

TREATMENT OF GESTATIONAL DIABETES MELLITUS: INSULIN OR METFORMIN?

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ABSTRACT**BACKGROUND**

Metformin has established as an ideal first-line treatment for type 2 diabetes and hypothetically a particularly attractive drug for use in pregnancy. Metformin is known to cross the placenta and its use in pregnancy has been limited by concerns regarding potential adverse effects on both the mother and the foetus. Randomised trials to assess the efficacy and safety of its use for Gestational Diabetes Mellitus (GDM) are lacking.

METHODS

Seventy six women with singleton pregnancy and diagnosed with GDM as per International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria were enrolled in study at 24 to 33 weeks of gestation. Subjects were randomly allocated to the intervention group (n=38) and active control group (n=38). Each subject in both groups received counseling on diet modification and physical activity, but failed to achieve glycaemic targets. Intervention group received metformin (with supplemental insulin if required). Active control group received human insulin (Regular, Neutral Protamine Hagedorn (NPH), or both). Primary outcome was neonatal birth weight. Secondary outcomes included maternal and neonatal complications with treatment satisfaction for allotted modality.

RESULTS

A total of 32 on metformin (Intervention group) and 33 on insulin (Active control group) subjects completed study. Of the 32 women assigned to metformin, 96.87% continued to receive metformin until delivery and 25% of the metformin group received supplemental insulin. There was no significant difference in mean birth weight between groups. There were no significant differences in neonatal and maternal complications between groups. However, treatment satisfaction (70.97%) was significantly better in metformin group whereas better control of postprandial plasma glucose was achieved in insulin group.

CONCLUSIONS

Metformin is an effective, safe, cheap, and convenient alternative to insulin in the treatment of GDM patients. However, to determine the predictors of the need for supplemental insulin in women treated with metformin, will require further study.

KEYWORDS

GDM, Metformin, Insulin, Birth weight, Treatment Satisfaction

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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is a commonly encountered complication in pregnancy and is a heterogeneous disorder resulting from an interaction between environmental and genetic risk factors.⁽¹⁾ GDM is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy."^(2,3) Diabetes during pregnancy whether symptomatic or not is associated with significant risk of adverse perinatal outcome.⁽⁴⁾ The prevalence of obesity and overweight is increasing worldwide.⁽⁵⁾ The prevalence of GDM is increasing as the occurrence of obesity, one of the risk factors predisposing to impaired glucose tolerance is

increasing. Regardless of criteria used for the diagnosis, the incidence of GDM is increasing, which affects 2-18% of all pregnancies worldwide.⁽⁶⁻⁸⁾ The detection of GDM during pregnancy provides an opportunity to identify women at risk of short-term and long-term complications. Some argue that pregnancy related hyperglycaemia might be completely physiological to provide nutrient to the foetus and whether there is a need to diagnose and treat GDM. It has been shown by Crowther et al and others that diagnosis and subsequent treatment are beneficial.⁽⁹⁻¹¹⁾ The aim of treatment is to maintain maternal blood glucose concentration within an acceptable range in a normal pregnancy. Interventions include lifestyle modification, Oral Hypoglycaemic Agents (OHAs), and insulin.

It is estimated that 70-90% of women diagnosed with GDM could achieve targeted glycaemic goals with lifestyle modification and nutrition therapy alone,^(12,13) but rest of the women often require additional treatment, which has conventionally been insulin.⁽¹⁴⁾ The disadvantages of insulin for the mother include the need to give injections, risks of hypoglycaemia, and increase in appetite and weight.⁽¹⁵⁾ Women maybe anxious about being on insulin and treatment

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compliance is an issue. It would be useful if there were alternative treatment options to insulin, preferably oral agents. Metformin, an oral biguanide, maybe a logical alternative to insulin for women with GDM who are unable to cope with the increasing insulin resistance of pregnancy. Metformin works primarily by decreasing hepatic glucose output, improving peripheral glucose uptake, and decreasing free fatty acid levels thus reducing insulin resistance.^(16,17) Outside pregnancy, metformin is as efficacious as insulin or a sulfonylurea in achieving glycaemic control in people with newly diagnosed type 2 diabetes and it is not associated with weight gain.⁽¹⁵⁾ Metformin crosses the placenta;⁽¹⁸⁻²⁰⁾ however, there is no evidence of adverse foetal effect and it is a class B drug in pregnancy.⁽²¹⁾

