

**COMPARISON OF METFORMIN WITH GLYBURIDE IN GESTATIONAL DIABETES: A DOUBLE BLIND RANDOMISED CLINICAL TRIAL**Miriam George Fenn<sup>1</sup>, Mini Isac<sup>2</sup>, Mary George<sup>3</sup>, Sara Korula<sup>4</sup>**HOW TO CITE THIS ARTICLE:**

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**ABSTRACT: AIMS:** To compare the effects of metformin and glyburide on gestational diabetes with regard to 1. Glycaemic control in antenatal period. 2. Neonatal outcomes. **STUDY DESIGN:** This is a prospective double blind randomized clinical trial. Patients were diagnosed to have Gestational diabetes mellitus with the 2 step test. Those cases not responding to diet therapy were randomized to two arms of treatment. Patients in Arm A were given started on glyburide (n=24): started at 2.5mg BID, next step 5mg and 2.5mg, then maximum dose of 5mg BID. If not controlled, Insulin was added. Those patients randomized to Arm B were given metformin: started at 500mg BID dosage, next step 850mg morning – 500mg with dinner, then maximum dose of 850mg BID. If not controlled, Insulin was added. The outcomes analyzed were maternal HbA1c in third trimester, patients who needed additional insulin for glycaemic control, patients with hypoglycaemic symptoms, maternal weight gain in pregnancy, mode of delivery. Perinatal outcomes analyzed were birth weight, cord blood C peptide levels, neonatal complications - jaundice, hypoglycaemia, shoulder dystocia. **ANALYSIS:** Excluding the 1 case from each arm lost to follow up, we had 46 patients (n=23 in each arm). Using SPSS software, characteristics were analyzed and using chi square test, the proportions in the two groups were compared. **RESULTS:** The two arms were comparable with regard to maternal and neonatal outcomes for gestational diabetes. No significant differences were found in treatment failure needing Insulin, rate of participants with glycosylated haemoglobin above 6. 5, rate of large-for-gestational-age newborns, and there were no newborns with hypoglycaemia in both the arms. **CONCLUSION:** Metformin and glyburide showed equal safety and efficacy when used in treatment of gestational diabetes mellitus.

**KEYWORDS:** Gestational diabetes, Oral hypoglycaemic agents.

**INTRODUCTION:** Gestational diabetes mellitus (GDM) is carbohydrate intolerance with its onset or first recognition in pregnancy. Incidence of GDM is on the rise. Indians and especially rice eating South Indians are 11 times more prone to GDM than whites. In our institution, incidence of GDM is between 10 and 12%.

Looking at the global picture, Vietnam, India and Cuba have the greatest prevalence of GDM, data from Africa are grossly lacking.<sup>1</sup> Treatment of gestational diabetes reduces serious peri natal morbidity, and may also improve the woman's health related quality of life.<sup>2</sup> Prompt management of mild GDM is associated with significant reduction in pre eclampsia and gestational hypertension.<sup>3</sup>

Insulin remains the only Federal Drug Administration - approved agent to treat GDM. But oral hypoglycemic agents are an attractive and increasingly common alternative. In 2012, a study by Most and Lang showed that insulin was necessary to reduce excess birth weight in babies of obese women with GDM.<sup>4</sup>

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Research suggests that glyburide and metformin can each effectively manage hyperglycaemia in pregnancy. The clinicians have been cautious in their usage in pregnancy as both these drugs have been shown to cross the placental barrier.<sup>5</sup> Conventionally, OHA have been used with caution in GDM, the concerns being teratogenicity and neonatal hypoglycaemia.

A Malaysian study in 1997 was the one of the first to report favorable outcome of the use of glyburide in pregnant women, study was done in comparison with insulin.<sup>6</sup> Langer et al in 2000 published their study which concluded that OHA in comparison to Insulin was safe and effective alternative.<sup>7</sup>

Oral hypoglycaemic agents (OHA) are convenient and more patient friendly as there is no need to inject, unlike insulin.

