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GESTATIONAL DIABETES;

TO COMPARE THE EFFICACY OF METFORMIN WITH INSULIN IN DIABETES MELLITUS IN TERMS OF FETOMATERNAL OUTCOME

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ABSTRACT… Objectives: To compare the efficacy of Metformin with insulin in gestational diabetes mellitus in terms of fetomaternal outcome. **Study Deign:** Randomized clinical trial study. **Setting:** Lady Aitchison Hospital Lahore. **Period:** January 2014 to March 2015. **Methodology:** Total 500 pregnant females with GDM were included in the study through non-probability, consecutive sampling. Patients were divided into 2 equal groups (A: B). Patients in group A were given tablet metformin 500 mg by oral route and group B was administrated regular injection Insulin by subcutaneous route. **Results:** The mean age of females was 32.14±6.13 years. The mean gestational age was 31.07±3.8 weeks. There were 78 (15.6%) females who had 0 parity, 107 (21.4%) females had parity 1, 175 (35%) females had parity 2, 95 (19%) females had parity 3, 33 (6.6%) females had parity 4 and 12 (2.4%) females had parity 5.There were 54 (10.8%) cases had PTB, out of which 12 (4.8%) had PTB with metformin while 42 (16.8%) had PTB with insulin. There were 115 (23%) neonates required NICU admission, out of which 37 (14.8%) neonates with metforminand78 (31.2%) neonates with insulin. There were 87 (17%) neonates who had neonatal hypoglycemia, out of which 23 (9.2%) neonates with metformin and64 (25.6%) neonates with insulin. The difference was significant between both groups for all fetal outcomes (P<0.05). **Conclusion**: The metformin is more effective in preventing adverse fetal and maternal outcome as compared to insulin.

Key words: Gestational diabetes mellitus, metformin, insulin, preterm birth, neonatal intensive care unit admission, and neonatal hypoglycemia

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INTRODUCTION

Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with appearance or first detection during pregnancy, affects 2-10% pregnancies in the United States.[1,2] Women with gestational diabetes have a 35-60% risk of developing DM over next 10-20 years.[1]

Hyperglycemia in pregnancy results in both maternal and fetal complications. Maternal complications consist of hypertension, preeclampsia, increased risk of cesarean delivery, and long term risk of diabetes mellitus. Fetal complications include macrosomia, neonatal hypoglycemia, polycythemia, increased perinatal mortality, congenital malformation, hyperbilirubinemia, respiratory distress syndrome, and hypocalcaemia. Long term effects of macrosomia include increased risk of glucose intolerance, diabetes, and obesity in childhood.[3]

The risk factors, for GDM, which should be noted at the first prenatal visit, include obesity, age more than 25 years, past history of gestational diabetes, first-degree relative with diabetes, badobstetrical history, Polycystic ovarian syndrome and certain ethnic groups.

Women having insulin resistance are at risk for developing GDM. This leading to GDM is dueto changes of late pregnancy. In pregnancy, human placental lactogen and tumor-necrosis factor alpha induce changes in the insulin receptor and in post-receptor signaling. Various changes at the cellular level appear to be involved in reducing glucose uptake in skeletal muscle tissue.[5]

The blood sugar levels should be optimized to

decrease the incidence of fetomaternal complications. The previous study has shown thataggressive management in women with GDMreduced birth weight and macrosomia in infants bornto mothers who were exposed to the intervention compared with women who had received routine care.[6] Therefore, measures such as dietary modification, exercise, oral hypoglycemic agents, and insulin – are imperative to reduce the complications.[7]

When the above-mentioned measures do not fulfill the criteria to control blood glucose levels in pregnant women, the use of subcutaneous insulin therapy is the standard approach for management of GDM.[8,9,10] However, insulin use has its own set of problems including multiple daily injections, the risk of hypoglycemia and maternal weight gain.[11] It needs to be altered depending on the patient's weight and height, glucose levels and activity levels.[12] The issues relating to patients education and compliance as well as the cost of insulin should be considered. These arguments place oral hypoglycemic therapy into favors for women with GDM,.[13] However, it is important to take into account fetomaternal impact of oral hypoglycemic agentsfor the women with GDM. Metformin, which is used for T2D, is a foremost choice. Metformin has been found to have a transplacental transfer rate of 10–16%[14,15] this raises possible concerns about risks of fetal anomalies, and undesirable effects for mothers and the newborns after delivery limiting its role

The safety and use of Metformin in pregnancy is under consideration. But the inferences drawn from variety of trials, which are underpowered,[16,17,18,19] lack the ability to define the relative risks and benefits ofmetformin for GDM.

