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A PILOT STUDY ON EFFICACY OF METFORMIN AND INSULIN ON NEONATAL OUTCOMES IN GESTATIONAL DIABETES MELLITUS PATIENTS

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ABSTRACT

Background: Pregnancy is a potentially glucose intolerant condition and in all pregnancies insulin sensitivity decreases as pregnancy advances. This predisposes to development of gestational diabetes mellitus. ***AIM:*** Aim of this study is to assess the efficacy of Metformin and insulin on neonatal outcomes in GDM patients. ***Objective:*** To study and compare the difference in efficacy of Metformin and insulin on neonatal outcomes. ***Materials and method:*** It is a prospective observational study in which the sample size is divided into 2 groups. One receving Metformin and other Insulin. Optimum glycemic control between the two groups are studied along with maternal and neonatal outcomes. ***Results:*** Glycemic control of both the groups were 95%.Majority of insulin group(60%) have pre term delivery while majority of metformin group have normal delivery(85%). Neonatl hyperbilirubinemia was higher in insulin group(60%) than in metformin group(35%). ***Discussion:*** Through our study, it was found maternal glycemic control and most of the neonatal outcomes (birth weight, APGAR score) were comparable between two groups. Neonatal huperbilirubinemia and gestational age of delivery were having significant difference between two groups. ***Conclusion:*** Metformin is found to be as effective as Insulin in the treatment of Gestational Diabetes Mellitus. Compared to Insulin, Metformin is a safer, cheap and convenient first line drug of choice for Gestational Diabetes Mellitus.

KEYWORDS: Gestational Diabetes mellitus (GDM), Metformin, Insulin.

INTRODUCTION

According to WHO, Gestational Diabetes Mellitus is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. This definition includes women whose glucose tolerance will return to normal after pregnancy and those who will persist with glucose intolerance and type 2 diabetes. The latter group contain individuals who had unrecognized type 2 disease prior to pregnancy. The incidence of the condition is increasing in association with increasing obesity in the population and the increase in age specific maximum fertility.

Fetal and Maternal Morbidity Associated With GDM

GDM is associated with a higher incidence of maternal morbidity, including cesarean deliveries, birth trauma, hypertensive disorders of pregnancy (including pre-eclampsia), and subsequent development of T2DM. Perinatal and neonatal morbidities are also increased; the latter include macrosomia, shoulder dystocia and other birth injuries, respiratory distress, hypoglycemia, polycythemia and hyperbilirubinemia. Longterm sequelae in offspring with in utero exposure to maternal hyperglycemia include higher risks of obesity, impaired glucose metabolism, and diabetes later in life.

Pharmacotherapy

Metformin

Metformin belongs to the biguanide class, and is classified by the Food and Drug Administration (FDA) in the US as a category B drug in pregnancy. In the UK, NICE (2008) recommend that metformin is used as an adjunct or alternative to insulin in the preconception period and during pregnancy, when the likely benefits from improved glycaemic control outweigh the potential for harm. Metformin works to lower glucose levels by decreasing peripheral insulin resistance, intestinal absorption and hepatic production of glucose, and decreasing peripheral uptake and utilisation of glucose (Menato et al, 2008). In addition, the drug does not stimulate insulin secretion, cause hypoglycaemia, or stimulate the fetal pancreas to oversecrete insulin (Menato et al, 2008). Metformin, unlike insulin, does cross the placental barrier, which previously caused concern for its use in pregnant women.

Insulin

When blood glucose targets cannot be reached by diet and/or OADs, insulin is required. here is no evidence supporting the advantages of any one type of insulin or regimen of insulin over another. Thus, insulin type and regimens should be individualized [128–131]. It is

beneficial to pair rapid-acting with intermediate or long-acting insulin, in order to simulate the physiologic insulin secretion throughout the day. In women with diabetes, insulin requirements gradually increase throughout pregnancy: 0.7 units/kg/day in the first trimester; 0.8 units/kg/day from week 18; 0.9 units/kg/day from week 26; and 1.0 units/kg/day from week 36 until delivery. In some instances lower doses may suffice.