Metformin is a second generation biguanide. It is an insulin sensitizer that reduces the insulin resistance and basal plasma insulin levels, therefore it increases glycaemic profile. Besides suppressing hepatic glucose output, it increases insulin mediated glucose use in skeletal muscle, decreases fatty acid oxidation, increases splanchnic glucose turnover, decreases intestinal glucose absorption and facilitates weight reduction. Use of the drug in presence of renal disease is contra indicated.<sup>8,9</sup>

Glyburide is a second generation sulfonyl urea oral hypoglycaemic agent (OHA). Glybenclamide is synonymous with glyburide. It is effective only in those patients who have retained some degree of pancreatic insulin secreting function. After binding to specific receptors on the beta cell membrane, they close the potassium ATP channels, thereby opening the calcium channels. Rise in cytoplasmic calcium levels stimulates insulin release. This drug very effectively reduces postprandial hyperglycaemia. It also enhances the peripheral tissue sensitivity to insulin. There seems to be no increased risk of fetal anomalies associated with use of glyburide.<sup>10</sup>

**AIMS:** To compare the effects of metformin and glyburide on gestational diabetes with regard to

1. Glycaemic control in antenatal period.
2. Neonatal outcomes.

**MATERIALS AND METHODS:** This is a prospective double blind randomised clinical trial. At the planning stage, approval of the Institution Ethics Committee was obtained.

**Diagnosis of GDM:** 2 step test: screening 50gm GCT done on all pregnant patients. If the one hour value is above 140mg% then 100gm GTT is performed, where blood sugar levels are checked as Fasting, followed by 100gm glucose administered and sugar levels checked at 1, 2 and 3 hours. Carpenter and Coustan values of below 95mg%, 180mg%, 155mg% and 140mg% respectively are considered normal. If 2 of these values are abnormal, the patient is diagnosed to be gestational diabetic.

When gestational diabetes is diagnosed, patients are put on a diabetic diet for a minimum of 2 weeks. If after diet, the FBS and 1 hour PPBS are above 95mg% and 140mg% respectively, pharmacotherapy is initiated after randomization. Block Randomization was done using computer generated random numbers in blocks of 4. Totally, 48 patients were recruited in the study- 24 in each arm.

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They are randomized to either glyburide arm (A) or metformin arm (B) till the maximum dose and, if not controlled then Insulin is added.

Outcomes measured: Maternal glycaemic control (HbA1c in third trimester), Birth weight, cord blood C peptide levels.

**Setting:** Tertiary care hospital.

Gestational diabetics not controlled on diet are randomly assigned to glyburide (arm A) or metformin (arm B). Patients signed the Informed Consent form. The physician and patient were blinded as to which OHA arm, tablets being dispensed in sealed envelopes from the pharmacy.

Metformin is started at 500mg BID dosage, next step 850mg morning – 500mg with dinner, then maximum dose of 850mg BID. If not controlled, Insulin is added.

Glyburide started at 2.5mg BID, next step 5mg and 2.5mg, then maximum dose of 5mg BID. If not controlled, Insulin is added.

Sugars are monitored, fasting sugar and 1 hour post prandial every 2 weeks to check glycaemic status. HbA<sub>1c</sub> done at 3<sup>rd</sup> trimester. Any hypoglycaemic symptoms are noted, UTI, candidiasis, pre eclampsia are recorded. Weight gain during pregnancy is recorded.

**Neonatal Outcomes:** Mode of delivery is noted. Birth weight, shoulder dystocia, cord blood for C peptide level estimation, Neonatal sugars – 3 and 6 hours, hyperbilirubinaemia is recorded. C peptide reference value of >1.7 µg/L was taken, being the 90<sup>th</sup> percentile for the total HAPO study cohort, which is known to correlate with chances of neonatal hypoglycaemia.<sup>11</sup>

**RESULTS:** Of the 48 patients recruited, 1 each was lost to follow up in each arm. Thus we analyzed 46 cases, 23 in each arm of the study.

The characteristics studied in each arm were analyzed using SPSS software. Proportions in the two groups were compared using Pearson's chi square test. All parameters compared were having 'p' value more than 0.05 Hence, none of the variations was significantly statistically.