There are data from over 35 years ago reporting use of metformin in women with GDM or type 2 diabetes in pregnancy in South Africa. Published cohort studies showed similar perinatal mortality and morbidity for women treated with metformin compared with insulin.⁽²²⁻²⁴⁾ Additional data regarding use of metformin in pregnancy comes from studies of women with polycystic ovarian syndrome, also associated with insulin resistance. Metformin has been shown to increase ovulation rates and fertility⁽²⁵⁻²⁷⁾ and continuing it through pregnancy may reduce risks of miscarriage^(28,29) and GDM. Rates of preeclampsia and perinatal loss were not increased in women taking metformin compared with the community delivery population.⁽³⁰⁾ The lack of prospective randomised data, however, creates uncertainty about the use of metformin in women with diabetes in pregnancy. In Kolkata, we carried out a prospective randomised single centre open label trial comparing metformin with insulin treatment in women with GDM. The aim of the trial is to test the hypothesis that in women with GDM. Metformin treatment compared with insulin will result in similar perinatal outcomes and be associated with improved treatment-related satisfaction.

METHODS

Ethics and Trial Design

The trial was a randomised 1:1 parallel group open labelled single centre active controlled study with an intervention period from randomisation (24 to 33 weeks of gestation) to delivery. Institutional ethics committee approved study protocol. The trial was registered in ctr.nic.in, CTRI/2014/08/004835. The study was conducted between February 2014 and July 2015.

The study design included a screening visit (24 to 32 weeks of gestation), a randomisation visit, and subsequently patients treated with metformin or insulin had several appointments with a diabetologist and an obstetrician as necessary.

Participants

Subjects were recruited from outpatient departments. Eligible participants for the study were women aged ≥ 18 and ≤ 35 years with singleton pregnancy at 24 to 34 weeks of gestation. Those who were thought to meet eligibility criteria were invited to a screening visit. Written informed consent was obtained from all participants at the randomisation visit. All the participants were counseled about diet modifications and exercises and were instructed to maintain habits during study period.

Inclusion criteria were at least one abnormal plasma glucose value at screening OGTT as per IADPSG criteria who failed to achieve glycaemic targets with trial of diet modifications and exercises for 1 week.

Exclusion Criteria included the following

1. Diagnosis of diabetes before 24 weeks of pregnancy.
2. Pre-pregnancy diagnosis of diabetes.
3. HbA1c $> 7.0\%$.
4. Renal, hepatic, or cardiac failure.
5. Diabetic ketoacidosis.
6. Pregnancy with multiple fetuses.
7. Fetal growth restriction.
8. Ruptured membranes.
9. A fetal anomaly.
10. Bad obstetric history.
11. Preeclampsia and eclampsia.
12. Chronic hypertension.
13. Other major comorbid illness.
14. Placental abnormalities or low lying placenta.
15. Oligohydramnios or polyhydramnios.
16. Gestational hypertension.
17. Unwilling to participate in the study.

Interventions

Study participants were randomly assigned to receive 1) Metformin (500 mg to 2000 mg in divided dosages as per glycaemic status. Patients also received supplemental insulin if required. 2) Insulin (Regular, neutral protamin hagedorn or both) was started at randomisation visit according to fasting and 2-hour postprandial plasma glucose values. Patients were frequently followed up as deemed suitable and monitored for glycaemic targets, any drug-related adverse events, hypoglycaemia, adherence to diet modifications along with foetal and maternal wellbeing. Dosages of metformin or insulin were titrated to achieve glycaemic targets, fasting plasma glucose ≤ 95 mg/dL and 2-hour postprandial plasma glucose ≤ 120 mg/dL. Additional insulin supplement was given in metformin group if glycaemic targets were not achieved with lifestyle modification and maximum metformin dosage of 2 grams per day.

