



Efficacy of metformin in improving glycaemic control & perinatal outcome in gestational diabetes mellitus: A non-randomized study

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Background & objectives: Gestational diabetes mellitus (GDM) can cause adverse perinatal outcome if not treated. Although insulin therapy has been the main treatment modality over decades but considering its cost and parenteral mode of administration, it does not seem to be appropriate, especially in low-resource settings. The objective of this study was to evaluate the role of metformin in GDM and know its efficacy as well as adverse effect on foetus and mother.

Methods: All pregnant women with GDM who were not controlled on medical nutrition therapy and required metformin therapy were included in the study. Careful monitoring of blood sugar was done. Development of any maternal or foetal complications and adverse effect were recorded.

Results: A total of 2797 pregnant women were screened, of whom 233 (8.3%) were found to have GDM. Of the 64 women with GDM (28.7%) who required metformin therapy, majority (93.8%) achieved blood sugar control, whereas three (4.7%) women failed. Caesarean section rate was 54 per cent, and 15.6 per cent neonates were large for gestational age. Only two (3.1%) women had gastrointestinal side effects which were minor and got resolved with time. No case of hypoglycaemia or perinatal mortality was reported.

Interpretation & conclusions: Our findings indicate that metformin may be used as a safe and effective oral hypoglycaemic agent in GDM, especially in low-resource settings where cost, storage and compliance are logistic issues. However, long-term follow up studies are needed to solve issues related to its safety in pregnancy.

Key words Gestational diabetes mellitus - insulin - low resource metformin - oral hypoglycaemic agent

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance which is detected for the first time during pregnancy¹. The prevalence of GDM is increasing globally, and it varies according to the diagnostic criteria used and the population screened. Uncontrolled GDM may lead to a number of maternal, foetal and neonatal complications such as increased

risk of infection, pregnancy-induced hypertension (PIH), preterm labour, polyhydramnios, macrosomia, higher chances of operative delivery, development of type 2 diabetes in later life, respiratory distress syndrome (RDS), large for gestational age (LGA) and other metabolic complications such as hypoglycaemia, polycythaemia and hypocalcaemia²⁻⁴.

It has been now proved that adequate blood sugar control can significantly improve perinatal outcome^{5,6}. Although lifestyle modification including diet control and exercise is considered the first line of treatment, insulin needs to be added if the blood sugar is not optimally controlled with the above measures. Insulin does not cross the placenta; therefore, historically, it has been the only choice to establish euglycaemia in pregnant women when the diet therapy fails to achieve blood sugar control. However, considering the cost and parenteral mode of administration, it does not seem to be appropriate, especially in low-resource settings with poor literacy and insulin storage facilities. Moreover, multiple daily injections and risk of hypoglycaemia and weight gain make it undesirable for many patients.

Metformin is a second-generation biguanide which acts as an insulin sensitizer that reduces insulin resistance and basal plasma insulin levels. It also suppresses hepatic glucose output, increases insulin-mediated glucose uptake and utilization and improves lipid profile by decreasing triglyceridemia, fatty acid and low-density lipoprotein cholesterol levels whereas slightly increasing high-density lipoprotein cholesterol and decreasing intestinal absorption of glucose⁷. As metformin crosses placenta, there are concerns regarding its safety in pregnant women, but it has not been reported to cause any harm in animal or human studies done so far⁸. Unlike sulphonylureas, metformin does not cause hypoglycaemia and foetal hyperinsulinemia⁹. Metformin has the advantage of its oral route of administration, low cost and better patient acceptability. Therefore, it may be a preferred alternative to insulin therapy. With this background, this prospective non-randomized interventional study was conducted to evaluate the efficacy and safety of metformin among pregnant women with GDM.

