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Research Article

Metformin Vs Insulin for Treatment of Gestational Diabetes-A Randomized Clinical Trial

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Abstract:

Background: The incidence of gestational diabetes is increasing day by day. It carries a risk of adverse maternal and neonatal outcomes affecting the normal quality of life of pregnant females and babies.

Aim: To compare the maternal and neonatal outcomes in women treated with metformin versus insulin for the management of gestational diabetes mellitus.

Materials and Methods: We carried a prospective, randomized controlled trial on 80 patients with gestational diabetes at Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, Telangana State from January 2014 to June 2015. The sample was categorized randomly into Group I (n=40) who received Metformin with insulin and Group II (n=40) who received insulin. various outcome measures like birth weight of babies, maternal gain in birth weight, mode of delivery, BMI of mothers were measured and compared.

Results: The mean age of the patients was 31.35 ± 4.02 and 30.21 ± 4.14 years in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.2152). The mean gestational age of the patients at the beginning of study was 29.32±2.60 and 30.02±2.13 weeks in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.1916).

Conclusion: Patients with gestational diabetes can be safely given metformin as it shows less maternal side effects and is also preferred when compared to subcutaneous insulin by mothers.

Keywords: Gestational diabetes, Metformin, Insulin, Pregnancy, birth weight

Introduction:

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition in pregnancy.[1, 2] The incidence of GDM depends on the diagnostic criterion and varies widely in different racial groups. Various studies have shown a wide range of incidence of about 1% to 14%.[3-6]

GDM is associated with increased risk of adverse maternal and neonatal outcomes e.g., it increases the risk of pre-eclampsia, caesarian section and type 2 diabetes after pregnancy. Regarding neonatal outcomes, it can increase the risk of still birth, neonatal death, congenital defects, macrosomia, neonatal hypoglycemia and shoulder dystocia.[7, 8]

Subcutaneous insulin therapy is the standard treatment of GDM. But insulin therapy has many disadvantages e.g. multiple daily injections, risk of maternal hypoglycemia and weight gain. So oral therapy for GDM will be accepted as much safer and easily usable by females.

Metformin, an oral bigaunide that lowers glucose levels with a low risk of hypoglycemia, appears to be a good alternative to insulin in women with GDM. Metformin acts by reducing insulin resistance, improving insulin sensitivity probably by activation of AMP kinase and decreasing ATP concentration of hepatocytes. Hence metformin is now gaining access and is regularly being used for the management of GDM in pregnant females. Reduction in neonatal weight after use of metformin has been reported by some studies.[2-5] But some studies have documented normal weight of neonates after metformin therapy.[3, 4]

Materials and Methods:

Study design and participants:

We carried a prospective, randomized controlled trial on 80

patients with at Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, Telangana State from January 2014 to June 2015. The study was conducted after obtaining institutional ethical committee approval and informed consent from all the participants. The sample was categorized randomly into Group A (n=40) who received Metformin and additional insulin if needed and Group B (n=40) who received insulin.

The pregnant women were screened for presence of high risk factors including BMI above 25 kg/m2, previous history of macrosomic baby with weight 4 kg and above, previous history of GDM, family history of diabetes in first degree relatives, previous history of poor obstetric outcome (abortion, congenital anomalies, intrauterine fetal death, neonatal death), presence of polyhydramnios, pregnancy induced hypertension in present pregnancy and history of polycystic ovarian syndrome and presence of glycosuria in the present pregnancy.

Procedure:

Women included in the study were between 18 to 40 years of age and had GDM diagnosed with a singleton pregnancy between 20 and 36 weeks of gestation. Patients were said to have gestational diabetes mellitus (GDM) if she had the following results on oral glucose tolerance test (OGTT), usually undertaken after 20 weeks of gestation (Fasting Glucose >7.0mmol/L, 2 hour Glucose >11.1mmol/L).[10]

Exclusion Criteria:

1. Women who have contraindications for metformin intake,
2. A recognized fetal anomaly on ultrasound examination
3. Presence of any other medical disorder (including type 1 and type 2 diabetes),
4. A positive OGTT before 26–28 weeks of pregnancy consistent with diagnosis of overt diabetes in pregnancy and
5. Fetal growth restriction (birth weight <10th centile for its gestational age on ultrasound comparing with a 1st dating or early 2nd trimester scan).

Randomisation:

Randomization was done as the eligible patients entered the study with odd number assigned to metformin treatment and even number for insulin treatment irrespective of body weight and GTT values at study entry. Blinding was not possible because of different routes of administration of drugs.

