Section: Biochemistry

Research

METFORMIN VERSUS INSULIN IN TREATMENT OF GESTATIONAL DIABETES MELLITUS – A RANDOMISED CONTROLLED TRIAL

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Abstract

Background: Metformin is a logical treatment for women with gestational diabetes mellitus, but randomized trials to assess the efficacy and safety of its use for this condition are lacking. Diabetes is a condition in which the body either does not produce enough insulin or cannot use insulin properly. The present study was done to compare the efficacy and outcome of using metformin and insulin in GDM patients. The aim of the study is to find out various outcomes and side effects of treatment of gestational diabetes through Metformin, Insulin. **Materials and Methods:** A randomized open label trial was carried out in the labour room of Department of Obstetrics and Gynaecology. All GDM women attending OPD of our hospital. 140 GDM Patients were studied in accordance of inclusion criteria were included. The patients were divided into 2 groups. Group A (n=70) were treated with metformin (dose adjusted to requirements) and Group B (n=70) were treated with insulin (dose adjusted to requirements) outcome measured. **Result:** Majority of the women belong to age group 20 to 30 years. Mean age in metformin group is 27.04 +/-4.21 and insulin group is 26.2+/-3.67. Weight gain of the mothers is found to be more in the insulin group when compared to metformin group, this is statistically significant. less number of patients developed PIH among metformin group when compared to the insulin group. This was statistically significant. We had 2 preterm deliveries among metformin group and 1 among insulin group. Among the metformin group babies, macrosomia (wt >4kgs), hypoglycaemia, respiratory distress and needed ICU admission statistically significant in our study. All patients in metformin group reported no side effect with the drug. **Conclusion:** Metformin is a safe alternative for control of gestational diabetes compared to insulin.

INTRODUCTION

During the recent years, there is an increased incidence as well as increased morbidity due to gestational diabetes mellitus (GDM). Approximately, GDM occurs in about 1–14% of all pregnancies, this depends on the population and the diagnostic tests used.[1] Gestational diabetes is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1] Gestational diabetes is one of the most common medical complication of pregnancy and it has many short- and long-term complications for both mother and offspring. GDM always has increased maternal risk for preeclampsia, caesarean section, and an increased risk for developing type 2 diabetes in future after pregnancy.[2] There is also an increased chances of having more of neonatal death, still birth and congenital defects in the fetuses5 due to excess mother-to-fetus glucose transfer.[3] Macrosomia which is also another important adverse effect of Gestational diabetes, this also causes increased risk for instrumental delivery, increased caesarean section and shoulder dystocia during vaginal birth and neonatal hypoglycaemia after birth. The intrauterine hyperglycaemic environment might cause the fetus to develop type 2diabetes or insulin resistance in later life.[4] Hence the management of GDM is done mainly done for glycaemic control to reduce the incidence of complications. Previously studies have demonstrated that controlling glycemic levels in women with GDM reduced birth weight and incidence of macrosomia in babies born to mothers who had participated in the intervention group compared with women who were in the control

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group. Thus the management of GDM includes-dietary therapy, exercise, oral hypoglycemic agents, insulin - are necessary to reduce the complications.[5] When an appropriate diabetic diet, along with physical exercise, does not control glycemic levels in pregnant women, subcutaneous insulin therapy is generally the standard for management of GDM. However, disadvantages of insulin are multiple daily injections, chances of hypoglycemia and maternal weight gain, requires modification based on the patient's body mass index, glucose levels and lifestyle. Thus, proper guidance for insulin dose change is necessary to ensure the safe self-administration of insulin. Meanwhile, substantial costs of health education on the safe use of insulin and the cost of the drug itself are important factors. So a safe and effective oral therapy is more needed and is highly preferred for women with GDM. So, it is highly essential to compare the effects of oral hypoglycemic agents on both maternal and neonatal outcomes for the women with GDM. Metformin, which is first line medication for Type 2Diabetes, also becomes first choice of drug in GDM. Metformin has been found to have a maternal-to-fetal transfer rate of 10–16%. which was thought to be associated with fetal anomalies, potential adverse effects for mothers and the newborns after delivery, it has not been widely used in GDM. Nowadays, studies have increased and focusses on examining the efficiency and safety of metformin in the management of GDM. However, there are some case-control trials, some observational studies 2, others are randomized controlled trials (RCTs) which are very few to confirm the benefits of metformin for GDM. So the use of metformin is still controversial in pregnant women, especially in our population.[6] Therefore, the aim of this study is to provide effects of metformin with insulin on glycemic control, maternal and neonatal outcomes in GDM in our hospital population.