Material & Methods

This prospective non-randomized interventional study was conducted among the pregnant women attending the antenatal clinic at department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, from October 1, 2011 to August 30, 2014. All women were screened by 75 g oral glucose tolerance test first in early pregnancy and then at 24 wk of gestation if found negative earlier. Cut-off values were taken according to American Diabetes Association (ADA) criteria 2011 (fasting plasma glucose ≥ 92 , one hour ≥ 180 and two hour ≥ 153 mg/dl)¹⁰. Women were labelled as having GDM

if one or more values were found abnormal. All women with GDM were started with medical nutrition therapy (MNT) and exercise. Four-point blood sugar profile (fasting and post-meals) was done after two weeks of starting MNT. Those who were not controlled on diet (≥ 2 abnormal plasma glucose values: fasting >95 mg/dl and two-hour post-meal value >120 mg/dl) were started on metformin therapy. Informed written consent was obtained from all the women who were started on metformin after explaining its possible side effects. The exclusion criteria included those with grossly deranged liver or kidney function tests, history of any prior adverse reaction (lactic acidosis) or allergy to metformin or any history of major congenital anomaly in previous pregnancies. Ethical clearance for this study was obtained from Ethics Committee of the Institute (CTRI/2011/08/001956).

Metformin was started with 500 mg tablet once 15 min before breakfast, and blood sugar profile was done after one week. If two or more values were deranged, the dose was increased to twice daily dose and then increased gradually upto a maximum of 2500 mg according to the requirement. Liver and kidney function tests were repeated at monthly interval for monitoring of side effects. Routine antenatal care was provided. Home blood sugar monitoring was done every two weekly with seven-point blood sugar profile. Dose adjustments were made based on the glycaemic status. Antenatal surveillance was started with biophysical profile from 28 wk and non-stress test from 32 wk period of gestation (POG). Obstetric ultrasound was performed once at 32 wk POG for foetal growth parameters, liquor and placenta and was repeated if required. Development of any antenatal complications such as PIH, preterm labour, chorioamnionitis, polyhydramnios, cholestasis of pregnancy, macrosomia or intrauterine growth restriction was also recorded.

Mode of delivery was individualized according to the obstetric indication. Those who failed to go into spontaneous labour were induced at 38 wk POG. All the neonates were assessed at birth by neonatologist and monitored for the development of hypoglycaemia and other metabolic complications including hyperbilirubinemia, polycythaemia, hypokalaemia and development of RDS. Neonate was considered LGA if birth weight was $>90^{\text{th}}$ percentile based on growth standard¹¹. Hypoglycaemia was defined as blood sugar value <40 mg/dl. Hyperbilirubinemia was defined as serum bilirubin of at least 12 mg/dl within first seven days of birth. Polycythaemia was defined as

haematocrit >60 per cent measured in cord blood of all infants. RDS was defined as the need for respiratory support with oxygen, continuous positive pressure or intermittent positive pressure ventilation during first 24 h after delivery. In addition, neonatal intensive care unit admission rates, congenital anomalies, birth injuries, exchange transfusions and the need for phototherapy were also documented.

Statistical analysis: An earlier study conducted in India showed that GDM prevalence based on single abnormal value was 10.87 per cent¹². Considering this value as a hypothetical prevalence by allowing 2 per cent error margin, the required sample size for 80 per cent power at 5 per cent level of significance was calculated to be 1919, and by allowing a 15 per cent dropout rate a minimum sample size was fixed as 2210. Data were analyzed using SPSS, IBM Version 19.0 (IBM Corp., Armonk, NY, USA). For continuous variables, means and standard deviation were calculated. Frequency data were summarized as percent values. Results obtained were analyzed for outcomes and presented as percentage.

Results

A total of 2797 pregnant women were screened during the study period of whom 233 were found abnormal (using ADA criteria 2011) making the occurrence of GDM to be 8.3 per cent. Of these 233, 10 (4.3%) women with GDM were excluded on the basis of exclusion criteria. Of the remaining 223 women, 28.7 per cent (n=64) required metformin therapy and the rest were controlled on MNT alone (Figure).

The demographic and clinical profile of the enrolled patients is summarized in Table I. The mean dose of metformin required was 1226.5±397.1 mg (500-2500 mg). Table II summarizes the details of patients according to the gestational age of starting metformin and its impact on treatment. Majority (n=60, 93.8%) of the pregnant women achieved blood sugar control on metformin therapy, whereas three (4.7%) women failed. Two (3.1%) women had gastrointestinal side effects which were minor and got resolved with time. Table III shows the details of maternal complications and mode of delivery among these women. No episode of hypoglycaemia was reported among the pregnant women who received metformin. There was no case of perinatal mortality.

