*Original Article*

# Metformin prevents macrosomia and neonatal morbidity in gestational diabetes

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**ABSTRACT**

***Objective:*** To assess the clinical efficacy of Metformin in the prevention of fetal macrosomia and neonatal morbidity in gestational diabetes pregnancies compared with insulin treatment.

***Methodology:*** *In this* interventional study, randomized clinical trial a total of 150 patients with gestational diabetes between 20-35 weeks of gestation were selected for pharmacological treatment using metformin or insulin during the study period form 20-Dec-2008 till 20-Dec-2010 from Antenatal OPD after screaning with 75 grams OGTT. The primary outcomes were fetal macrosomia and neonatal morbidity.

***Results:*** Patients on metformin and insulin were matched in age, parity, BMI and gestational age at study entry. Mean birth weight did not differ in both groups but fetal macrosomia was less in metformin group than in insulin group 18.67% V/S 10.65% P <0.05. Neonatal morbidity and NICU admissions were less in metformin group.

***Conclusion:*** Metformin is a safe and effective alternative to insulin in gestational diabetes. Metformin treatment resulted in less fetal macrosomia and fewer NICU admissions and neonatal morbidity with advantages of cheap oral therapy in our resource poor setting.

**KEY WORDS:** Metformin, Gestational diabetes, Macrosomia, Neonatal morbidity.

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## INTRODUCTION

Gestational diabetes (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy[1,2] and usually resolved at the end of gestation. However between one half and one third of women with gestational diabetes may develop non insulin diabetes 2-11 years post partum. GDM is diagnosed in approximately 3-7% of pregnancies.[3,4] In Pakistan the incidence is estimated to be about 3.45%.[5] The incidence of GDM increases as the pregnancy population is becoming older and fatter. Maternal hyperglycaemia is associated with an increased risk of perinatal complications especially fetal macrosomia defined as birth weight of >4kg. Macrosomia is associated with an increased risk of IUD, birth trauma especially shoulder dystocia, cesarean section and neonatal hypo glycaemia, moreover large for gestational age babies are at

increased risk of obesity, metabolic syndrome and type 2 diabetes later in life.[6-8]

Studies have demonstrated that effective treatment of hyperglycaemia in women with GDM can reduce adverse perinatal outcomes. The main purpose of treatment is to prevent fetal hyperinsulinemia and fetal macrosomia by reducing maternal glucose levels.[8,9] This is achieved by the diet advise and exercise initially but women usually require additional treatment which has conventionally been insulin which has shown to improve perinatal outcomes.[10,11] The disadvantages of insulin for mother includes the need to give injections, risk of hypoglycaemia, increase in appetite and weight gain.[12] Treatment compliance and cost with insulin is always an issue especially in poor countries like Pakistan, an alternative to insulin injections is preferably oral agents as a treatment option which are therefore much cheaper and palatable in comparison to insulin.

Metformin an oral bigaunide that produces euglycaemia instead of hypoglycaemia, appears to be a more logical alternative to insulin in women with GDM who are unable to cope with increasing insulin resistance of pregnancy. Metformin improves insulin sensitivity and hyperglycaemia by reducing hepatic gluconeogenesis and increasing peripheral glucose uptake and utilization, it also reduces markers of endothelial activiation which are intimately associated with insulin resistance.[13,14] Outside pregnancy metformin is as efficacious as insulin or a sulfonyl urea in achieving glycaemic control in people with newly diagnosed type 2DM and is not associated with weight gain.[15,16] Metformin crosses the placenta but no evidence of adverse fetal effects have been reported in studies done on women with PCOS treated with metformin and continued in first trimester and even throughout pregnancy.[17-20] Metformin is a class B drug in pregnancy.[21] No teratogenic effects have been demonstrated in animal models and reported outcomes of it use in pregnancy have been favorable.[22,23]

WHO ranks Pakistan as the 7$^{th}$ most prevalent country for diabetes mellitus. We have a population that brings specific challenges with respect to marked insulin resistance, low socioeconomic status in terms of affordability with cost of insulin, poor compliance and follow up with insulin treatment in pregnancy. Metformin instead of conventional insulin was tried in our population for treatment of GDM. Prevention of fetal macrosomy is the main target in the treatment of GDM.

The aim of study was to assess the clinical efficacy of metformin in the prevention of fetal macrosomia and neonatal morbidity in Gestational diabetes pregnancies compared with insulin treatment.

## METHODOLOGY

This randomized clinical trial comparing metformin with insulin in treatment of GDM was conducted between 20-12-2008 till 20-12-2010 in the Lyari General Hospital, Dow University of Health Sciences and private maternity hospitals. The study was approved by the Ethics review board of Dow University of Health Science. Informed written consent was obtained from participants.