The rationale of this study was to compare the efficacy of metformin with insulin in terms of fetomaternal outcome in gestational diabetes mellitus. There is variability in the literature that is published internationally. The study results may or may not differ from international data due to poor compliance and genetic variation from patient to patient, in the light of which new suggestions will be made for the liberal use of metformin in population and to minimize the use of parenteral therapy (insulin).

OBJECTIVE

To compare the outcome of Metformin with insulin in gestational diabetes mellitus.

PATIENTS AND METHODS

This randomized controlled trial study was carried out on 500 pregnant women with GDM admitted in the antenatal ward of Lady Aitchison Hospital from Jan 2014 to March 2015. Written informed consent was obtained. The women were included in the study through non-probability, consecutive sampling.

Demographic information on all variables included; patient's age, gestational age, body mass index and maternal weight gain during pregnancy were noted. The patients were divided in to two equal groups (A & B) by randomization. Patients in the group A were given tablet metformin 500mg by oral route and group B was administrated injection regular insulin by subcutaneous route. Maternal BSL (2 levels i.e. BSF, 1 hour post prandial) were done hospital laboratory until delivery and dose of metformin and insulin was adjusted according to BSL. Fetal monitoring was done by ultrasound in the third trimester for fetal weight evaluation. The women between 20-45 years of age and GDM, gestational more than 20 weeks were included in the study and women who were known diabetic, with history of recent myocardial infarction and twin pregnancy were excluded from the study.

The women were evaluated for outcome measures which were Preterm delivery (It will be considered if birth is at <37 gestational weeks on LMP) and Neonatal Hypoglycemia (It was assessed by serum blood glucose level (two or more neonatal glucose values <2.6 mmol per liter [46.8 mg per deciliter] within 24 hour of birth), and all the information was recorded on Performa. The data was analyzed by t and chi square depending on the nature of the variable. A p value of $\leq$ 0.05 was considered statistically significant.

RESULTS

We conducted this trial with 500 females included in the study with the mean age of 32.14±6.13 years. The mean gestational age was 31.07±3.8 weeks 24-38weeks). There were 78 (15.6%) females who had 0 parity, 107 (21.4%) females had parity 1, 175 (35%) females had parity 2, 95 (19%) females had parity 3, 33 (6.6%) females had parity 4 and 12 (2.4%) females had parity 5.

The mean weight of females before treatment was 70.18±10.96 kg, which was increased to 73.14±11.49 kg after treatment. The overall mean change in weight of females was 2.96±1.90kg. There were 114 (22.8%) females had normal BMI, 213 (42.6%) were overweight and 173 (34.6%) were obese.

With metformin, the mean weight of females before treatment was 69.62±10.93kg, which was increased to 72.05±11.73 kg after treatment, with the mean weight change of 2.44±1.81 kg. With insulin, the mean weight of females was 70.75±10.98kg, which was increased to 74.24±11.16 kg, with the mean weight change of 3.49±1.84 kg. Thus after treatment the difference was significant (P<0.05).

There were 54 (10.8%) cases had preterm birth, out of which 12 (4.8%) with metformin and 42 (16.8%) with insulin (Fig-1, Table-I).

There were 115 (23%) neonates required NICU admission, out of which 37 (14.8%) with metformin while 78 (31.2%) with insulin (Fig-2, Table-II).

There were 87 (17%) neonates had neonatal hypoglycemia, out of which 23 (9.2%) with metformin while64 (25.6%) with insulin (Fig-3, Table-III).

There was significant difference between both groups (P<0.05).