MATERIALS AND METHODS

This is a randomised, open label, hospital based, comparative study conducted at the Muslim Maternity and Children's Hospital, Hyderabad from October 2016 to October 2018. This study comprising of 140 women antenatal patients coming to the OPD of Muslim Maternity and Children's Hospital, Hyderabad (T.S). They have been followed up till the delivery and post natally till 6 weeks. The neonates have also been followed up till 2 weeks.

Group A: receiving metformin (dose as per requirement)

Group B: receiving insulin (dose as per requirement)

Sample Size Calculation

In metformin group 14% of women needed to supplemental insulin to achieve euglycemia from the previous study. Considering the 95% level of confidence interval (Z=1.96) with 10% precision (d=0.1) the minimum required sample size is

$$n = \frac{(Z\alpha_{/2})^2 \times p \times (1-p)}{(d)^2}$$

$$n = \frac{(1.96)^2 \times (0.14) \times (1-0.14)}{(0.1)^2} = 46.25 \cong 47$$

Therefore, the minimum required sample per group is 47.

Study considered:" Metformin compared with insulin in the management of gestational diabetes mellitus: A randomized clinical trial" by Shirin Niromanesh, Azin Alavi.[7]

For this study systemic randomisation technique has been used i.e, the first patient who came to the OPD has been assigned the number 1 and the second patient has been assigned the number 2, then again the third patient assigned the number 1 and the fourth patient assigned the number 2 and so on till 140 patients

Inclusion Criteria

All Singleton pregnant women who on DIPSI guidelines had values ranging >/= 140mg/dl-</=199mg/dl, who did not have any control after 2 weeks of diet control (i.e,FBS>/=95mg/dl and PLBS>/=120mg/dl).

Exclusion Criteria

Patients who are overt diabetes, with DIPSI value =/>200mg/dl, contraindication to metformin or insulin, Multiple pregnancies.

Women who fulfilled the above criteria were counselled and given details of the study. Entry into the study was guided by detailed history of present pregnancy, menstrual history, obstetric history, family history, past history, any medical illness, previous surgeries and habits followed by general physical examination (to note anaemia, edema, pulse rate, respiratory rate, blood pressure, temperature) and systemic examination (obstetric examination, CVS, RS, CNS examination). All the women were given 2 weeks of diet control. And after diet control a repeat FBS and PLBS values more than 90 and 120mg/dl respectively were randomised into 2 groups of n=70 in Group A and n=70 in Group B.

Then the repeat fbs, plbs was repeated weekly for 3 weeks and last trimester for dose adjustment and in metformin group if patient needed any additional insulin for further glycemic control was done.

Metformin – in Group A

The patients in this group (n=70) had been started with required dose of metformin (500mg bd) and FBS,PLBS was repeated every week for 3 weeks and last trimester. The maternal complications such as maternal weight gain, PIH, polyhydramnios, macrosomia, emergency lscs, shoulder dystocia and persistence after delivery and fetal complications

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such as congenital anomalies, NICU admissions for respiratory distress, fetal hypoglycaemia, fetal hyperbilirubinemia, any trauma during delivery has been closely monitored. The mothers have been followed up till 6 weeks and their babies for 2 weeks.

Insulin – in Group B

The patients in this group (n=70) had been started with required dose of human insulin 30/70(mixtard) and FBS, PLBS was repeated every week for 3 weeks and last trimester. The maternal complications such as maternal weight gain, PIH, polyhydramnios, macrosomia, emergency lscs, shoulder dystocia and persistence after delivery and fetal complications such as congenital anomalies, NICU admissions for respiratory distress, fetal hypoglycaemia, fetal hyperbilirubinemia, any trauma during delivery has been closely monitored. The mothers have been followed up till 6 weeks and their babies for 2 weeks.

RESULTS

The study was carried out at the ANC OPD of Muslim Maternity Hospital. A total of 140 women who fulfilled the above criteria were selected for the study. The patients were randomized and divided into 2 groups of 70 each.