The patients were selected from those attending the antenatal clinics and diagnosed with GDM after screening in antenatal clinic due to presence of high risk factors for diabetes mellitus. A 5Ogram oral glucose challenge test was done as an initial screening test (≥ 140mg / dl positive GCT) followed by a 75 gram OGTT as per WHO criteria for confirmatory purpose. (Diagnosis of GDM, at least two out of three abnormal high plasma glucose levels in a 75 gm OGTT FBS >95, 1 hour ≥ 180, 2 hour ≥ 155).

Women included in the study were between 18 and 45 years of age, having a diagnosis of GDM as per WHO criteria, were pregnant, having a singleton pregnancy between 20-36 weeks of gestation. The exclusion criteria were women who have a contra indication to taking metformin, a prepregnancy diagnosis of diabetes, a recognized fetal anomaly on ultrasound at study entry, presence of any other medical disorder like essential hypertension, renal disease, hepatic disease, hypothyroidism, ruptured membranes, presence of diabetic complications and fetal growth restriction.

After a diagnosis of GDM was made patients were counselled for dietary and lifestyle modification. They were taught home blood glucose monitoring. Those who failed to achieve euglycaema with diet and exercise were selected for metformin or insulin treatment. Target blood glucose levels were taken as FBS <100 mg/dl and post parandial of ≤126 mg/dl. Randomization was done as first patient of insulin and 2$^{nd}$ patient on Metformin irrespective of body weight and GTT blood glucose values at study entry. Background maternal demographic and clinical data were recorded at study entry. Biochemical tests including blood complete picture, urinanalysis, serum creatinine and liver function tests were done to exclude any contra indications for use of metformin. HbAIC (Glycosylated hemoglobin) level was measured and fetal

ultrasound to exclude fetal anomaly was done at study entry.

Metformin was started at a dose of 500 mg and increased upto 3,000mg daily in divided doses as tolerated by patient and depending on maternal glucose levels. Target values were taken as FBS of < 5.5mmol / lit (≤100 mg/dl) and. RBS 1½ hour postprandial < 7mmol / lit (≤126 mg/dl). If blood sugar levels were higher than cut off values with metformin, insulin was added but metformin continued. Metformin was stopped if significant preeclampsia, sepsis, pregnancy cholestasis or IUGR developed or with drug intolerance due to Gastrointestinal side effects. Insulin was added as supplementary treatment in patients not controlled with metformin alone in 1-2 weeks. Insulin was given as a combination of regular and intermediate acting Human insulin before meals twice daily. Patients were followed in the outpatient clinic at 1-2 weeks interval depending on blood glucose control between 28-36 weeks and then weekly till delivery. Fetal growth was monitored by symphysio fundal height measurements, maternal weight gain and growth ultrasound scans. At 36/37 weeks HbA1C was measured. At delivery pregnancy complications, mode of delivery and maternal complications were recorded. Neonatal outcome and neonatal morbidity was recorded upto 28 days after birth.

The primary outcome was incidence of macrosomia defined as birth weight of over 4000 grams. Secondary outcome were neonatal complications like hypoglycaemia (<40 mg / dl), respiratory distress syndrome, need for NICU (neonatal intensive care unit) admission, hyperbilirubinaemia needing photo therapy, trauma (Bruises, clavicular fracture, brachial nerve injury). Apgar score at 5min <7, prematurity < 37 weeks gestation and 1st week Neonatal death. Maternal outcomes included need for supplemental insulin in metfromin group, weight gain in pregnancy and mode of delivery.

***Statistical Analysis*:** SPSS version 16 is used for statistical analysis. Continuous results was expressed as mean and standard deviation of median and range according to data distribution using descriptive analysis. Categorical data is presented as proportions comparison between two groups is made with a two sample independent 't' test and chi-square test for categorical data, two tailed tests are used for analysis and statistical significance is taken at $P < 0.05$

## RESULTS

During the study period form December 12, 2008 till December 20, 2010 a total of 150 patients were selected after screening in antenatal OPD for treatment of gestational diabetes mellitus and randomized for treatment. A total of 75 patients were given oral metformin and 75 patients were put on insulin treatment.

