COMPARISON OF MEAN BIRTH WEIGHT OF NEONATES BORN TO FEMALES HAVING GESTATIONAL DIABETES ON METFORMIN VERSUS INSULIN

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ABSTRACT

Objective: To compare the mean birth weight of neonates born to women having gestational diabetes treated with oral metformin versus insulin.

Methodology: In this study, 360 females with gestational diabetes (GDM) were selected. The subjects were randomly divided into two equal groups. In group A, during first week of trimester, metformin was administrated in 750 mg once daily dose, two times per day during second week and thrice daily from the third week onwards. In group B, long-acting insulin was used to normalize fasting, and rapid-acting insulin was used to normalize postprandial glucose concentrations. Patients were followed till delivery and birth weight of baby was noted. All this information was recorded on proforma. Data was analyzed using SPSS-17 and t-test was applied to compare the mean birth weight in both groups. P value <0.05 was considered as statistically significant.

Results: The mean birth weight was 3459.9 ±238.9 grams. In metformin group, the mean neonatal birth weight was 3557.02 ±232.34 grams. In insulin group, the mean neonatal birth weight was 3362.79 ±203.72grams. There was significant difference between both groups and insulin group showed less birth weight as compared to metformin group (p <0.05).

Conclusion: Insulin was more beneficial in maintaining weight of fetus as compared to metformin in patients with gestational diabetes mellitus.

Key Words: Gestational diabetes mellitus, Metformin, Insulin, Mean birth weight, Neonates

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INTRODUCTION

Atypical and variable glucose regulation takes place in about 3-10% cases of pregnancies. The gestational diabetes mellitus (GDM) is reflected as the intolerance of glucose metabolism with inconstant variation or onset during pregnancy. It can cause about 90% of cases associated with diabetes mellitus (DM) in pregnancy[1,2]. Various complications due to uncontrolled GDM may results in pregnancy induced hypertension (PIH), increased risk of infection, preterm labor, higher chances of operative delivery, poly-hydramnios and macrosomia. In diabetic women, about 15-45% of babies are born with macrosomia which is a three fold higher than normo-glycemic controls. It has been stated that GDM has a significant and autonomous effect on the fetal macrosomia. The determination of birth weight is mainly associated with maternal factors rather than hyperglycemia[2]. It is recommended that gestational diabetes should be screen in all pregnant women during 24-28 weeks of gestation. The screening of GDM carried out by usual method is considered controversial. Recently, a two-step system is endorsed and established in the United States. It is explained as a 50-g, 1-hour glucose challenge test (GCT) and is monitored by an oral glucose tolerance test (OGTT) with administration of 100-g oral glucose at 3-hours, for the women with an uncharacteristic screening result[3].

In GDM, prompt medication with insulin or an oral agent[4,5] is important to attain a targeted effect and satisfactory glycemic control. During pregnancy, the aim of therapy is to obtain glucose levels as comparable to those of non-diabetic women. It has been stated that

the healthy pregnant women sustain their post-prandial blood glucose rises within a comparatively narrow range (70-120 mg/dL). In GDM, such glycemic control requires consideration by both the clinician and the patient. Metformin is a biguanide that acts generally by diminishing the hepatic clearance of glucose. The fetal levels of metformin are higher in comparison to the maternal levels[6].

Previously, one study reported that the mean birth weight with insulin was lower (3558 ±593 gm) than with metformin (3712 ±432 gm) which showed that there were more chances of development of macrosomia with metformin, although the difference was insignificant[7]. But another study reported the opposite results where the mean birth weight with insulin was higher (341 ±569 gm) than with metformin (3372 ±572 gm) which showed that there were more chances of development of macrosomia with insulin although the difference was again insignificant[8].

The rationale of present study was to compare the effects of metformin and insulin on the mean birth weight of neonates born to females with gestational diabetes. In different populations, effects of these treatment modalities have been observed as comparable but differences in results. This study was carried out to compare the mean birth weight of neonates born to women having gestational diabetes treated with oral metformin versus insulin in our population to detrmine which agent is more beneficial in maintaining weight of fetus in GDM patients.

METHODOLOGY

This was a comparative study carried out at Unit III, Department of Obstetrics & Gynecology, Sir Ganga Ram Hospital (SGRH), Lahore. Permission was taken from Institutional ethical committee to conduct this study. This study was completed in six months after approval of synopsis.