The resultant groups had similar distribution of age group, BMI and family history of diabetes. This was tested using the Pearson Chi-Square test and the p values were found to be 0.33, 0.41 and 0.72 respectively (p <0.005 Significant), ensuring nearly symmetric distribution in both the groups considered for study. (Table-1)

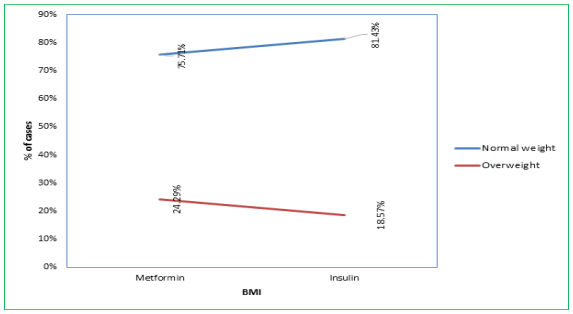

Figure 1: Comparison between body mass index in both the groups

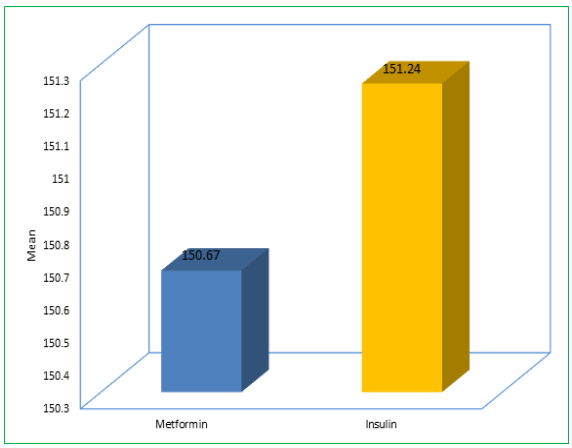

Figure 2: Comparison between DIPSI diagnosis in 2 groups

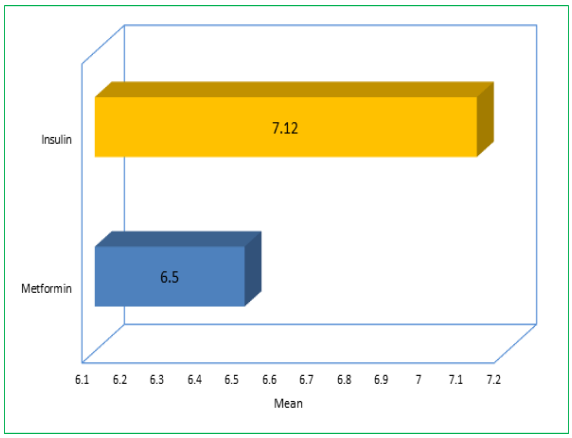

Figure 3:Comparison of weight gain among mothers in both the group

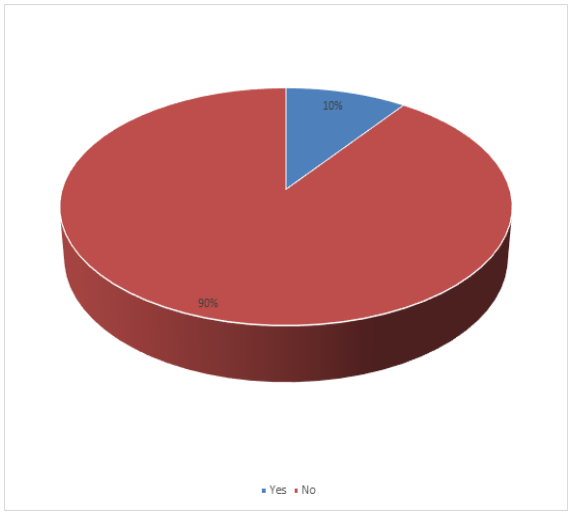

Figure 4: Shift to insulin

Table 1: Comparison of demographics of subjects in both the groups

Age (Years)	Metformin	Insulin	Total
<= 25	26	31	57
26 - 30	32	34	66
31 - 35	10	4	14
36 & Above	2	1	3
Total	70	70	140
Primi Para			
Yes	12	16	28
No	58	54	112

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Family History			
Yes	25	23	48
No	45	47	92
BMI			
Normal weight	53	57	110
Overweight	17	13	30
Mode of delivery			
Elective LSCS	28	27	55
Emergency LSCS	18	17	35
SVD	24	26	50