Details of foetal outcomes are presented in Table IV. The mean birth weight was 2753±565.4g. Ten (15.6%)

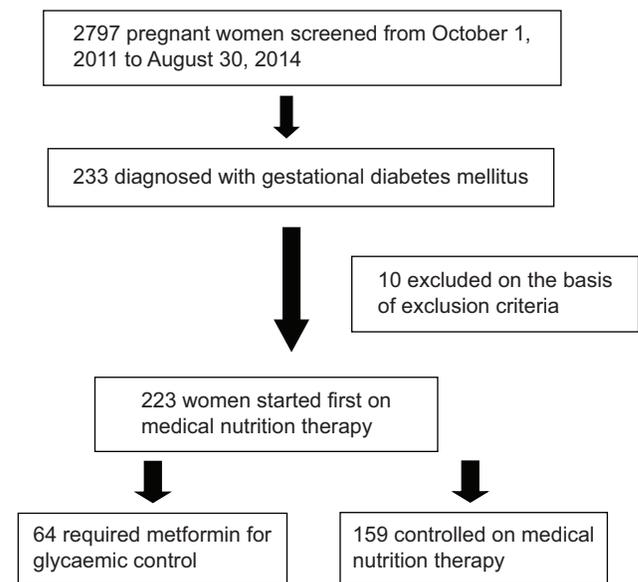


Figure. Flow chart showing enrolment of participants.

Table I. Demographic and clinical profile of patients (n=64)

Characteristics	Values
Age of participants (yr), mean±SD	29.1±4.4
Body mass index (kg/m ²), mean±SD	24.8±4.0
Gestational age at diagnosis (wk), mean±SD	20.7±6.6
Nulliparous, n (%)	15 (23.4)
Parity>1, n (%)	49 (76.6)
Previous history of gestational diabetes mellitus, n (%)	23 (35.9)
Family history of diabetes mellitus, n (%)	25 (39.5)

infants were LGA. All of them were monitored for hypoglycaemia for 48 h by checking capillary blood sugar. Five of them developed hypoglycaemia. Of these five, two responded to oral feeding while three required neonatal intensive care unit admission. None of them had shoulder dystocia. There was no perinatal morbidity or mortality.

Discussion

The increase in prevalence of diabetes can be attributed to urbanization, change in lifestyle and dietary habits, and it also varies according to the diagnostic criteria and the population being screened¹³. The association between timely diagnosis and treatment of GDM cannot be over emphasized. The earliest report about the use of metformin in pregnancy came from South Africa in 1970, where it was used for both type 2 diabetes and GDM¹². Some studies concluded

Table II. Gestational age of start of metformin therapy and its effect on treatment (n=64)

Characteristics	Value, n (%)
Gestational age at start of metformin therapy (period of gestation) (wk)	
<12	8 (12.5)
12-28	50 (78.1)
>28	6 (9.4)
Dose of metformin required (mg), mean±SD	1226.5±397.1
Number of women controlled with metformin monotherapy	60 (93.8)
Number of pregnant women who remained uncontrolled with metformin	3 (4.7)
Number of women who required additional insulin	1 (1.5)
Number of women who were non-compliant with metformin monotherapy	2 (3.12)

that women with GDM treated with metformin had a higher rate of perinatal mortality than the general population, but it was still lower than those who were left untreated¹⁴⁻¹⁶.

Metformin is an oral biguanide which enhances insulin sensitivity and decreases hepatic glucose output. Unlike insulin, it controls blood sugar level without causing hypoglycaemia or weight gain. Metformin has an ease of administration and storage. As it crosses placenta, there are concerns about its safety, especially in the first trimester. The adverse effects are mainly related to gastrointestinal system. Symptoms are often self-limiting and include nausea, vomiting, abdominal bloating, diarrhoea, anorexia and abdominal pain¹⁷. In our study, some of the participants had minor gastrointestinal side effects which resolved gradually. None of them had to discontinue therapy due to adverse effect. In another study, gastrointestinal side effects of metformin were encountered in 1.9 per cent of patients who required discontinuation of therapy¹⁸. It is preferred to commence metformin at a low dose (500 mg/day) and always with food to reduce gastrointestinal adverse effect. The women found metformin to be convenient as they did not need to take daily insulin injections. The time and workforce required to train the women for self-administration of insulin could also be avoided.