MATERIALS AND METHODS

The present study was conducted after clearance from the Institutional Human Ethical committee. It was carried out in the Gynaecology and Obstretics department of a tertiary care center.

Inclusion Criteria

- Age between 18-40 yrs
- Diagnosis of GDM
- Single fetus pregnancy with >28 weeks of gestation.
- No response to diet and exercise.

Exclusion Criteria

- Pre-pregnancy diagnosis of diabetes.
- Other co-morbidities
- Gestational hypertension.
- Pre-eclampsia.
- Fetal growth restriction.
- Fetal anomaly

Procedure

The sample population(40) was mainly divied into 2 groups. Group A receiving **METFORMIN(20)** and Group B receiving **INSULIN(20)**. Basic demographic data were recorded using a performa. Subjects were followed through out their pregnancy period with blood glucose and maternal weight monitoring every 2 weeks.

The main maternal outcomes recorded includes Fasting blood glucose, Random blood glucose and 1 hr Post prandial bloodglucose levels. At the time of birth neonatal outcomes such as Pre term labour, birth weight, Apgar score at 5min, Hypoglycemia, Hyperbilirubinemia and respiratory distress were recorded. Mode of delivery (normal, emergency LSCS, elective LSCS) was also recorded.

RESULTS AND DISCUSSION

The collected data on study parameters from insuin group and metformin group were subjected to stastistical treatment using appropriate statistical tools. Frequency and percentage were calculated for categorical study variables as descriptive statistics. Since collected data did not obey normality assumption, nonparametric statistical procedures were employed, for stastisticaly comparing groups based on various study parameters (chi-square test was used for comparing insulin and metformin group based on categorical variables if expected frequencies were greater than 5, otherwise Fishers exact test has been applied.

Glycemic Control

Table 1: Data and test of significance for comparison of insulin and metformin group based on glycemic control.

Group	Glycemic control		Chi-square	P
	Well controlled	Poorly controlled		
Insulin	19 (95%)	1 (5%)	0.000	1.000 $_{NS}$
Metformin	19 (95%)	1 (5%)		
Total	38 (95%)	2 (5%)		

NS: not significant (Chi-square=0.000, P=1.000).

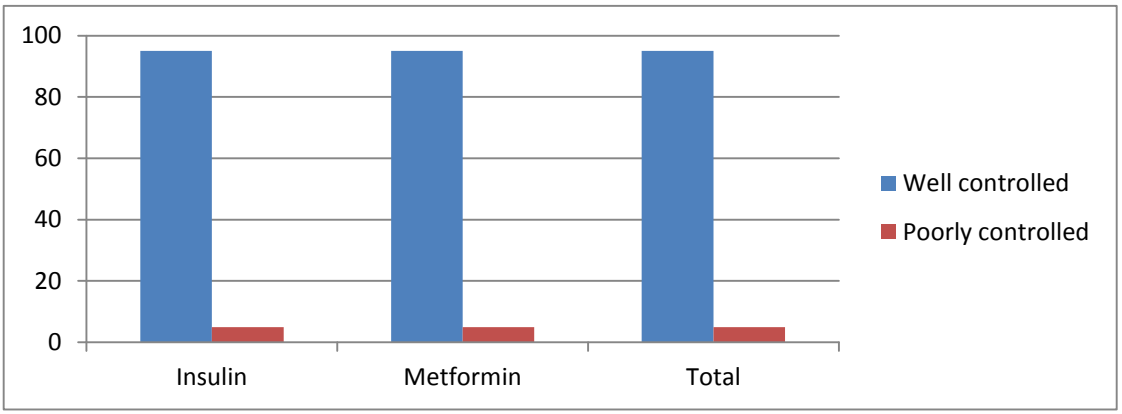

Figure 1: Glycemic control of insulin and metformin.

Here we take a total of 40 patients of which 20 receving metformin and other 20 receving insulin. The results shows that the glycemic control in metformin group is about 95% and the same is in insulin. Hence it is proved that the glycemic control in both the groups are the same. As the P value is greater than 0.5 it is not statistically significant.

Gestational Age

Table 2: Data and test of significance for comparison of insulin and metformin group based on gestational age.