Table 2: Comparison of complications in among mothers in both the group

PIH			
Yes	14	29	43
No	56	41	97
Polyhydramnios / PROM/ PPROM			
Yes	5	6	11
No	65	64	129
Preterm			
Yes	2	1	3
No	68	69	137

Table 3: comparison of complications in among children in both the group

Macrosomia	**Metformin**	**Insulin**	**Total**	**P-Value**
Shoulder Dystocia	**Metformin**	**Insulin**	**Total**	**Shoulder Dystocia**
Yes	1	4	5	Yes
No	69	66	135	No
Yes	3	16	19	0.001
No	67	54	121	
Fetal Hypoglycemia				
Yes	3	15	18	0.001
No	67	55	122	
NICU Admission				
Yes	12	18	30	0.217
No	58	52	110	
Hyperbilirubinemia				
Yes	7	7	14	1.0
No	63	63	126	

Table 4: Comparison of subjects in both the group in various studies

Stuides	**Metformin(age in years)**	**Insulin(age in years)**	**Significance**
Age			
Rowan et al,[8]	33.5	33	No
Kristiina terti et al,[9]	32.8	32.7	No
Niromanesh et al,[7]	30.7	31.8	no
Our study	26.6	27	no
Gravida			
Nirmanesh et al,[7]	12/80	16/80	0.69
Rowan et al,[8]	248/363	252/370	0.98
Our study	58/70	54/70	0.71
Family history			
Rowan et al,[8]	162/363	181/370	no
Niromanesh et al,[7]	39/41	34/46	no
Our study	25/45	23/47	no
screening methods			
Pachal v jain et al,[10]	0.7	No	
Our study	0.657	No	
Weight gain			
Rowan et al,[8]	8.1+/-5.1	6.9+/-5.3	0.006
Niromanesh et al,[7]	11.3+/-3.8	13.7+/-3.1	<0.001
Our study	6.5+/-1.155	7.12+/-1.819	0.017

Table 5: Comparison of shoulder dystocia among both the groups in various studies

Study	**P value**	**significance**
Shoulder dystocia		
Panchal et al,[10]	0	Not significant
Niromanesh et al,[7]	0.681	Not significant
Our study	0.172	Not significant
PIH		
Niromanesh et al,[7]	0.058	Not significant
Rowan et al,[8]	0.14	Not significant

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Our study	0.006	significant
polyhydramnios/PROM/PPROM		
Panchal et al,[10]	0.51	no
Niromanesh et al,[7]	1	no
Our study	0.753	no
Preterm Deliveries		
Niromanesh et al,[7]	0.148	no
Gui et al,[11]	0.001	yes
Rowan et al,[8]	0.04	yes
Our study	0.559	no
Macrosomia		
Niromanesh et al,[7]	0.005	significant
Panchal et al,[10]	0.14	Not significant
Our study	0.017	significant
fetal hypoglycemia		
Niromanesh et al,[7]	1	no
Rowan et al,[8]	0.008	yes
Our study	0.002	yes
NICU admission		
Rowan et al,[8]	0.47	no
Niromanesh et al,[7]	0.443	no
Our study	0.217	no
Hyperbilirubinemia		
Rowan et al,[8]	0.85	no
Niromanesh et al,[7]	0.101	no
Our study	1	no

DISCUSSION

Various studies on comparison between metformin and insulin has shown that metformin is a good alternative to insulin. In fact it is shown to have better outcome in terms of maternal weight gain and macrosomia. Some of the studies have also shown to have less development of PIH. On the contrary, insulin has shown to have better glycemic control when compared to metformin which sometimes needs insulin support for control of sugars.

There is no statistical difference between age of two groups. It is similar to the study done by rowan et al8 and kristiina terti et al,[9] except that the mean age group in our study is slightly lower than the above studies. Our p value using chi square is 0.333. There is no statistical difference in between the 2 groups in gravid changes as seen in above 2 groups. Our p value here is 0.71.

