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A COMPARITIVE EFFICACY STUDY OF METFORMIN AND INSULIN ON NEONATAL OUTCOMES AMONG GESTATIONAL DIABETES MELLITUS PATIENTS

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ABSTRACT

***Background*:** To compare the efficacy of Metformin and Human Insulin on neonatal outcomes in gestational diabetes mellitus patients. ***Methods*:** A total of 120 patients with GDM were selected in which 60 patients with metformin and 60 patients with insulin. Neonatal outcomes such as Gestational age, birth weight, APGAR score, Hypoglycemia, Hyperbilirubinemia and respiratory distress were collected at the time of birth. ***Result*:** 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. All other neonatal outcomes (body weight, neonatal hypoglycaemia, neonatal respiratory distress) and mode of delivery were comparable. ***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, insulin, metformin, OGTT.

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 at gestation. The word gestational implies that diabetes is induced by pregnancy ostensibly because of exaggerated physiological changes in glucose metabolism. Use of the term gestational diabetes has been encouraged to communicate the need for increased surveillance and to stimulate women to seek further testing postpartum. The most important perinatal correlate is excessive fetal growth, which may result in both maternal and fetal birth trauma.

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. Long term consequences in offspring with in utero exposure to maternal hyperglycemia include higher risks of obesity, impaired glucose metabolism, and diabetes later in life.[1]

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. 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.[2]

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 was mainly divied into 2 groups. Group A receiving **METFORMIN(60)** and Group B receiving **INSULIN(60)**. 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.

OBSERVATION AND RESULTS

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	57 (95%)	3 (5%)	0.000	1.000NS
Metformin	57 (95%)	3 (5%)		
Total	114 (95%)	6 (5%)		

P-NS: P value not significant(Chi-square=0.000, P>0.05)

Total 120 patients were recruited in to the study. 60 patients receiving insulin and 60 receiving metformin. 57 patients of the metformin group (95%) and 57 patients of the insulin group (95%) has good glycemic control. From table1, there do not exist significant difference between insulin and metformin group based on glycemic control (chi square= 0.000, P>0.05). Both metformin and insulin group achieved good glycemic control (95%).

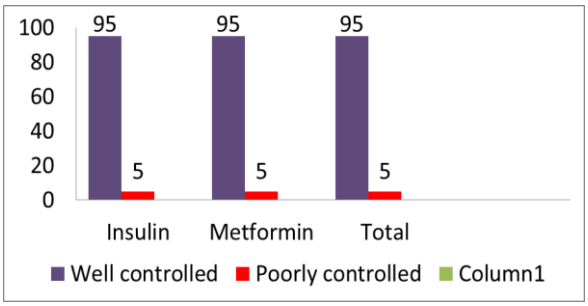

Figure 1: Percentage distribution of glycemic control between Insulin and Metformin.

GESTATIONAL AGE OF DELIVERY

Table 2: Data and test of significance for comparison of Insulin and Metformin group based on gestational age of delivery.

Group	Gestational age of delivery		Chi-square	P
	Normal (38-42 weeks)	Pre term Less than 37 weeks		
Insulin	24 (40%)	36 (60%)	25.920	0.000*
Metformin	51 (85%)	9 (15%)		
Total	75 (62.5%)	45(37.5%)		

*P: P value significant (Chi-square=25.920,P<0.05)

Majority of patients in insulin group (36 patients, 60%) reported to have preterm babies while majority of patients in metformin (51 patients, 85%) group has normal gestational age. 9 patients of metformin group (15%) reported to have preterm babies. From table 2, there exists significant difference between insulin and metformin group based on gestational age (chi square= 25.920, P <0.05).

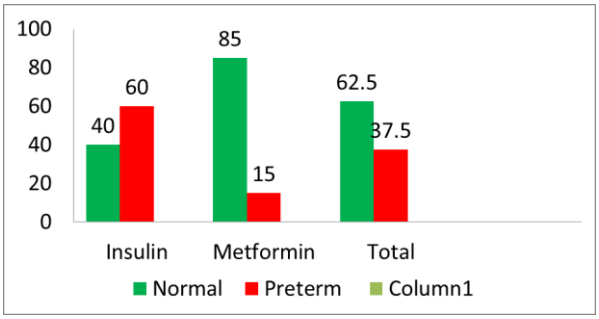

Figure 2: Percentage distribution of Insulin and Metformin group based on gestational age of delivery.