Mean age, parity and BMI at study entry did not differ in both groups (Table-I) Total weight gain in pregnancy was lower in metformin group mean

Table-I: Maternal Characteristics (n=150).

| S. No | Variable | Insulin Group | | | Metformin Group | | | P-Value |
|---|---|---|---|---|---|---|---|---|
| | | N=75 Mean ± S.D | Min | Max | N=75 Mean ± S.D | Min | Max | |
| 1 | Age | 30.88 ± 3.6 | 23 | 40 | 30.29 ± 3.06 | 23 | 39 | |
| 2 | Parity | 2.76 ± 1.19 | 1 | 6 | 2.75 ± 1.03 | 1 | 5 | |
| 3 | BMI at study entry | 28.74 ± 2.69 | 20 | 37 | 29.17 ± 1.94 | 24 | 35 | 0.253 |
| 4 | Total weight gain in pregnancy | 12.89 ± 1.34 | 10 | 17 | 10.49 ± 2.15 | 6 | 14 | 0.001 |
| 5 | FBS in OGTT | 102.11 | 89 | 110 | 100.89 | 88 | 120 | 0.079 |
| 6 | 2 hours post load RBS in OGTT | 236.41 | 180 | 309 | 231.56 | 188 | 280 | 0.058 |
| 7 | GEST age at study entry | 29.20 ± 1.48 | 26 | 34 | 29.53 ± 1.33 | 27 | 34 | 0.168 |
| 8 | GEST age at delivery | 37.53 ± 0.99 | 35 | 39 | 37.33 ± 1.43 | 29 | 39 | 0.184 |
| 9 | HbA1C at entry | 5.19 ± 0.59 | 3.4 | 6.0 | 5.4 ± 0.47 | 4.5 | 6.5 | 0.286 |
| 10 | HbA1C at 36/37 weeks | 5.37 ± 0.48 | 5.0 | 6.0 | 5.7 ± 0.47 | 5.0 | 7.0 | 0.341 |
| 11 | Vaginal Delivery | 33 (44%) | | | 50 (66.7%) | | | 0.004 |
| 12 | Induced Labour | 14 (18.7%) | | | 20 (26.7%) | | | 0.001 |
| 13 | Caesarean Section | 42 (56%) | | | 25 (33.3%) | | | 0.004 |

10.49kg as compared with 12.9kg in insulin group which is significant P < 0.05 (Table-I). The Fasting blood sugar and post load blood sugars in OGTT with 75 grams glucose load at diagnosis were also similar. The mean gestational age at study entry and delivery did not differ in both groups. HbA1C at study entry and at term were also similar. More patients delivered vaginally in metformin group 50 (66.7%) as compared with 33 (44%) in insulin group. The caesarean section rate was 56% in insulin group and 33.3% significantly lower in metformin group P 0.004.

The mean birth weight of newborns did not differ 3.4kg V/S 3.6kg in metformin v/s insulin group (Table-II). Macrosomic babies with birth weight > 4kg were 14 (18.67%) in insulin group and8 (10.67%) in metformin group P < 0.05. There was no difference in apgar scores of newborns at 5 minutes in both groups. However NICU admissions were less in metformin group. 14 (18.75).than in insulin group 19 (25.3%) P < 0.05. There is no significant difference in mean blood glucose levels of neonates at birth in both groups. However neonatal hypoglycemia requiring NICU admission was more in insulin group 20 (26.67%) as compared to 10 (13.33%) in metformin group. More neonates needed photo therapy in insulin group. Nine (12%) than in metformin group 4 (5.3%) P < 0.05. No birth trauma occurred in both groups and the incidence of RDS was same in both groups. No perinatal deaths occurred in both groups.

Eighteen patients in metformin group needed supplemental insulin. These patients were obese with greater BMI and had raised blood sugars at study entry. Small for gestational age infants were more in metformin group than in insulin group 10 (13.33%) in metformin group and 5 (6.67%) in insulin group.

## DISCUSSION

Our study showed that metformin is safe and an effective alternative to insulin for treatment of gestational diabetes Mellitus. Insulin resistance, an important feature of pregnancy and being more marked in gestational diabetes can be dealt more effectively with metformin. Metformin is an insulin sensitizer which targets insulin resistance without enhancing insulin production; in addition it reduces plasma insulin levels and hence reduces fetal macrosomia. In our population where daily blood glucose monitoring is very difficult metformin is a safe alternative to achieve glycaemic control thus avoiding neonatal complications of gestational diabetes mellitus. Similar results with use of metformin in GDM have been observed in other studies.[24-26] A group of 150 patients had been selected for the study and assigned for treatment with insulin or metformin, 24% required insulin supplementation in metformin group but the dose of supplemental insulin was small. Metformin was continued throughout pregnancy upto a maximum dose of 3000mg without any significant side effects. The patients were matched in age, parity, BMI at study entry gestational age at study entry and blood glucose levels in OGTT.

