycemia between Metformin and diet only group. There was no significant difference in birth weight or neonate macrosomia between the three groups. Incidence of pre-eclampsia, caesarean section or neonatal RDS were found in all three groups without much difference. Our study is consistent with observations of other study in PCOS patients treated with Metformin.[1-23] The results obtained by Hellmuth et al in a combined cohort study of GDM and T2DM mothers were different to our results in which there was increased rates of preeclampsia and perinatal loss were observed in mothers treated with metformin.[18] The reason of difference might be because of inadequately matched control groups in the study performed by Hellmuth et al.[18] The metformin group had other increased risk factors for pre-eclampsia unrelated to metformin use, i.e. they were older and more obese. In addition, their antihyperglycemic medication was started seven weeks later than in the women treated with insulin. In our study, control patients for metformin patients were matched for pre-pregnancy BMI and age. As a consequence, there were no significant differences in BMI or age of the patients between the groups. The disturbance in glucose metabolism was slightly more severe in insulin group. That is why neonatates of insulin group have more incidences of hypoglycemia. Very recently, a larger prospective randomized study comparing metformin and insulin in the treatment of GDM was published. There was no difference in neonatal complications or birth weight. Though rate of preterm delivery was higher in metformin-treated mothers.[20] In our study, the incidence of preterm delivery was very low. In the study by Rowan et al, the rate of overall neonatal hypoglycemia was similar but the rate of severe hypoglycemia was lower in the Metformin group compared to the insulin group.[20] Similarly, the incidence of neonatal hypoglycemia was higher in insulin treated patients in our study. The caesarean section rate was not reported by Rowan et al.[20] In this study, there was no difference in caesarean section rate between the metformin and the insulin group. The limitation of this study lies in the selection and assignment of patients. It was not randomized and it is probable that insulin-treated patients were slightly more hyperglycemic than metformin-treated patients as judged by the glucose values in diagnostic OGTT. Patients were given metformin or insulin without any strict criteria. The study had limited power to detect differences in many of the outcome variables, especially in those with low incidence.

CONCLUSION

Study that metformin is equally effective in the treatment of GDM patients and without higher risks for maternal or neonatal complications compared with insulin. However, further randomized clinical studies with large number of patients and with long-term follow-up of children is required in order to determine the role of Metformin as an alternative treatment to insulin in GDM patients.

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