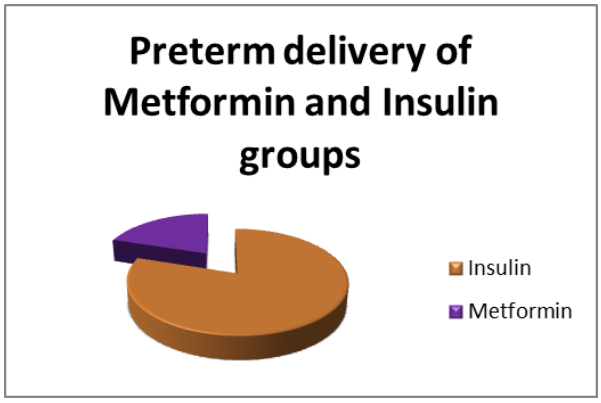

Figure 2.1 Preterm Delivery distribution between insulin and Metformin.

MODE OF DELIVERY

Only six patients of the insulin group (10%) and nine patients of the metformin group (15%) was having normal delivery. 51 patients of both the group (85%) was having elective LSCS. None of the patients of metformin group needed emergency LSCS while 3 patients of the insulin group(5%) needed emergency LSCS. From table3, there do not exist significant difference between insulin and metformin group based on mode of delivery (chi square= 3.600, 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	6 (10%)	51 (85%)	3(5%)	3.600	0.165NS
Metformin	9 (15%)	51 (85%)	0(0%)		
Total	15 (12.5%)	102 (85%)	3 (2.5%)		

P-NS: P value not significant (Chi-square=3.600, P>0.05)

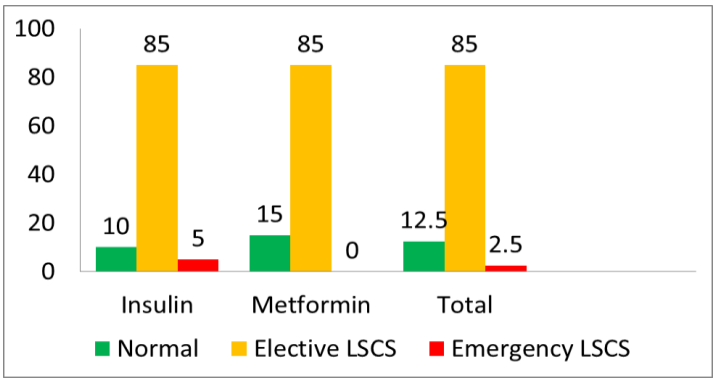

Figure 3: Percentage distribution between Insulin and Metformin based on mode of delivery.

APGAR SCORE

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	51 (85%)	9 (15%)	.686	0.408NS
Metformin	54 (90%)	6 (10%)		
Total	105 (87.5%)	15(12.5%)		

P-NS: P value not significant(Chi-square=.686, P=.408)

Of the 60 patients of insulin group 51 (85%) was having APGAR score greater than eight. 9 patients of insulin treated group (15%) have APGAR score less than 8. Though metformin group has no wide difference, 54 patients out of 60 (90%) have APGAR score greater than 8 and only 6 patients have(10%) APGAR score less than 8. From table 4, there do not exist significant difference between insulin and metformin group based on APGAR score (chi square= 0.686, P>0.05).

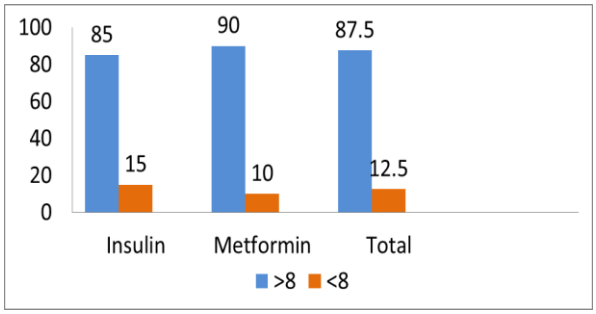

Figure 4: Percentage distribution between Insulin and Metformin based on APGAR score.

BIRTH WEIGHT

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

Group	Birth weight			Chi-square	P
	Normal (2.5Kg-3.5Kg)	SGA Below 2 Kg	LGA Above 3.5Kg		
Insulin	45 (75)	9 (15)	6 (10)	3.697	.157NS
Metformin	48 (80)	3 (5)	9(15)		
Total	93 (77.5)	12 (10)	15 (12.5)		

P-NS: P value not significant (Chi-square=.3.697, P=.157 NS)

Out of 60 insulin treated patients 45 patients (75%) have normal birth weight obtained, 9 patients (15%) have SGA babies and 6 patients(10%) have LGA babies. Metformin has comparatively better results as 48 out of 60 (80%) normal delivery and 3 patients (5%) having SGA. But the occurrence of LGA was more among metformin (9out of 60,15%). as compared to insulin. From table 5, there do not exist significant difference between insulin and metformin group based on birth weight (chi square= 3.697, P>0.05).