Group	Gestational age		Chi-square	P
	Normal	Pre term		
Insulin	8 (40%)	12 (60%)	8.640	0.003*
Metformin	17 (85%)	3 (15%)		
Total	25 (62.5%)	15(37.5%)		

*significant (chi square=8.640, P=0.003).

Total 40 patients were taken to assess the effect of gestational age between insulin and metformin. Majority of patients in insulin group, (60%) reported to have pre term delivery. While majority of patients in metformin group has normal gestational age. From table 2, there exists significant difference between insulin and metformin group based on gestational age (chi square= 8.640, P <0.05).

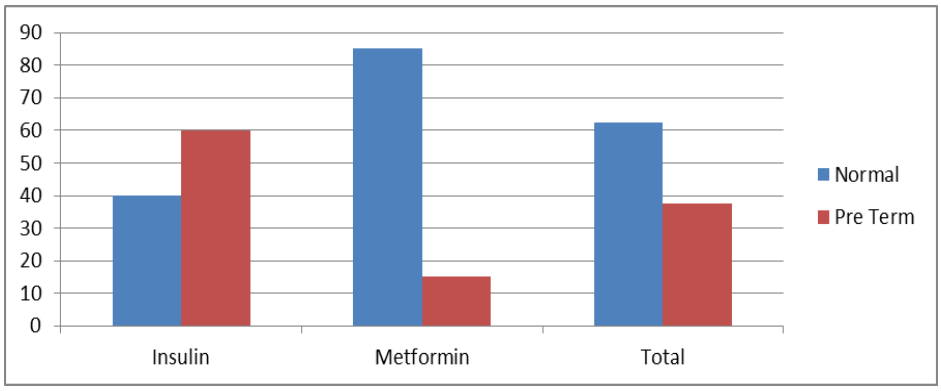

Figure 2: Gestational age distribution of insulin and metformin.

Mode of Delivery

The next comparison is on the basis of mode of delivery. Mainly 3 modes were selected. Normal delivery, elective LSCS and emergency LSCS section. Total 40 patients were recruited, of which 20 belongs to insulin and 20 belongs to metformin. The percent of normal delivery is less in both insulin and metformin groups. Insulin showed about 5% emergency cessarian section whereas it was none in metformin. Metformin showed an increased elective cessarian section of about 95%. From table3, there do not exist significant difference between insulin and metformin group based on mode of delivery (chi square= 1.444, P>0.05).

Table 3: Data and test of significance for comparison of insulin and metformin group based on mode of delivery.

Group	Mode of delivery			Chi-square	P
	Normal	Elective LSCS	Emergency LSCS		
Insulin	2 (10%)	17 (85%)	1(5%)	1.444	0.486NS
Metformin	1 (5%)	19 (95%)	0		
Total	3 (7.5%)	36 (90%)	1 (2.5%)		

NS- not significant (chi square= 1.444, P>0.05).

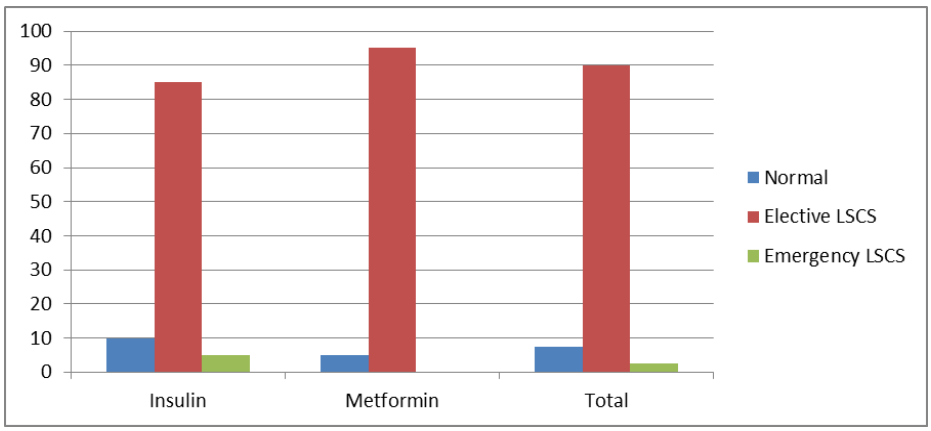

Figure 3: Mode of delivery of insulin and metformin.