Outcomes

Primary endpoint was to test whether there was a difference between neonatal birth weights in the metformin and insulin groups. Secondary endpoints were gestational hypertension, maternal weight gain, preeclampsia, mode of delivery, gestational weeks at delivery, induction of delivery, shoulder dystocia, neonatal hyperbilirubinaemia, neonatal hypoglycaemia, Apgar score at 5 min after delivery, neonate transfer to intensive care unit, respiratory distress, preterm birth (< 37 wk. of gestation) and satisfaction with the allotted treatment modality.

Assessments

All assessments were performed at the randomisation visit and at the study end visits if not stated otherwise.

OGTT

A sample for fasting plasma glucose was obtained. Glucose (75 gm) in water was then given orally and plasma glucose was

obtained at 60 and 120 minutes after glucose administration. The baseline investigation was performed at screening visit.

Laboratory

Glucose was measured by glucose oxidase method. HbA_{1c} was analysed by high performance liquid chromatography. Baseline biochemistry was performed at screening visit.

Other Assessments

A standard electronic scale was used to measure weight. Foetal ultrasound was carried out in Department of Radiology by experienced radiologist for all the subjects at baseline and thereafter as required. Subjects were evaluated for both maternal and fetal wellbeing by obstetrician at randomisation visit and thereafter as per obstetrician advice.

Safety

Adverse events were collected and recorded at all contacts with subjects after randomisation visit until the last contact, i.e. 7 days after delivery. A clinical examination was performed at the randomisation and followup visits. All biochemistry needed for assessment of eligibility was remeasured at delivery. Self-monitored blood glucose values and blood pressure were obtained at each visit.

Randomisation

A simple random sampling was performed creating a list including numbers 1-76 and intervention/active control treatment in a 1:1 ratio. An independent statistician created the list by computer software. Study subjects were allocated a randomisation number consecutively at the randomisation visit. They were then provided the corresponding medication. No blocking or stratification was performed.

Blinding

Study participants, study personnel, and investigators were not blinded to the allocated study intervention. All baseline data collection and its recording in the database were made before the randomisation code was broken.

Statistics

Descriptive statistical analysis has been carried out in the present study. Data is presented as means with SDs for continuous measurements as medians with IQRs or counts with percentages for categorical measurements. Significance is assessed at 5% level of significance. Normality of data tested by Shapiro-Wilk test. Unpaired t-test or Wilcoxon Mann-Whitney test has been used to find the significance of study parameters between two groups of patients according to the distribution of data. Chi-square/Fisher exact test has been used to find the significance of study parameters on categorical scale between two groups.

RESULTS

Participant flow

Participant flow is shown in flow chart (Figure 1). In study metformin arm (n=38), 3 patients withdrew consent, 2 patients lost to follow up, 1 patient violated protocol, and one patient discontinued metformin and continued on insulin treatment to maintain normoglycaemia because of gastrointestinal side effects. In the insulin group (n=38), 2 patients withdrew consent, 1 patient lost to follow up and 2

patients had violation of protocol. For the analyses, all subjects were referred to their original treatment groups.

Baseline data

The baseline maternal characteristics are seen in Table I. In this study, there were no differences in baseline maternal characteristics between the metformin and insulin groups.

Outcomes

As shown in Table II, there were no statistically significant differences in maternal data between metformin and insulin groups in this study except for postprandial plasma glucose and treatment satisfaction.

Neonatal data are presented in Table III. In this study, there were no statistically significant differences in birth weight (grams). There were no other significant differences in terms of neonatal complications between the groups. In study, there was one stillbirth at gestational week 38 in the insulin group. The likely cause of which was an umbilical cord complication. Data of this pregnancy were included in the results of maternal and neonatal data until birth.

Need for additional insulin among patients on metformin

In this study, 25% of the patients in the metformin group (8/32) needed additional insulin to maintain adequate glucose control. Maternal baseline characteristics such as age, parity, OGTT at randomisation, and HbA_{1c} did not differ significantly in the metformin subgroups (Metformin only and metformin with additional insulin).