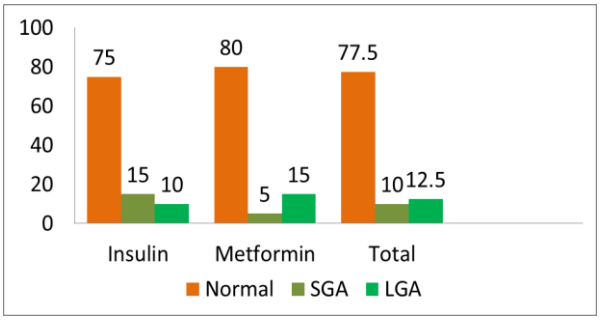

Figure 5: Percentage distribution between Insulin and Metformin based on neonatal birth weight.

NEONATAL HYPOGLYCEMIA

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

Group	Neonatal hypoglycemia		Chi-square	P
	Absent	Present		
Insulin	48 (80)	12 (20)	2.353	0.125NS
Metformin	54 (90)	6 (10)		
Total	102 (85)	18(15)		

P-NS: P value not significant (Chi-square=2.353, p>0.05)

Neonatal hypoglycemia occurrence was more among insulin group, 12 patients out of 60, (20%). On the other hand, only 6 patients out of 60(10%) developed neonatal hypoglycemia in metformin group. From table 6, there do not exists significant difference between insulin and metformin group based on neonatal hypoglycemia (chi square= 2.353, P >0.05).

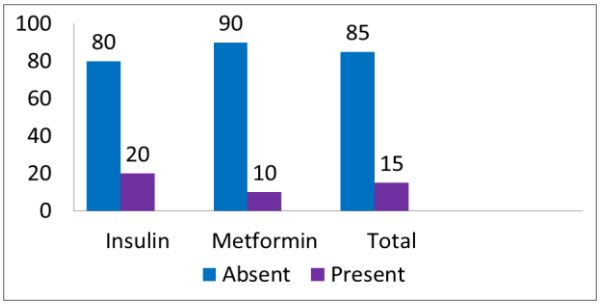

Figure 6: Percentage distribution between Insulin and Metformin based on neonatal hypoglycemia.

NEONATAL HYPERBILIRUBINEMIA

Table 7: Data and test of significance for comparison of Insulin and Metformin group based on neonatal hyperbilirubinemia.

Group	Neonatal hyperbilirubinemia		Chi-square	P
	Absent	Present		
Insulin	24 (40%)	36 (60%)	4.800	.028
Metformin	36(60%)	24 (40%)		
Total	60(50%)	60(50%)		

*: significant (Chi-square=4.800,P<0.05)

Majority of patients in insulin group, 36 out of 60 (60%) reported to have neonatal hyperbilirubinemia. While only 24 out of 60(40%) have neonatal hyperbilirubinemia in metformin group. From table 7, there exists significant difference between insulin and metformin group based on neonatal hyperbilirubinemia (chi square= 4.800, P <0.05).

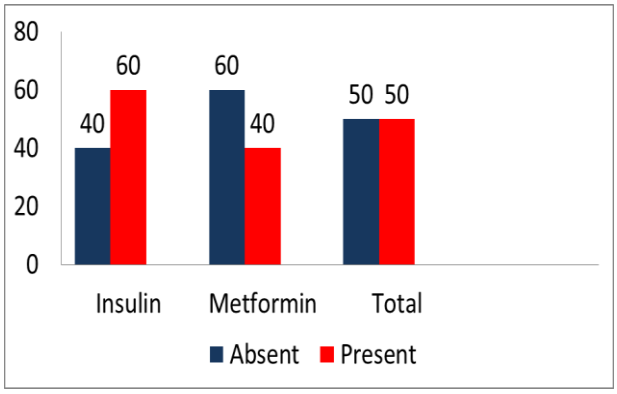

Figure 7: Percentage distribution between insulin and metformin based on neonatal hyperbilirubinemia.

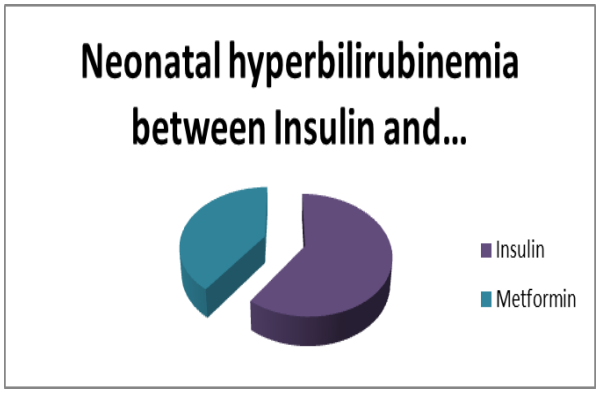

Figure 7.1: Neonatal hyperbilirubinemia distibution between insulin and Metformin.