Apgar Score

Insulin and metformin was then compared on the basis of APGAR score on 40 patients. Score less than 8 was greater among insulin group and score greater than 8 was comparatively greater in metformin group. Metformin showed 90% of good APGAR score and insulin showed only 85%. The result is not statistically significant but still metformin gives better result than insulin. From table 4, there do not exist significant difference between insulin and metformin group based on APGAR score (chi square= 0.229, P>0.05).

Table 4: Data and test of significance for comparison of insulin and metformin group based on APGAR score.

Group	APGAR Score		Chi-square	P
	>8	<8		
Insulin	17 (85%)	3 (15%)	0.229	0.633NS
Metformin	18 (90%)	2 (10%)		
Total	35 (87.5%)	5(12.5%)		

NS- not significant(Chi-square=0.229, P=0.63).

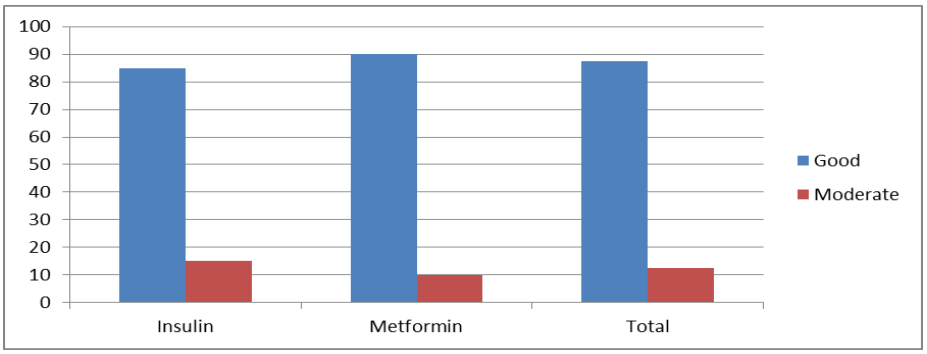

Figure 4: APGAR score distribution between insulin and metformin.

Birth Weight

Maternal hyperglycemia prompts fetal hyperinsulinemia, particularly during the second half of pregnancy. This in turn stimulates excessive somatic growth leading to excessive fetal growth.

For comparison of neonatal birth weight the outcomes are divided into 3 categories Normal weight(2.5-3.5Kg), low birth weight(<2Kg) and LGA(>3.5) and assessed in a total of 40 patients. Both and insulin and metformin shows equal percent of normal babies while LGA was found out more in metformin(20%) insulin(10%) and small birth weight was more in insulin(15%) metformin (5%). From table 5, there do not exist significant difference between insulin and metformin group based on neonatal birth weight score (chi square= 1.667, P>0.05).

Table 5: Data and test of significance for comparison of insulin and metformin group based on birth weight.

Group	Birth weight			Chi-square	P
	2-3.5	<2	>3.5		
Insulin	15 (75%)	3 (15%)	2 (10%)	1.667	0.435NS
Metformin	15 (75%)	1 (5%)	4 (20%)		
Total	30 (75%)	4 (10%)	6 (15%)		

NS- not significant (chi square= 1.667, P>0.05).

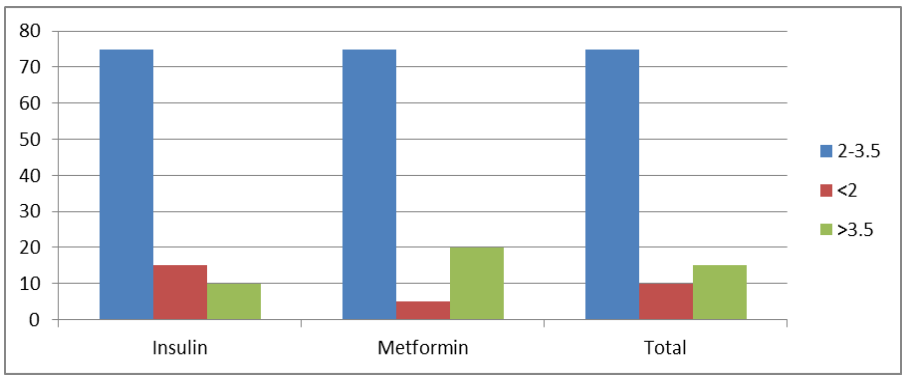

Figure 5: Birth weight distribution between insulin and metformin.