There is no statistical difference between family history of two groups. It is similar to the study done by rowan et al8 and niromanesh et al. our p value using chi square is 0.72. There is no statistical difference between body mass index in both the groups. It is similar to the study done by Rowan et al8 and Niromanesh et al,[7] Here we in our study have used DIPSI method which is an Indian method of screening test. There is no statistical difference between dipsi method of screening in both the groups. It is similar to the study done by Panchal v jain.[10]

The weight gain in metformin is less when compared to insulin group. The statistical value is significant as in rowan et al and niromanesh et al. Though few of the Indian studies have shown to have no significant statistical difference such as Panchal v Jain.[10]

This is according to shabana munshi et.al in which there are no significant statistical difference in various modes of delivery in a patient treated with either metformin or insulin in GDM patients. The above mode of delivery is from panchal et al. It was found statistically not significant. The p value was found to be 0.999 which is not significant.

In our study also we have found that there are no significant statistical difference in various modes of delivery in a patient treated with either metformin or insulin in GDM patient. The p value is found to be 0.939.

Shoulder dystocia has not been shown to have any statistical significance. The p value that was got in our study was 0.172. it is similar to niromanesh et al and panchal et al. Studies like Niromanesh et al,[7] and rowan et al have shown to have no significance for PIH in both the groups. Metaanalysis by gui et al,[11] has shown to have significant statistical significance p value 0.02. Our study also has shown to have significant p value of 0.006 i.e, metformin has protective effects against PIH when compared to insulin. According to previous study polyhydramnios /prom in both groups was not significant and even in our study it is found to be insignificant.

According to previous study by niromanesh et al there is no significance statistically among incidence of preterm birth. But according to metanalysis by Gui de et al,[11] and rowan et al ,preterm delivery has been shown to have increased bin the metformin group when compared to insulin. According to our present study, we have found preterm deliveries in both groups to be insignificant statistically.

we have not found any still births or any congenital anomalies among the babies in our study population.

In our study persistence of diabetes beyond 6 weeks in post-partum is statistically insignificant value. P value 0.154. In previous study by niromanesh et al the macrosomia was found to be more in insulin group when compared to metformin group. But was

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statistically insignificant in the study conducted by Panchal et al.[10]

In our study macrosomia was statistically significant, i.e the macrosomia was found to be more in insulin group when compared to metformin group. In previous study by niromanesh et al the fetal hypoglycemia between 2 groups statistically did not show any difference. But in the study conducted by rowan et al fetal hypoglycaemia was seen to be more in babies among the insulin group.

In our study fetal hypoglycemia was statistically significant i.e fetal hypoglycaemia was seen to be more in babies among the insulin group. According to our study, the NICU admission among babies with RDS among the 2 groups was statistically not significant. It is similar to studies conducted by Rowan et al and Niromanesh et al.[7,8] According to our study, the babies with hyperbilirubinemia among the 2 groups was statistically not significant. It is similar to studies conducted by rowan et al and Niromanesh et al.[7]

CONCLUSION

In present study test results for 3 parameters namely PIH (p=0.006), Macrosomia(p=0.001)and Fetal Hypoglycemia(p=0.002) were positive for treatment administered through Metformin. The PIH was observed in 14 candidates (32%) through Metformin treatment whereas it was observed in 29 (67.44%) candidates in treatment through insulin. In case of Macrosomia, the results tested favourable for treatment through Metformin as there were only 3 cases (18.75%) of Macrosomia against 16 (81.25%) cases through insulin. In the 3rd case of Fetal Hypoglycemia, the incidences were significantly lower for Metformin, i:e; 3 (16.66%) against 15 (83.33%) incidences for insulin.

The 2 groups were also checked for total weight gain, post lunch blood fasting blood sugar, gestational age at diagnosis and method of administration-dipsy. The weight gain was higher in case of insulin administration by 8.7% and the correlation was found to be significant (p=0.017). Both the groups showed similar blood sugar levels of 116.01 (Metformin) and 114.19 (Insulin) although the average rise in blood sugar was slightly higher for metformin by 1.59%. The dipsy levels were similar in both the cases – Metformin 150.67 against Insulin 151.24. Out of the 4 parameters considered for study, the method of treatment showed significant impact (p<.005) along with weight gain (p=0.017). No cases of perinatal death or other anomality occurred in this study.

Metformin is a safe alternative for control of gestational diabetes compared to insulin. Metformin resulted in significant reduction in total weight gain of the mother, reduced PIH in the mothers when compared to insulin. Metformin also resulted in significantly less macrosomia in the babies, less fetal hypoglycemia among the babies when compared to insulin. Only disadvantage with metformin is that it sometimes may need additional insulin support for proper glycemic control.

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