Sample size was calculated with 95% confidence level, 80% power of test and taking magnitude of mean birth weight i.e. 3558±593g with insulin and 3712±432g with metformin[7]. Accordingly, 360 cases were needed; these were randomized as 180 in metformin (group A) and 180 in insulin (group B). A total of 360 patients who fulfilled the inclusion criteria were enrolled by convenient sampling technique from the OPD of Obstetrics & Gynecology Department, SGRH, Lahore. The patients with age 20-40 years and singleton pregnancy (on ultrasound) with diagnosis of GDM, between 12 and 34 weeks of gestation (through LMP) were included in this study. On the other hand, patients who have allergies, sensitivity or unable to take medication (through history); pre-eclampsia (20 weeks post gestation and blood pressure is higher than 140/90 mmHg and excretion of protein above 0.3 g per day in urine); essential hypertension needing anti-hypertensive treatment; fetal growth constraint (the development of fetus is less than 5 percent of gestational period); patients having systemic diseases like DM (RBS>200mg/dl) before pregnancy, deranged LFTs (ALT >40IU, AST >40IU) and RFTs (serum creatinine >1.2mg/dl); and mental disabilities (through medical record) were excluded from this study. GDM was operationally defined as following: After an overnight fast of 10 hours, OGTT was performed by giving 75-g glucose and serial measurements were taken. The 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). GDM was confirmed after one or more anomalous values. Informed consent was obtained from all individuals who participated in this study. Demographic profile (name, age, gestational age, parity and medical illnesses) were obtained from each patient. 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 glucometer. Dose adjustments were made based on the glycaemic status.

In group A, during first week of trimester, metformin was administrated in 750 mg once daily dose, two times per day during second week and it was given three times daily during the rest of testing period. In group B, the administration of insulin was carried out conferring the guidelines of hospital: long acting insulin was used to normalize fasting, and rapid-acting insulin was used to normalize postprandial glucose concentrations. Patients were followed till delivery and birth weight of baby was noted. All this information was recorded on proforma.

Data were analyzed using SPSS-17. For quantitative variables like age, gestational age and birth weight, calculation of mean and standard deviation was done. Frequency and percentage was calculated for the qualitative variables like parity. t-test was applied to compare the mean birth weight in both groups. Data was stratified for BMI (normal, under & overweight and obese). T-test was applied to see the effect of BMI on mean birth weight. The p value <0.05 was considered as significant.

RESULTS

Overall mean age was 30 ±6.14 years. The mean age of females in metformin group was 29.9 ±6.05 year while the mean age of females in insulin group was 30.1 ±6.25 year. In both groups, mean height, mean weight, mean BMI are shown in Table 1. The minimum weight of patient was 50 kg while maximum weight was 80 kg. The mean birth weight of neonates in both groups was

determined (Table 1). There was significant difference between both groups and insulin showed less birth weight as compared to metformin ($p < 0.05$). The frequency of females with underweight, normal BMI and obesity is given in Figure 1.

Among normal BMI, overweight, obese and underweight females, the mean of neonatal birth weight randomized to metformin group and to insulin group is given in Table 2. There was significant difference observed in the mean birth weight of neonates randomized to metformin and neonates randomized to insulin group in each stratified BMI group ($p<0.05$).

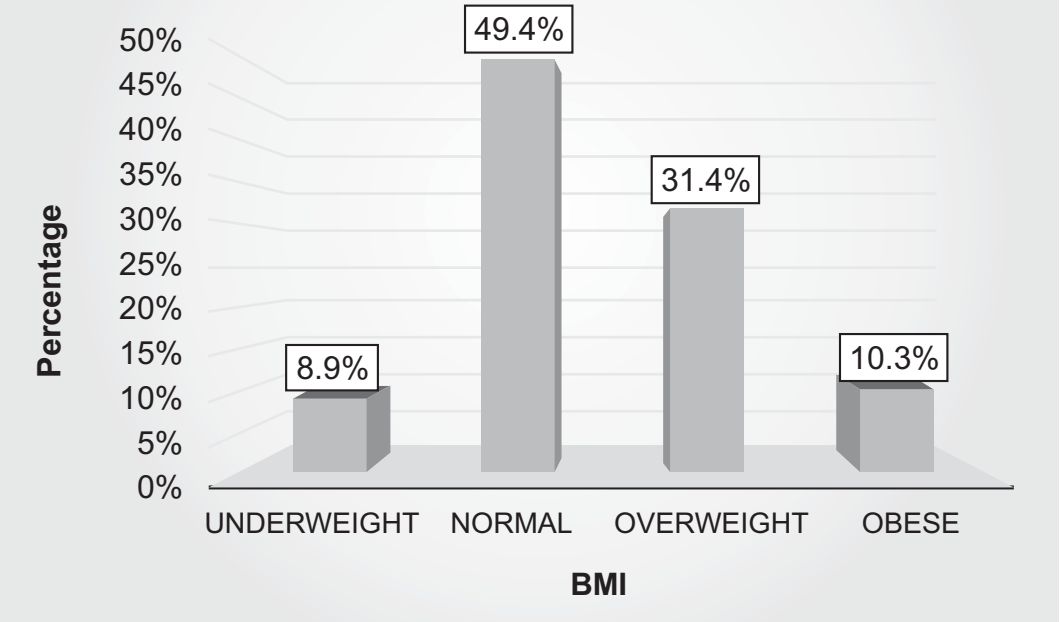
Table 1: Comparison of demographic data of patients in both groups

