Original Article

The use of metformin *versus* insulin in the management of diabetes mellitus in pregnancy — a randomized control trial

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The Primary objective was to determine whether metformin given to pregnant women with diabetes mellitus during antenatal period until delivery effectively control blood sugar in comparison to insulin or not. Secondary objective was to determine the pattern of association of adverse pregnancy outcome including incidence of pregnancy induced hypertension, preeclampsia, Caesarean section, postpartum haemorrhage, maternal weight gain during pregnancy and incidence of the baby's admission to the neonatal unit. In this study, of the 80 women assignment for metformin, 90.6% continued to receive metformin until delivery and 48.3% received supplemental insulin. The rates of other outcomes did not differ significantly between the groups. There were no serious adverse events associated with the use of metformin. The numerical variables were compared between the two groups by the students independent sample T test or Mann Whitney test as appropriate, Chi-square test or Fisher exact test has been employed for intergroup comparison of categorical variables.

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Key words **: Metformin, insulin, gestational diabetes mellitus.**

Gestational diabetes is a complication in about 5% of pregnancies, is increasing in prevalence and is associated with complications to the pregnancy and long-term risk of diabetes in both mother and offspring. Intervention to change lifestyle and if maternal hyperglycemia persists, treatment with additional insulin has been to improve perinatal outcome. Oral metformin is a good option for women with gestational diabetes mellitus. It improves sensitivity, and is not associated excessive weight gain or hypoglycemia.

Material and methods

160 women diagnosed with gestational diabetes had received prenatal care at the Obstetrics Endocrine Diabetes Clinic of the IPGMER, Kolkata, have been included as an inclusion criteria directional study was one year.

Inclusion Criteria :

- Singleton pregnancy in the first trimester
- Age less than 35 years
- absence of matter for lactic acidosis (renal failure, chronic liver disease, severe chronic pulmonary disease, coronary insufficiency, history of thromboembolic phenomenon)

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- Absence of anatomic and/ or chromosome anomalies of the conceptus detected by ultrasound.
- Patients willing to participate after having signed the free informed consent form.

Exclusion Criteria :

- Treatment with systemic steroids in the past 3 months
- previous pregnancy complicated by preeclampsia prompting delivery before 32 weeks gestation
- Known sensitivity to metformin
- Acute condition at the time of trial entry with the potential to alter renal function such as dehydration sufficient to require intravenous infusion.
- Acute or chronic diseases which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, hepatic insufficiency.
- multiple pregnancy
- HbA1C >8
- any other consideration which in the opinion of the investigator should not be included

Study design : Randomised control trial, open label.

Result : A total of 160 GDM patients were included in the study. They were randomly selected for equal distribution between Group A and Group B which were to receive treatment by insulin and metformin respectively (Table 1&2).

In Group A (treated by Insulin), the mean age of the patients was 30.69 years and the mean gestational age at delivery was 37.79 weeks. Five out of 80 patients (6.25%) had a family history of diabetes and 17 out of 80 patients

Table 1 — *The Maternal Parameters Studied are Outlined*

Maternal parameters studied	Insulin Group A (n=80)	Metformin Group B (n=80)	p Value
Mean Gestational Age	37.79±1.1 weeks	38.05±1.1 weeks	Not significant
H/O Diabetes	5/80 (6.25%)	5/80 (6.25%)	1.000
H/O PCOS	17/80 (21.25%)	13/80 (16.25%)	0.544
Parity P1	63/80 (78.75%)	66/80 (82.5%)	0.135
Parity P2	14/80 (17.5%)	7/80 (8.75%)	0.135
Parity P3	3/80 (3.75%)	7/80 (8.75%)	0.135
Mean Systolic Blood Pressure	120.35±6.8 mm Hg	122.75±8.3 mm Hg	Not significant
Mean Diastolic Blood Pressure	78.83±5.1 mm Hg	78.7±4.6 mm Hg	Not significant
Mean Maternal weight gain	13.75 kg	10.56 kg	Not significant
BMI	26.98	26.07	Not significant
HBA1C – 1st trimester	7.64	7.62	0.710
HBA1C – 2nd trimester	6.66	6.67	0.920
HBA1C – 3rd trimester	5.28	5.56	0.004
MBG - 1st trimester	129.89	130.17	0.841
MBG - 2nd trimester	112.05	114.62	0.068
MBG - 3rd trimester	101.72	102.65	0.321
Caesarean delivery	60/80 (75%)	60/80 (75%)	1.000

Table 2 — *Neonatal Outcomes are Tabulated*

Neonatal outcomes	Insulin Group A (n=80)	Metformin Group B (n=80)	p Value
Mean birth weight	3050.12 ± 269.7 gms	3043.6 ± 269.4 gms	0.879
Apgar score (at 5 mins)	8.18	8.16	0.83
Neonatal Hypoglycaemia	4/80 (5%)	3/80 (3.75%)	1.000
Neonatal hyperbilirubinemia	1/80 (1.25%)	1/80 (1.25%)	1.000
Neonatal Seizures	1/80 (1.25%)	1/80 (1.25%)	1.000
Neonatal RDS	2/80 (2.5%)	1/80 (1.25%)	1.000
NICU admissions	6/80 (7.5%)	4/80 (5%)	1.000