Vanky *et al*¹⁹ have shown that metformin crosses the placenta and foetus is exposed to levels of metformin

Table III. Details of maternal outcome (n=64)

Characteristics	Number of cases, n (%)
Pregnancy induced hypertension	4 (6.3)
Premature rupture of membrane	4 (6.3)
Preterm labour	6 (9.4)
Intrauterine growth restriction	4 (6.3)
Antepartum haemorrhage	1 (1.6)
Cholestasis of pregnancy	5 (7.8)
Polyhydramnios	1 (1.6)
Urinary tract infection	2 (3.1)
Mode of delivery	
Vaginal delivery	27 (42.2)
Vacuum assisted delivery	1 (1.6)
Forceps delivery	1 (1.6)
CS	35 (54.6)
Nature of labour	
Induced	28 (43.7)
Spontaneous	36 (56.2)
Indications of CS (n=35)	
Foetal distress	18 (51.4)
Contracted pelvis	2 (5.7)
Failed induction	6 (17.1)
Malpresentation	4 (11.4)
Previous two or more LSCS	2 (5.7)
Macrosomia	1 (2.8)
Placenta previa	2 (5.7)
LSCS, lower segment caesarean section	

comparable to therapeutic level in adults. In a systematic review and meta-analysis it has been concluded that though human experience with metformin during the first trimester of pregnancy is reassuring but there is a need for specific studies designed to evaluate the teratogenicity²⁰. Although 12.5 per cent of the pregnant women were started on metformin in the first trimester, no case of congenital anomaly was observed in the present study.

Sixty women achieved good glycaemic control while four of the remaining failed to achieve euglycemic status with metformin in our study. Three of them were non-compliant to the treatment and one required insulin therapy for glycaemic control. In the metformin versus insulin for the treatment of gestational diabetes (MiG) trial¹⁸, 46.3 per cent of the women in metformin arm required supplemental insulin to maintain euglycaemia. In other studies 10, 18

Table IV. Details of foetal outcome (n=64)

Characteristics	Values, n (%)
Birth weight (g), mean±SD	2753.5±565.4
SGA	9 (14.1)
AGA	43 (67.2)
LGA	10 (15.6)
Apgar at one minute <7	2 (3.1)
Neonatal intensive care unit admission	9 (14)
Hypoglycaemia	3 (4.7)
Respiratory distress syndrome	4 (6.9)
Jaundice	2 (3.1)
SGA, small for gestational age; AGA, appropriate for age; LGA, large for gestational age	

and 14 per cent of the participants have been reported to need insulin, respectively²¹⁻²³. The reason behind this varying number may be difference in age, body mass index and racial composition of the population.

The percentage of women developing hypertensive complications and preterm labour in the present study was 6.3 per cent each whereas it was 12 and 7.2 per cent each in the study by Rowan *et al*¹⁸. Only 15.6 per cent neonates were LGA compared to 19.3 per cent in the study done by Rowan *et al*¹⁸. Although only 4.7 per cent of the women remained with uncontrolled level of GDM with metformin, this higher number of LGA neonates in the present study may be due to other associated factors such as constitutional or genetic. The higher rate of caesarean section (54%) and SGA neonates (14.1%) in the present study may be explained by the fact that the majority of the pregnant women booked in our tertiary referral centre had one or more high-risk factors.

In a meta-analysis, six studies consisting of 1388 participants were analyzed²⁴. The use of oral hypoglycaemic agent (OHA) was not associated with risk of neonatal hypoglycaemia, incidence of caesarean section or incidence of LGA babies. As metformin crosses the placenta, neonatal follow up is required to accept metformin as safe in pregnancy. A trial (Metformin in GDM - The offspring follow up) was conducted among women who had participated in the MiG trial, and body composition was measured in their children at two years age. It was found that children exposed to metformin had more subcutaneous fat, but overall body fat was similar as in children whose mothers were treated with insulin alone but further follow up was recommended²⁵.

In conclusion, metformin may be used as a safe and effective OHA in the management of GDM. It may prove to be a boon in low-resource settings where cost, storage and compliance are logistic issues. However, long-term follow up studies in pregnancy are needed to solve issues related to its safety on foetus and mother.

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Conflicts of Interest: None.

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