Maternal Baseline Characteristics	Metformin (n=32)	Insulin (n=33)	p-value
Age (years)	25.61±4.72	26.3±3.84	0.52
Gravida	1.84±0.86	1.73±0.76	0.58
History of GDM	4 (12.5)	7 (21.21)	0.51
Obesity (BMI ≥30)	7 (21.88)	10 (30.3)	0.44
OGTT 0h (mg/dL)	100.03±10.79	102.67±9.61	0.30
OGTT 1h (mg/dL)	215.22±15.34	216.61±22.39	0.77
OGTT 2h (mg/dL)	182.69±17.33	179.0±20.98	0.44
Gestational weeks at Randomisation	27.77±2.49	28.33±2.57	0.38
HbA _{1c} %	5.87±0.33	5.88±0.34	0.96
Dose of metformin (mg) or/and insulin (IU)	500-2000 (median 1500)	4-42 (median 14)	
Type of insulin		short-acting only 26% (n=9), intermediate-acting only 14% (n=4), short- and intermediate-acting 60% (n=20)	

Table I: Maternal Baseline Characteristics

Maternal data	Metformin (n=32)	Insulin (n=33)	p-value
Total weight gain (kg)	10.89±1.62	11.57±2.14	0.67
PIH #or preeclampsia	0	0	0
Polyhydramnios	0	0	0
HbA1c % at 36 Gestational week	5.68±0.24	5.67±0.21	0.83
Fasting 0h (mg/dL)	85.41±5.96	82.27±5.57	0.32
Post prandial 2h (mg/dL)	121.28±11.0	113.06±11.71	0.005
Hypoglycaemia	1 (3.1)	3 (9.09)	0.57
Gestational week at Labour	37.48±1.29	37.64±1.6	0.67
Labour induction	12 (37.5)	8 (24.24)	0.29
Vaginal delivery	8 (25)	10 (30.3)	0.64
Caesarean section	24 (75)	23 (69.7)	0.64
Treatment Satisfaction	23 (70.97)	10 (30.3)	0.002

Table II: Maternal Data and Delivery

Neonatal Data	Metformin (n=32)	Insulin (n=33)	p-value
Birth weight (grams)	2840±320	2850±570	0.93
Apgar Score at 5 min	8.71±0.78	8.88±0.70	0.36
Hypoglycaemia	2 (6.25)	4 (12.12)	0.41
Hyperbilirubinaemia	3 (9.38)	2 (6.06)	0.62
Respiratory Distress Syndrome (RDS)	1 (3.13)	2 (6.06)	0.57
Prematurity	7 (22.58)	10 (30.3)	0.57
Neonates to NICU	3 (9.38)	5 (15.15)	0.47
Foetal Anomaly	0 (0)	0 (0)	0
Shoulder dystocia	0 (0)	1 (3.03)	0.32
Macrosomia (≥4Kg)	0 (0)	1 (3.03)	0.32
Stillbirth	0 (0)	1 (3.03)	0.32