(21.25%) had a history of PCOS. Most patients had a parity of P1 (78.75%), while a parity of P2 and P3 were found in a lesser number of patients (17.5 % and 3.75% respectively). In Group B (treated by Metformin), the mean age of the patients was 31.55 years and mean gestational age was 38.05 weeks. Family history of diabetes was seen in 5 out of 80 (6.25%) patients and 13 out of 80 (16.25%) had a history of PCOS. Similar to Group A, most patients (66 out of 80) had a parity of P1 (82.5%), while P2 and P3 were found in only 7 patients (8.75%) each.

The mean systolic blood pressure (SBP) was found to be 120.35 mm Hg in Group A, while it was 122.75 mm Hg in Group B. The mean maternal weight gain in Groups A and B were 13.75kg and 10.56kg, and the mean BMI was 26.98 and 26.07 respectively. HBA1C values and mean blood glucose levels were measured in 1st, 2nd and 3rd trimesters in each group. The HBA1C values of third trimester was found to be statistically significant (p=0.004) by Student's unpaired t test. Number of Caesarean deliveries were same in both groups, that is, 75%.

Outcomes related to the neonate were also studied. The average birth weight in the 2 groups were 3050.12 grams and 3043.6 grams respectively. Neonatal hypoglycaemia developed in 4 out of 80 (5%) and 3 out of 80 (3.75%) in groups A and B respectively. Neonatal seizure and neonatal jaundice were observed equally in the 2 groups as 1 out of 80 (1.25%) and 3 out of 80 (3.75%) respectively. Neonatal respiratory distress syndrome (RDS) was seen in 2 out of 80 (2.50%) in Group A, while in Group B it was in 1 out of 80 (1.25%). Overall NICU admissions were higher in Group A (7.50%) compared to Group B (5%).

Discussion

In the present study we compared the performance of metformin and insulin in controlling blood sugar levels and their adverse outcomes. The mean maternal weight gain in our study was found to be significantly higher in the group receiving Insulin (13.75kg) than in the Metformin group (10.56kg). Similar results were also seen in studies done by Spaulonci *et al*[1], Rowan *et al*[2], Ainuddin *et al*[3] and Niromanesh *et al*[4]. However, study done by Pranathi *et al*[5] and Hamadani *et al*[6] showed insignificant difference in weight gain in the two groups.

In our study mean birth weight was found to be higher in the Insulin group (3050.12 ± 269.8 grams) while it was lower in the Metformin group (3043.6 ± 269.4 grams). However, the difference was not statistically significant (p=0.879). In study by Tertti *et al*[7], similar result was obtained. But studies by Ainuddin *et al*[3] and Niromanesh *et al*[4] showed statistically significant difference in the 2 values.

Neonatal hypoglycaemia was slightly higher in Insulin group (5%) compared to Metformin group (3.75%) but not statistically significant (p=1.000). Similar result was seen in study by Tertti *et al*[7] and Gui *et al*[8].

Neonatal RDS was slightly higher in Insulin group (2.5%) in our study compared to Metformin group (1.25%) but not statistically significant (p=1.000). Tertti *et al*[7] and Gui *et al*[8] also found no difference in rate of RDS in the 2 groups. However, Mesdaghinia *et al*[9], found statistically significant increase in rate of RDS in Insulin group than Metformin (15 *versus* 6) with a p value 0.038.

In our study rate of Neonatal hyperbilirubinemia and neonatal seizures were found to be same in both Insulin and Metformin groups (p=1.000). Gui *et al*[8] found similar results for hyperbilirubinemia. Mesdaghinia *et al*[9], and Balani *et al*[10] found statistically significant increase in rate of Neonatal hyperbilirubinemia in Insulin group than Metformin. Neonatal seizures was not included in the above mentioned studies.

NICU admissions were higher in the insulin (7.5%) verses metformin (5%) group in our study, but difference was not statistically significant (p=1.000). Tertti *et al*[7] and Gui *et al*[8] also found similar results where difference in rates of NICU admissions in the 2 groups were not statistically significant. However, Mesdaghinia *et al*[9], found sta-

tistically significant increase in rate of NICU admissions in Insulin group than Metformin (33 *versus* 14) with a p-value 0.002.

We found no significant increase in neonatal complications among women with gestational diabetes mellitus who were randomly assigned to metformin as compared with those who were assigned to insulin. In our study 48.3% of women taking metformin required supplemental insulin. However women receiving combined treatment required less insulin and gained less weight than those taking insulin alone. The strengths of the trial are that it took place within routine clinical practice and included the spectrum of women with a diagnosis of gestational diabetes mellitus. A weakness is that treatment was open label, since blinding was not considered practical or ethical.

Conclusions :

In women with gestational diabetes mellitus, metformin alone or with supplemental insulin is not associated with increased perinatal complications as compared with insulin. The women preferred metformin to insulin treatment.

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