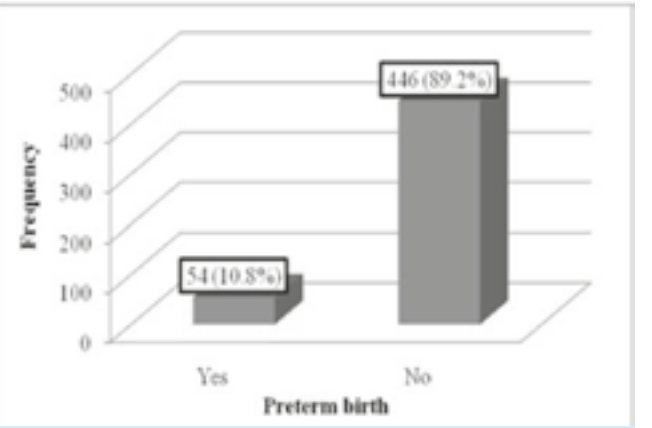

Fig-I. (Distribution of preterm birth)

		Study group		Total
		Metformin	Insulin	
PTB	Yes	12 (4.8%)	42 (16.8%)	54 (10.8%)
	No	238 (95.2%)	208 (83.2%)	446 (89.2%)
Total		250 (100%)	250 (100%)	500 (100%)

Table-I. (Comparison of preterm birth in both study groups)

		Study group		Total
		Metformin	Insulin	
NICU admission	Yes	37 (14.8%)	78 (31.2%)	115 (23%)
	No	213 (85.2%)	172 (68.8%)	385 (77%)
Total		250 (100%)	250 (100%)	500 (100%)

Table-II. (Comparison of NICU admission in both study Of neonates)

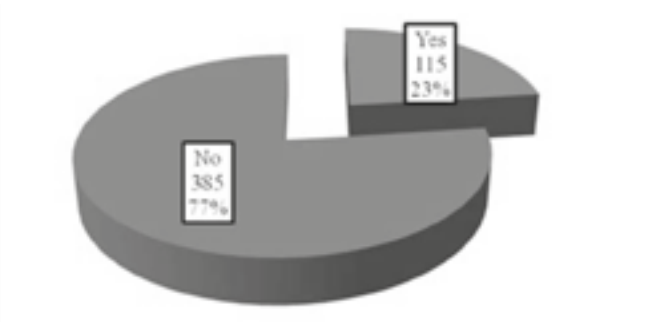

Fig-2. Distribution of NICU admission

		Study group		Total
		Metformin	Insulin	
Neonatal hypoglycemia	Yes	23 (9.2%)	64 (25.6%)	87 (17%)
	No	227 (90.8%)	186 (74.4%)	413 (83%)
Total		250 (100%)	250 (100%)	500 (100%)

Table-III. (Comparison of neonatal hypoglycemia)

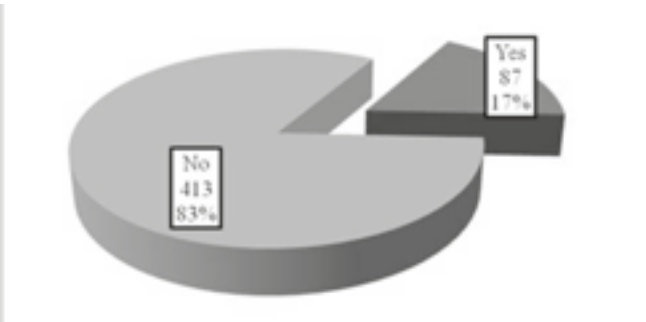

Fig-3. Distribution of Neonatal hypoglycemia in both study groups

DISCUSSION

In this trial we observed that the mean age of 32.14±6.13 years. The mean gestational age was 31.07±3.8 weeks 24-38weeks). There were 78 (15.6%) females who had 0 parity, 107 (21.4%) females had parity 1, 175 (35%) females had parity 2, 95 (19%) females had parity 3, 33 (6.6%) females had parity 4 and 12 (2.4%) females had parity 5.

The mean weight of females before treatment was 70.18±10.96 kg, which was increased to 73.14±11.49 kg after treatment. The overall mean change in weight of females was 2.96±1.90kg. There were 114 (22.8%) females had normal BMI, 213 (42.6%) were overweight and 173 (34.6%) were obese.