NEONATAL RESPIRATORY DISTRESS

Table 8: Data and test of significance for comparison of insulin and metformin group based on neonatal respiratory distress.

Group	Neonatal respiratory distress		Chi-square	P
	Absent	Present		
Insulin	36 (60%)	24 (40%)	1.319	.251
Metformin	42(70%)	18 (30%)		
Total	78 (65%)	42(35%)		

NS: not significant (Chi-square=1.319, P=0.251)

24 patients (40%) out of 60 devoloped neonatal RDS while only 18 (30%) patients developed neonatal RDS in metformin group. From table 8, there do not exists significant difference between insulin and metformin group based on gestational age (chi square= 1.319, P >0.05).

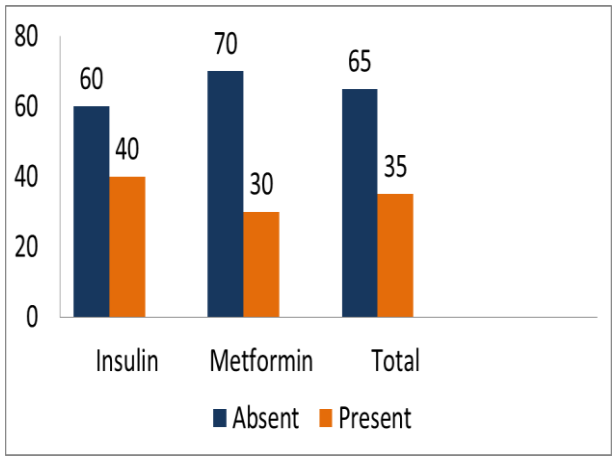

Figure 8: Percentage distribution between insulin and metformin based on neonatal respiratory distress.

DISCUSSION

The efficacy of Metformin and Insulin was determined by glycemic control. The glycemic control was assessed by the periodic monitoring of FBS and PPBS during the course of therapy. In our study both the drugs show equal effectiveness in achieving the desired plasma glucose levels(p=1.000) which was similar to the study conducted by Munshi S et al.[3] Theoretically metformin is an alternative to insulin in the treatment of hyperglycemia during pregnancy. Pre term birth is one that occurs before the start of 37 week of pregnancy. In our study a significant difference (p=0.000) was observed based on gestational age. Majority of patients in insulin group (36 patients, 60%) reported to have preterm babies while majority of patients in metformin (51 patients, 85%) group has normal gestational age. Our result coincides with the study done by Kristina Tertii et al[7] and in contrast with study done by Rowan J et al[3] which states that frequency of preterm birth was higher in the metformin group than in insulin group. Cesarean delivery at or near term has frequentlybeen used to avoid traumatic birth of a large infant in a woman with diabetes. The perinatal goal is to avoid difficult delivery from excessive fetal size and concomitant birth trauma associated with shoulder dystocia. In our study, mode of delivery has no statistical significance, (p=0.165). Cessarian section was equal in both groups. Thus our study is comparable with Moore et al study.[4] Newborns of a GDM mother experience a rapid drop in plasma glucose concentration after delivery. Low glucose concentrations defined as < 45 mg/dL are particularly common in newborns of women with unstable glucose concentrations during labor. In our study total 15% of population developed neonatal hypoglycemia and it is not statistically significant (p=0.125) between two groups. Hypoglycemia was more reported in insulin group in our study which was similar to the study done by Kristiina Tertii et al.[5] The pathogenesis of hyperbilirubinemia in neonates of diabetic mothers is uncertain. A major contributing factor is newborn polycythemia, which increases the bilirubin load. Polycythemia is thought to be a fetal response to relative hypoxia. According to Hay (2012), the sources of this fetal hypoxia are hyperglycemia-mediated increases in

maternal affinity for oxygen and fetal oxygen consumption. Together with insulin-like growth factors, this hypoxia leads to increased fetal erythropoietin levels and red cell production. In our study neonatal hyperbilirubinemia was common among insulin group. Newborns of GDM mothers were thought to be at increased risk for respiratory distress from delayed lung maturation. Subsequent observations challenged this concept, and gestational age rather than diabetes is likely the most significant factor associated with respiratory distress syndrome.

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.

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