Group A patients were given metformin therapy (500mg-2 Grams) in intermittent doses daily for the management of GDM, Additional insulin was initiated if target values were not met with metformin alone. To group B patients subcutaneous NPH insulin was given. The dose of insulin and metformin was dependent upon the glycemic control of the patient. Patients were asked to measure their blood sugar levels daily and note it on a dairy and after every week, their doses of metformin and insulin were adjusted according to the control of their blood sugar levels. Birth weight of the baby was calculated immediately after birth and was presented in Kilograms.

Data analysis

Data were stored and analyzed using SPSS version 20. The frequencies and percentages were reported for all categorical variables. Mean with SD were reported for all continuous variables. The analysis was performed to compare the metformin alone group with metformin plus insulin group using two samples independent student t-test for continuous data and chi-square Fisher's exact test for categorical data. Two tailed tests were used for all analysis and statistical significance was considered at $P < 0.05$.

Results

We noticed the following findings from our study which were categorized as patient characters (Table 1 and Graph 1) and study outcomes (Table 2, Graph 2:Table 3, Graph 3).

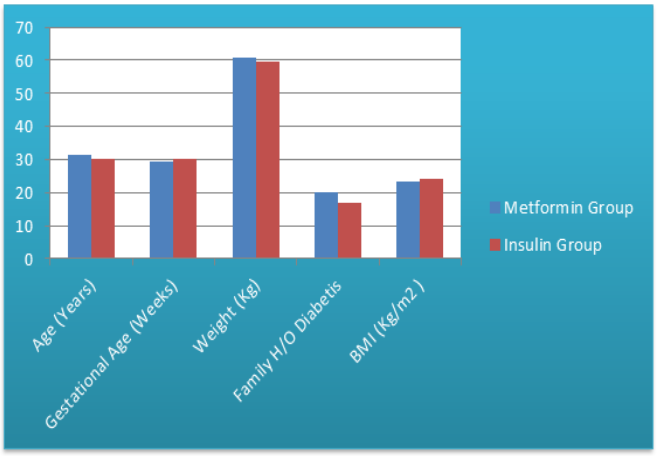
Patients Characters:

1. The mean age of the patients was 31.35 ± 4.02 and 30.21 ± 4.14 years in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.2152).
2. The mean gestational age of the patients at the beginning of study was 29.32±2.60 and 30.02±2.13 weeks in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.1916)
3. Positive family history of diabetes was seen in 20 (50%) and 17 (42.5%) patients in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.6152).
4. The mean body weight of mothers at the beginning of study was 60.58±5.21 kg and 59.47±4.20 in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.2974).
5. The mean body mass index (BMI) at the beginning of study was 23.26 ± 5.48 and 24.32 ± 4.95 in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.3668).

Table 1: Patients Characteristics at the beginning of study

Parameters	Metformin Group (n=40)	Insulin Group (n=40)	P-value
Age (Years)	31.35 ± 4.02	30.21 ± 4.14	0.2152
Gestational Age (Weeks)	29.32±2.60	30.02±2.13	0.1916
Weight (Kg)	60.58±5.21	59.47±4.20	0.2974
Positive Family History of Diabetes	20 (50%)	17 (42.5%)	0.6152
BMI (Kg/m2)	23.26 ± 5.48	24.32 ± 4.95	0.3668

Graph 1: Patients Characteristics at the beginning of study



Study Outcomes:

1. The mode of delivery was vaginal in 22 (55%) and 25 (62.5%) mothers in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.5815).
2. When the primary outcome of our study i.e. mean weight of babies were measured we found it to be 3.14±0.30 Kg and 3.86±0.12 Kg in metformin and insulin groups respectively, with the difference being statistically significant (p<0.0001).
3. However the maternal weight gain occurred in both groups after starting the therapy and at the time of child birth was 9.05±1.53 Kg and 9.42 ±1.32 in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.2504).

Table 2: Mode of Delivery

Mode of Delivery	tformin Group (n=40)	ulin Group (n=40)	P Value
Vaginal	22 (55%)	25 (62.5%)	0.5815
Cesarean Section	18 (45%)	15 (37.5%)	