Glycosylated hemoglobin were similar in both groups at study entry and at delivery indicating good glycaemic control in both treated groups. More patients delivered vaginally in metformin group 66.7% as compared with 44% in insulin group. Caesarean section rate was higher in insulin group than in metformin group. However

Table-II: Neonatal Characteristics (n=150.

| *S. No* | *Variable* | *Insulin Group* | | | *Metformin Group* | | | *P-Value* |
|---|---|---|---|---|---|---|---|---|
| | | *N=75 Mean ± S.D* | *Min* | *Max* | *N=75 Mean ± S.D* | *Min* | *Max* | |
| 1 | Birth Weight | 3.6 ± 0.46 | 2.7 | 5.0 | 3.4 ± 0.4 | 2.8 | 4.0 | 0.059 |
| 2 | Birth WT > 4KG | 14 (18.67%) | | | 8 (10.67%) | | | 0.001 |
| 3 | SGA (Small For Gestational Age) | 5 (6.67%) | | | 10 (13.33%) | | | 0.000 |
| 4 | A/S at 5 min | 8.6 ± 0.91 | 5 | 10 | 8.8 ± 0.43 | 6 | 9 | 0.731 |
| 5 | NICU admissions | 19 (25.3%) | 14 (18.7%) | 0.001 | | | | |
| 6 | Blood Glucose at Birth | 44.53 ± 11.8 | 20 | 68 | 48.12 ± 8.2 | 21 | 74 | 0.22 |
| 7 | Hypoglycaemia | 20 (26.67%) | 10 (13.33%) | 0.000 | | | | |
| 8 | Hyperbilirubinaemia | 9 (12%) | | | 4 (5.3%) | | | 0.000 |
| 9 | Birth Trauma | --- | | | --- | | | --- |
| 10 | RDS | 3 (4%) | | | 3 (4%) | | | --- |

no difference in ceasarean section rate was found in studies conducted by Ijas H in 2010 and Tertti in 2008.[26,27] The caesarean section rate was not reported in MIG trial by Rowen et al.[24] There was no significant difference in the mean birth weight between the two groups. Similar results regarding birth weight was observed in other studies[25-27] but the incidence of macrosomia was similar in both groups which do not corresponds to our study.

The incidence of macrosomia was 18.67% in insulin group v/s 10.67% in metformin group in our study P 0.001. In MIG trial rates of macrosomia observed were 19.3% v/s 18.6% in metformin v/s insulin group P 0.83. Results comparable with MIG trail were reported by Tertti in 2008 where incidence of macrosomia was 22.2% in insulin group v/s 15.8% in metformin group. Ijas H in 2010 reported a lesser incidence of macrosomia 10% v/s 8.5% in insulin v/s metformin group.[8,24,26,27] Results of 5 minutes Apgar score at birth were also same in both groups. Neonatal NICU admissions were significantly lower in metformin group (18.7% v/s 25.3%) than in insulin group because of lesser hypoglycaemia and hyperbilirubinaemia at birth in metformin group. MIG trial also reported significantly less incidence of severe hypoglycaemia at birth in infants of women taking metformin.[24,26]

Small for gestational age infants were more in metformin group than in insulin group. This is in contrast to study conducted in India where SGA infants were more in insulin group.[25] However all other studies reported a high incidence of SGA infants and preterm deliveries in metformin group.[24,26,27] Maternal weight gain in pregnancy was significantly lower in metformin group 10.94kg compared to 12.89kg in insulin group which is comparable with other studies.[8,24,27,28]

Our experience thus suggests that metformin is a safe effective alternative to insulin where life style measures are inadequate to achieve or maintain euglycaemia resulting in relatively less burden on treating physicians and at the same time giving financial relief to patients with GDM, because of lesser cost of metformin & less monitoring required with oral metformin treatment.

In conclusion metformin treatment in gestational diabetes resulted in less fetal macrosomia fewer NICU admissions, reduced incidence of severe neonatal hypoglycaemia and hyperbilirubinaemia with additional advantages of cheap oral therapy in a resource poor setting like Pakistan.

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***Conflicts of Interest & Ethical Review:*** This study was done as part of requirement of Ph-D in Clinical Sciences at Dow University of Health Sciences. All financial burdens were taken by myself and helped by administration of Lyari General Hospital and patients themselves at private obstetric clinics. Informed written consent was taken from patients and patient acceptability was good. This study was entirely non profitable and was approved by Ethics Review Board of Dow University of Health Sciences in 2008 before starting the project.

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