	<b>Arm A (on Glyburide)</b>	<b>Arm B (on metformin)</b>
Number of patients	n=23	n=23
Maternal parameters		
Need for Insulin	In 6 cases	In 2 cases
Hypoglycaemic symptoms on OHA	6	3
Maternal wt gain of 10 kg or more	4	3
Caesarean sections performed	11	15
Hb A <sub>1c</sub> > 6.5	2	2

Table 1. 1

Of the gestational diabetics picked up from the outpatient, after randomization we studied 23 patients in each arm. Namely arm A given Glyburide and arm B given Metformin for sugar control after failure of diet therapy. Regarding failure of glycaemic control, 6 in Glyburide arm needed Insulin whereas only 2 patients in Metformin arm needed Insulin.

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Hypoglycaemia while on treatment with oral hypoglycaemic agents (OHA) happened in 6 patients in glyburide group compared to only 3 in metformin group. Maternal weight gain of 10 kilogram or more in pregnancy was comparable in both groups (4 and 3 respectively).

Caesarean section had to be resorted to, in 15 of the metformin group, and only in 11 in the glyburide group.

As far as glycaemic control is concerned, poor control denoted by HbA<sub>1c</sub> of more than 6.5 was noted in 2 patients in each arm.

	<b>Arm A (on Glyburide)</b>	<b>Arm B (on Metformin)</b>
Neonatal parameters		
Foetal weight > 3.5kg	4 babies	5 babies
Cord blood C peptide levels > 1.7 µg/L	5	8
Neonatal Jaundice	3	0
Neonatal Hypoglycaemia	0	0
Shoulder dystocia	0	1

Table 1. 2

Foetal parameters: Birth weight larger than 90<sup>th</sup> percentile (>3.5 kg ) was 4 and 5 respectively in arm A and arm B. Cord blood C peptide level greater than 90<sup>th</sup> percentile (ref value from HAPO study cohort) seen in 8 babies in metformin arm and only 5 babies in glyburide arm, but statistically not significant. In this series, none of the babies had hypoglycaemia ascertaining the safety and good glycaemic control achieved by both the OHA arms.

**DISCUSSION:** This clinical trial of Gestational Diabetes mellitus was done as a comparison of the maternal and foetal outcomes, between patients on glyburide and patients on metformin. Failure of glycaemic control with glyburide was more, compared to metformin. Hypoglycaemic symptoms were also more in the glyburide arm.

There were more number of Caesarean sections performed in the metformin group (15 compared to 11 in the glyburide arm). From the maternal side, HbA<sub>1c</sub> levels and weight gain during pregnancy were comparable in both the arms. There was no significant weight gain in the glyburide arm.

When foetal parameters were studied, cord blood C peptide levels were high in 8 patients in metformin group (n=23) compared to 5 in glyburide group (n=23). But neonatal hypoglycaemia was nil in both arms, reflecting good antenatal and intra partum sugar control. Birth weight more than 3.5 kg was also comparable in both arms (4 and 5 respectively).

One delivery had shoulder dystocia – this patient was in arm B, birth weight 3.83kg, and cord blood C peptide was 4.07, the highest in this study. But the 3hr and 6 hr neonatal sugars were 81mg% and 66mg% respectively.

**CONCLUSION:** In our institution incidence of GDM during the study period was 11%. Among the 46 patients randomized to both the OHA arms, only 8 patients needed Insulin in addition for sugar control. Hb A<sub>1c</sub> was normal in 42 patients. Cord blood C peptide levels was > 90<sup>th</sup> percentile in 13

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patients. But none of the babies had neonatal hypoglycaemia. We experienced one shoulder dystocia, and one baby had cleft lip and palate.

To summarize, none of the parameters studied in the mother and the baby were statistically significant, probably due to the small sample size.

Overall, both glyburide and metformin were equally well tolerated, and seem to be equally efficacious in achieving glycaemic control in gestational diabetes and had comparable favourable neonatal outcomes.

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