Table III: Neonatal Data

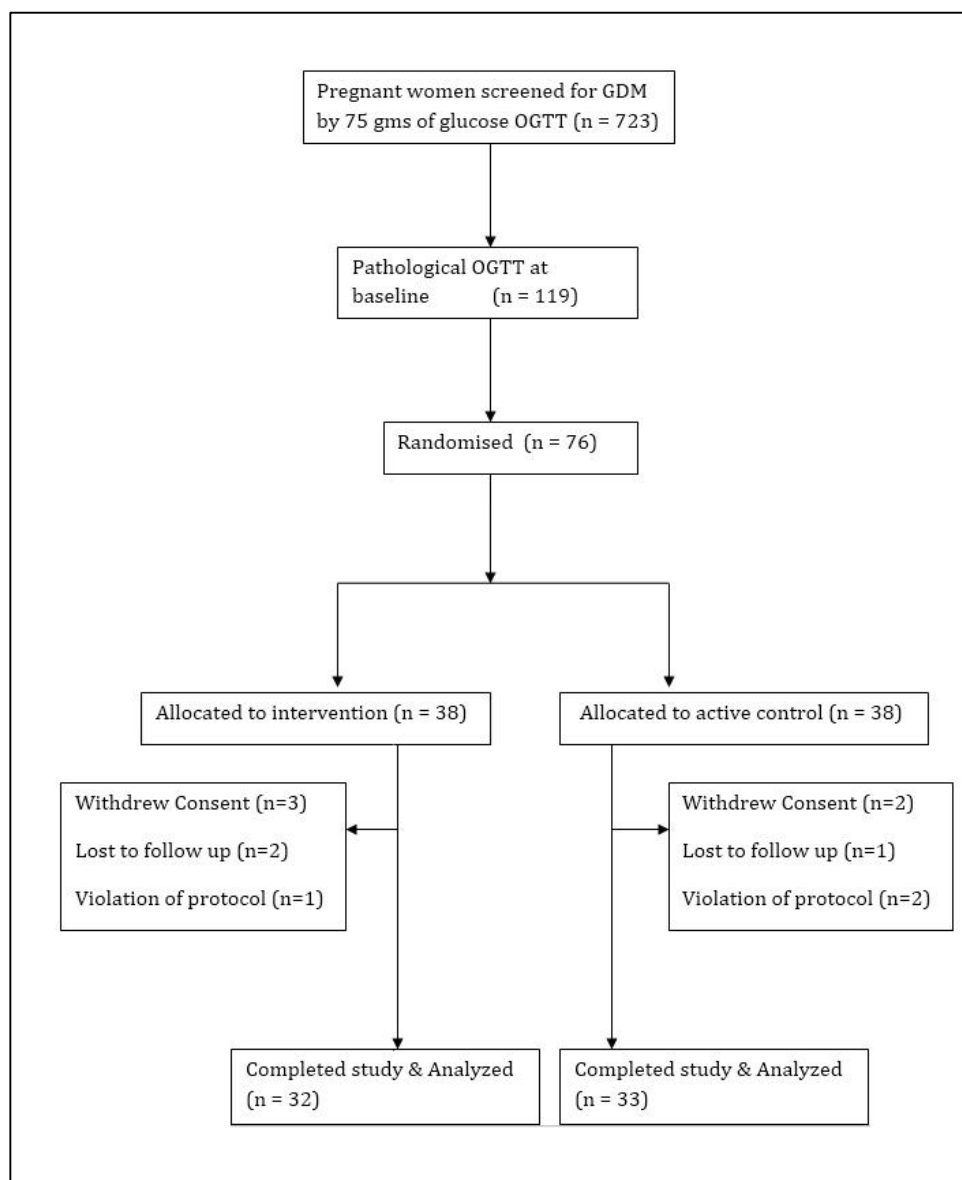


Fig. 1: Flow Chart

DISCUSSION

Using medication during pregnancy requires consideration of the risks and benefits for the mother as well as for the unborn child. Possible long-term consequences that could affect the neonate and child must be evaluated. The medication must be essential, beneficial, and cannot be harmful. If there is a well-documented pharmacological treatment for a given condition during pregnancy, an alternative drug must be documented sufficiently effective and safe before it can be considered for use during pregnancy. The use of metformin in gestational diabetes needs to fulfil these criteria. Thus, metformin must be confirmed to be safe for the mother and child and it must be effective in comparison to insulin.

In this study, there were no significant differences in mean birth weight and the other data describing the condition of the newborn between the insulin and metformin groups. The mean birth weight (2840 g) and the occurrence of neonatal hypoglycaemia (6.5%) in the metformin group were much less compared with the results of Rowan et al⁽³¹⁾ (3372 g and 15%, respectively).

Metformin did not increase the maternal risks of blood pressure problems, assisted vaginal delivery or caesarean sections, since there were no differences in maternal data between the metformin and insulin groups. Comparison of the results of study with those from previous randomised trials sets limitations; because cut off values used for medical treatment, target glucose values during medication and population ethnicity between the studies vary. Ijas et al⁽³²⁾ reported more assisted vaginal deliveries and intra-labour caesarean sections for prolonged labour in the metformin group than the insulin group. In other randomised trials as also in present study, there were no differences in the mode of delivery.^(31,33-35) Thus, metformin does not seem to increase delivery complications.