Parameters (n=360)	**Groups**		**P value**
	Metformin (Mean±S.D)	**Insulin** (Mean±S.D)	
Age (years)	29.9±6.05	30.1±6.25	>0.05
Height (meter)	1.65±0.09	1.66±0.08	>0.05
Weight	64.79±9.23	66.22±9.03	>0.05
BMI	23.93±4.41	24.34±4.39	>0.05
Birth Weight	3557.02±232.34	3362.79±203.72	0.000

Table 2: Comparison of birth weight of neonates in both groups after stratification of BMI of females

Parameters (n=360)	**Study groups**		**P value**
	Metformin	**Insulin**	
Underweight	3584.31±246.93	3292.06±196.04	0.001
Normal	3571.8±228.39	3358.82±213.93	0.000
Overweight	3519.24±231.39	3386.13±190.75	0.001
Obese	3561.78±249.89	3363.53±206.21	0.012

Figure 1: Distribution of patients in different BMI categories



DISCUSSION

We conducted a randomized trial on 360 females with the mean age of 30±6.14 years and BMI of 24.14±4.4kg/m^2. About 14-46% of those receiving metformin require additional insulin for glycemic control and to minimize the frequency of macrosomia and its associated risks to the infant[8,9]. Metformin seems to be an active and non-toxic agent used for the management and treatment of GDM. Nevertheless, patients with numerous risk factors for development of resistance to insulin may not encounter their treatment aims with metformin alone and may entail additional insulin injection. Evidence proposes the use of metformin instead of insulin in women with GDM in view of maternal weight gain and neonatal outcomes[10].

In our trial, mean neonatal birth weight was noted as 3459.9 ±238.9 grams. There was significant difference between both groups and insulin showed less birth weight (3362.79 ±203.72 gm) as compared to metformin (3557.02 ±232.34 gm), with a p value <0.05.

Our results are not in conformity with the study by Setji et al[11] which showed that the mean birth weight with insulin was higher (3413 ±569 gm) than with metformin (3372 ±572 gm) signifying that there were more chances of development of macrosomia with insulin although the difference was insignificant (p value= 0.33). However, our findings are supported by the results of a study by Lautatzis et al[12] which showed that the mean birth weight with insulin was lower (3558 ±593gm) than with metformin (3712 ±432gm) and favoured more chances of development of macrosomia with metformin, although the difference was insignificant (p value= 0.145). Tertti et al demonstrated that the birth weight with metformin was 3761 ±598 gm while with insulin it was 3759 ±642 gm. The difference was found to be insignificant (p >0.05). In their recent study, Tertti et al[13] reported birth weight with metformin as 3604 ±488 gm while with insulin it was 3589 ±448 gm. Although the difference was again found to be insignificant (p >0.05) but the mean birth weight with insulin was low as compared to metformin.

Ijas et al[14] found that with metformin the mean birth weight was higher 3712 ±432 gm as compared to insulin 3558 ±593 gm. The difference was insignificant but it favored the insulin which can control birth weight more than metformin. Moore et al[15] found that with metformin the mean birth weight was higher 3451.8 ±727.5 gm as compared to insulin 3500.2 ±700.5 gm. The difference was insignificant (p >0.05). Niromanesh et al[16] demonstrated that with metformin the mean birth weight was higher 3300 ±400 gm as compared to insulin 3400 ±400 gm. The difference was insignificant (p >0.05). In other studies, it has been found that with metformin the mean birth weight was higher 3143.7 ±446.6 gm as compared to insulin 3237.6 ±586.8 gm. The difference was insignificant (p >0.05)[17-20].

We stratified data for different BMI statuses of pregnant females included in our study. There were 8.9% females who were underweight, 49.4% had normal BMI, 31.4% were overweight and 10.3% were obese. Significant differences were observed in both study groups in each stratified BMI group (p<0.05).

CONCLUSION

Insulin was found to be more beneficial in maintaining weight of fetus as compared to metformin. Insulin is therefore recommended for management of gestational diabetes to prevent babies from development of macrosomia which may also help in planning vaginal delivery and can reduce cesarean sections rate as well.

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CONTRIBUTORS

NS conceived the idea, planned the study and drafted the manuscript. MS and SA helped acquisition of data and did statistical analysis. NM helped acquisition of data. MIU critically revised the manuscript and supervised the study. All authors contributed significantly to the submitted manuscript.