Neonatal Hyperbilirubinemia

A major contributing factor to neonatal hyperbilirubinemia is newborn polycythemia, which increases the bilirubin load. Polycythemia is thought to be a fetal response to relative hypoxia.

Hyperbilirubinemia is a major complication of neonates in GDM patients. It was more found in insulin group about 60% and in Metformin group it was found to be only 35%. Since p value is less than 0.5 the result is statistically significant and hence it proves metformin to be better drug choice. From table 6, there exists significant difference between insulin and metformin group based on neonatal hyperbilirubinemia (chi square= 3.751, P <0.05).

Table 6: Data and test of significance for comparison of insulin and metformin group based on neonatal hyperbilirubinemia.

Group	Others		Chi-square	P
	Absent	Present		
Insulin	8 (40%)	12 (60%)	3.751	0.049*
Metformin	13 (65%)	7 (35%)		
Total	21 (52.5%)	19(47.5%)		

*- significant (chi square= 3.751, P <0.05).

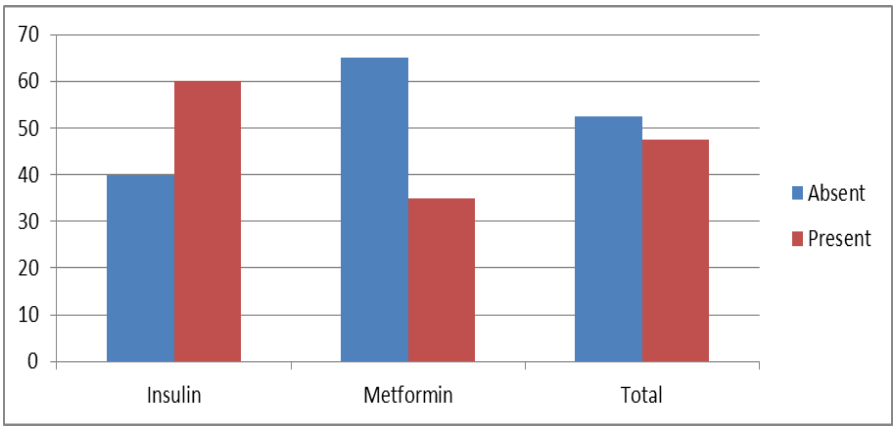

Figure 6: Neonatal hyperbilirubinemia between insulin and metformin.

SUMMARY

The present pilot study was conducted to compare the efficacy of metformin and insulin on neonatal outcomes, to determine whether the sample size will meet the conclusion of previous references. Gestational diabetes is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. Gestational implies that diabetes is induced by pregnancy—ostensibly because of exaggerated physiological changes in glucose metabolism. Thus our study typically excluded all the overt diabetes cases and included 40 GDM cases through OGTT. Of which 20 patients received insulin and 20 patients received metformin. From this study it was found that metformin is comparable with insulin and can be used as an alternative to insulin. Effectiveness via glucose control was almost same for both groups. Preterm delivery was significantly higher in insulin group than in metformin group. Regarding neonatal outcomes, neonatal hyperbilirubinemia was significantly lower in metformin treated group. Thus through our study metformin is comparatively safer for GDM patients. We suggest metformin as a easier and convenient first line drug of choice for gestational Diabetes mellitus patients.

CONCLUSION

Through our study, Metformin is found to be as effective as Insulin in the treatment of Gestational Diabetes Mellitus. Compared to Insulin, Metformin is a safer, cheap and convenient first line drug of choice for Gestational Diabetes Mellitus.

Future studies should include large population, longer duration and must include severity criteria for selection of subjects.

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