Since metformin does cross the placenta, it is essential to know whether this is neutral, beneficial, or harmful to the foetus of mothers on metformin with GDM. The safety of metformin was evaluated in study. The present results indicate that there is no increased risk to the foetus or the offspring when metformin is compared to insulin in GDM patients.

In randomised trials, comparing metformin with insulin in the treatment of GDM, less neonatal hypoglycaemia,^(31,35) and more preterm births⁽³¹⁾ were reported in the metformin group compared to the insulin group, but the difference in the rate of preterm births was not associated with other neonatal complications. In present study, there was no significant difference in occurrences of neonatal hypoglycaemia and preterm births between metformin and insulin groups. In fact, there were more preterm births in the insulin group than in the metformin group in the study of Mesdaghinia et al.⁽³⁶⁾ There was no difference in incidence of preterm births between the groups in other studies^(32,34,35) nor in this study. The risk of Respiratory Distress Syndrome (RDS) was low in this study and was not increased by the use of metformin according to previous studies.^(31,33-35) In the study of Mesdaghinia et al⁽³⁶⁾ RDS was reported even more often in the insulin group than in the metformin group.

In this clinical study, the efficacy of metformin compared with insulin in GDM patients was evaluated. The target glucose values during medication were the fasting plasma glucose <95 mg/dL and postprandial plasma glucose 2 hours <120 mg/dL.

Comparing glycaemic control between metformin and insulin groups is not fully relevant because the metformin group included patients needing additional insulin. Still in study, maternal glycaemic control was evaluated by HbA1c values at 36 gestational week, fasting, and postprandial plasma glucose. In this study, there was significant difference between the metformin and insulin groups for the postprandial plasma glucose levels at delivery. Postprandial plasma glucose was lower in insulin group in this study. Two randomised trials have reported better glucose control among metformin users than that insulin users based on postprandial glucose levels^(31,35) and on both fasting and postprandial values in an observational study of Rai et al.⁽³⁷⁾

Some patients on metformin need additional insulin to meet glycaemic targets. In this study, 25% of GDM patients in the metformin group needed additional insulin compared to 14-46% in previous randomised trials comparing metformin with insulin in GDM patients.⁽³¹⁻³⁵⁾ In the study of Moore et al⁽³³⁾ none of the metformin-treated patients needed additional insulin. The varying results in different studies with respect to the need for additional insulin maybe explained first by different glucose inclusion criteria in the OGTT and second by different fasting and postprandial glucose treatment targets. In this study, the patients needing additional insulin did not differ significantly with respect to age, parity, their OGTT, or HbA_{1c} values. Study showed no association between BMI, glucose values in OGTT, and a need for additional insulin contrary to the findings of Ijas et al.⁽³²⁾ The reason for this different result maybe chance, but the number of subjects in the study by Ijas et al⁽³²⁾ was greater than that in the present study.

Metformin often causes gastrointestinal side effects. However, in this study, only 1 patient (3.2%) and in other randomised trials ⁽³¹⁻³⁵⁾ only 0-6% of patients had discontinued metformin because of gastrointestinal symptoms. In the study of Rowan et al,⁽³¹⁾ 77% of metformin-treated patients would choose metformin again.

There was one stillbirth in this study apparently due to an umbilical cord complication in the insulin group. There was one stillbirth in the metformin group in the study of Moore et al⁽³³⁾ and one stillbirth in the insulin group in the study of Rowan et al.⁽³¹⁾ In other randomised trials, there have been no stillbirths reported.^(32,34-36) When children of GDM patients exposed to metformin in utero have been compared to children exposed to insulin. It has been found that their weight and total body fat was similar, but metformin exposure was associated with more subcutaneous fat in the arm at age of 2 years.⁽³⁸⁾ This may, in fact, suggest a favourable fat distribution relating to use of metformin.

Current study shows that metformin is safe and effective in treatment of gestational diabetes mellitus. Acceptability of metformin is better than insulin as it is noninjectable and with negligible risk of hypoglycaemia. However, small percentage of patients may need additional insulin. Limitation of current study is small sample size. Future study involving large sample size may be useful in guiding the decision.

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