Graph 2: Percentage of cases in relation to the Mode of Delivery

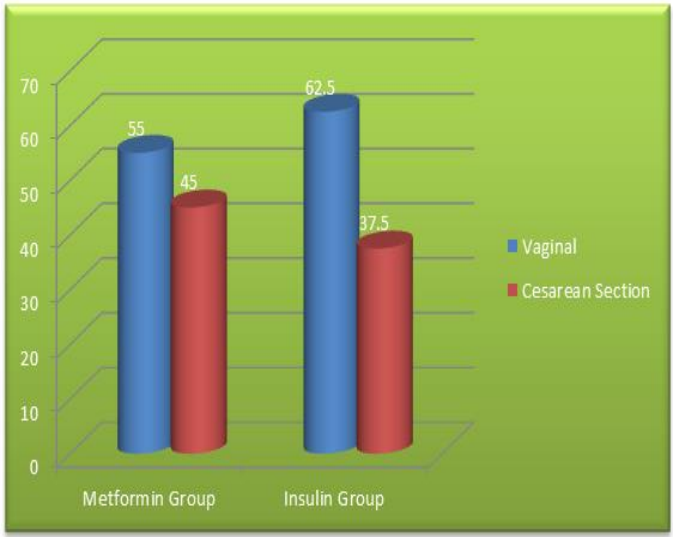
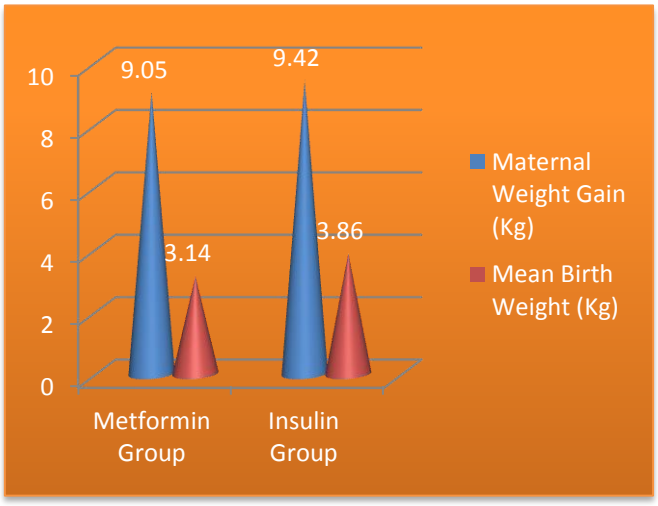


Table 3: Study outcomes

Study Outcome	Metformin Group (n=40)	Insulin Group (n=40)	P Value
Maternal Weight Gain (Kg)	9.05±1.53	9.42 ±1.32	0.2504
Mean Birth Weight (Kg)	3.14±0.30	3.86±0.12	<0.0001*

*=Highly significant

Graph 3: Study outcomes



Discussion:

Diabetes is considered as an important factor that complicates pregnancy and is on the rise especially in the South Asian countries like India and Pakistan. Our study was conducted to meet the needs of this high-risk population on a background of low resource setting where health facilities especially medicines are not available free of cost. With optimal GDM management, the incidence of adverse events such as macrosomia, stillbirth and other adverse effects can be reduced. Improvements in dietary habits, exercise, oral and subcutaneous hypoglycemic agents are routine used methods for GDM. There is a controversy regarding oral (metformin) and subcutaneous (insulin) therapy regarding maternal and neonatal outcomes. In this present controlled trial, we compared metformin with insulin and compared their effects on maternal and neonatal weight.[9, 11]

We found a mean weight gain of maternal weight of 9.05±1.53 Kg and 9.42 ±1.32 in metformin and insulin groups respectively, with the difference being statistically insignificant (p=0.2504). However Ainuddin et al found a mean weight gain of 9.8±1.5 Kg in metformin group and 12.5±1.1 Kg in insulin group, the difference being statistically significant (P<0.0001).[2] Niromanesh et al also found significant weight gain 13.7±3.1 in insulin versus 11.3±3.8 in metformin group.[3] Other studies also found similar results and suggested that metformin has a beneficial effect on the weight of mothers.[12, 13]

Our finding of mean birth weight of 3.14±0.30 Kg and

3.86±0.12 Kg in metformin and insulin groups respectively, with the difference being statistically significant (p<0.0001).

was similar to Ainuddin et al, who also found lower birth weight in metformin group 3.4±0.4 kg versus 3.7±0.5 kg in insulin group.[2] Niromanesh et al also found similar results with 3.3±0.4kg in metformin group and 3.4+0.4Kg in insulin group (p= 0.004).[3] However, in contrast to our study Terttieti al et al did not found any significant difference in birth weight of neonates in metformin versus insulin groups.[4]

When the percentage of caesarean section was compared, it was found that 45% in metformin group and 37.5% in insulin group. Similar to our finding of insignificant difference in caesarean and vaginal mode of deliveries, Balani et al (p-value 0.67) and Ainuddin et al (P=0.3510) also found the same outcomes.[2, 14] Conversely, Ijas et al found significant difference in the mode of dlivery (P=0.04).[15]

Limitations:

1. A relatively small sample size,
2. Long individual study period and a High drop-out rate.
3. Blinding was not possible due to different route of administration of the treatments.

Conclusion:

Metformin is a safe drug for the management of gestational diabetes mellitus because of its less monitoring and comparatively comparable maternal side effects. The only problem we noticed in our study and in related studies also with metformin therapy is lower birth weight of neonates. Further studies on a larger sample size and with more parameters is recommended.

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