With metformin, the mean weight of females before treatment was 69.62±10.93kg, which was increased to 72.05±11.73 kg after treatment, with the mean weight change of 2.44±1.81 kg. With insulin, the mean weight of females was 70.75±10.98kg which was increased to 74.24±11.16 kg, with the mean weight change of 3.49±1.84 kg. Thus after treatment the difference was significant (P<0.05). In a randomized trial by Rowan, mean weight gain was 0.94±0.3 with metformin and 2.72+0.4 with insulin. (20)But another study by Tertti reported that weight gain was 0.4±2.9kg and 2.0±3.3kg with metformin and insulin.[16]

There were 54 (10.8%) cases had preterm birth, out of which 12 (4.8%) with metformin and 42 (16.8%) with insulin. There were 115 (23%) neonates required NICU admission, out of which 37 (14.8%) with metformin while78 (31.2%) with insulin. There were 87 (17%) neonates had neonatal hypoglycemia, out of which 23 (9.2%) with metformin while64 (25.6%) with insulin. There was significant difference between both groups (P<0.05).

In the study by Rowan PTB was observed in 0% cases with metformin and 10% with insulin, NICU admission in 6% with metformin and 19% with insulin, hypoglycemia in 9% with metformin and 18% with insulin.(20) The study by Terstti supported our results and reported that with metformin, PTB occurred in 4.4% cases, NICU admissions in 42.2% cases and neonatal hypoglycemia in 34.1% cases. With insulin, PTB occurred in 11.1% cases, NICU admissions in 62.2% cases and neonatal hypoglycemia in 57.8% cases. However, the difference was insignificant (P>0.05).[16]

When compared with insulin, metformin was associated with less maternal weight gain (pooled mean difference −1.14 kg (95% CI −2.22 to −0.06)), lower gestational age at delivery (pooled mean difference −0.16 weeks (−0.30 to −0.02)), and more preterm birth (pooled risk ratio 1.50 (1.04 to 2.16)). A trend was observed towards a lower rate of any neonatal hypoglycaemia (pooled risk ratio 0.78 (0.60 to 1.01)).[21]

In Tertti study NICU admission was 18% with metformin and 21% insulin group, hypoglycemia in 34% and 57% with metformin and insulin respectively.[16]One more study reported contradictory results as reported in our study. It was observed that PTB was 12.1% with metformin and 7.6% with insulin and the statistical difference was

obtained as significant (P<0.05).(21) In another cohort of women studied by Rowan and Hughes with diabetes, maternal/fetal outcomes were as good in women using metformin as those on insulin alone, even though women in the metformin group were at higher risk of poor outcomes.[22]

In a study conducted by Niromanesh etal the maternal weight gain was reduced in the metformin group (P<0.001). Two groups were comparable according to neonatal and obstetric complications (P>0.05).[23]

Mesdaghinia and colleagues conducted a prospective randomized trial in which it was seen that maternal weight gain during pregnancy, preterm labor and hospitalization of infants were higher in in insulin group. But there were no significant statistical differences between the two groups regarding neonatal hypoglycaemia.[24]

In a study conducted by Spaulonci et al it was seen that women using metformin had less weight gain and lower frequency of neonatal hypoglycemia as compared to those using insulin.[25]A recent study has indicated a lesser maternal weight gain but higher incidence of preterm labor with metformin.[26]

CONCLUSION

It is concluded that metformin is more effective in controlling blood glucose and prevent adverse fetal outcome as compared to insulin and we have proved this through this randomized trial. Thus in future we can recommend metformin instead of insulin for control of GDM in future as we have got local magnitudes which will help us in implementation of metformin and will minimize the use of the use of parenteral therapy i.e. insulin.

Authorship: TM was the principal researcher and collected the data, RA deigned the research Protocol, IM and ZM helped in designing the research protocol, HM gave the computer help, KS did the statistical analysis, SFI and SFZ helped is writing and finalizing the manuscript.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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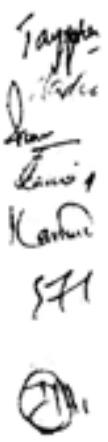
1	Tayyaba Majeed	Principal researcher and collection of data	
2	Rabia Adnan	Designed the research Protocol	
3	Irum Majeed	Helped in designing the research protocol	
4	Hamis Mahmood	Give the computer help	
5	Kanwal Saba	Did the statistical analysis	
6	Sardar Fakhar Imam	Helped is weiting and finalizing the manuscript	
7	Muhammad Al-Fareed Zafar	Helped is weiting and finalizing the manuscript	
8	Mulazim Hussain Bukhari	Supervised the research	