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Original Research Paper

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COMPARATIVE EFFICACY OF METFORMIN AND INSULIN IN THE TREATMENT OF GESTATIONAL DIABETES - A RANDOMISED CONTROL STUDY.

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ABSTRACT

AIMS AND OBJECTIVES: To compare the efficacy of insulin over metformin in the management of gestational diabetes mellitus and to compare maternal and foetal outcome in patients treated with Metformin and Insulin. **MATERIALS AND METHODOLOGY**: This was a hospital based randomised control study conducted over a period of 12 months from April 2020 to March 2021 amongst 104 pregnant women attending antenatal OPD of Department of Obstetrics and Gynaecology ,Guwahati medical college and hospital, Assam. Open label RCT Randomization process was used to randomize participants into Insulin and Metformin group. Maternal and foetal variables were followed up among both the groups and the results were compared. **RESULTS:** Metformin when compared with Insulin was showing similar efficacy and safety in terms of variables like Fasting and Post Prandial blood glucose control.Metformin significantly reduces the incidence of polyhydramnios, fasting hypoglycaemia, post prandial hyperglycaemia and excessive weight gain during pregnancy. In the foetus, Metformin use was found to have reduced incidence of large for gestational age babies and indirectly preventing its related complications like need for LSCS, occurrence of shoulder dystocia at labour and neonatal hypoglycaemia. Insulin use in Gestational diabetes showed better neonatal outcome in terms of APGAR score and neonatal hypoglycaemia. But comparative efficacy of Insulin to Metformin in terms of post prandial blood glucose control was better, thus reducing the incidence of complications of poor glycaemic control in Gestational diabetes.**CONCLUSION:** Compared with Insulin, Metformin also can be used as an effective treatment of Gestational Diabetes but efficacy of Insulin is more than Metformin in terms of maternal and foetal outcomes. Further larger trials are needed to confirm.

KEYWORDS :

INTRODUCTION:

Diabetes is a group of metabolic disorders characterized by hyperglycaemia resulting from defects in insulin secretions, action or both[1] . Gestational diabetes mellitus is defined as glucose intolerance of various degrees that is first detected during pregnancy[2] . Pregnancy is a potentially glucose intolerant condition, and in all pregnancies, insulin sensitivity decreases as the pregnancy advances. GDM develops if there is inadequate insulin secretion to compensate for the increased insulin resistance[3-5]. GDM is diagnosed in approximately 3-7% of pregnancies and incidence of GDM increases in older and more obese pregnant women[5] .

Gestational Diabetes mellitus is associated with increased risk of complications of pregnancy and prenatal mortality. Detection and treatment of gestational diabetes mellitus reduces and eliminates the risks for the foetus. It also improves the woman's quality of life[6,7]. GDM increases the risk of certain pregnancy complications like pregnancy-induced hypertension and adverse perinatal outcome, and carries the risk of later development of type 2 diabetes mellitus (T2DM)[8] . Treatment of GDM can prevent short-term maternal and neonatal complications. The initial management for GDM includes nutritional modification and physical activity[9]. Almost 30% of women with GDM cannot be managed with diet and lifestyle modification alone and require pharmacological therapy to reduce the associated maternal and neonatal short and long term effects of GDM[10,11] . Insulin historically has been considered the standard therapy for GDM management in cases refractory to nutrition therapy and exercise, and this has continued to be reinforced by the American Diabetes Association (ADA). Insulin, which does not cross the placenta, lowers blood glucose by stimulating peripheral glucose uptake and inhibiting gluconeogenesis by the liver[8]. However, it requires multiple daily injections and subsequently the need to train the patients is the technical aspect of treatment, and higher medical cost. In addition, hypoglycaemia occurs in approximately 70% of women who use insulin some time during their pregnancy[12-14] . Oral anti hyperglycaemic drugs (OADs) (such as metformin and glyburide) on the other hand can cross the placenta to the foetus. In addition, all oral agents lack long-term safety data. Therefore, they have not been approved by the U.S. Food and Drug Administration and insulin continues to be the American Diabetes Association (ADA) recommended first-line therapy[15] . With this background the study was done to compare the efficacy of insulin and metformin in the treatment of gestational diabetes mellitus.

MATERIALS AND METHODOLOGY:

This was a hospital based randomised control study conducted over a period of 12 months from April 2020 to March 2021 amongst 104 pregnant women attending antenatal outpatient department of Department of Obstetrics and Gynaecology ,Guwahati medical college and hospital, Assam. Open label RCT Randomization process was used to randomize participants into Insulin and Metformin group. Maternal and foetal variables were followed up among both the groups and the results were compared.

INCLUSION CRITERIA : Pregnant women with singleton pregnancy diagnosed with gestational diabetes mellitus(GDM) in pregnancy from 22 weeks to 34 weeks gestation.

EXCLUSION CRITERIA:

1. Patients who are known case of Diabetes Mellitus, Multiple Pregnancy, Essential Hypertension ,Pre- eclampsia at the time of recruitment.
2. Women with gestational age less than 22 weeks and more than 34 weeks.
3. Women not willing to have their delivery at study setting area.

All selected subjects were approached personally and briefed about the study. After taking informed consent, selected subjects were followed up during their subsequent antenatal visits. A detailed history has been taken including maternal age, menstrual history, obstetric history, past history and family history of diabetes. At the booking visit, a general, systemic , obstetric examination and routine investigations were done. A Diabetes In Pregnancy Study group India (DIPSI) recommended screening test was advised. A 2 hours blood glucose value < 120mg/dl was considered normal.120-140 mg/dl has been considered impaired glucose tolerance and value greater than 140 mg/dl has been considered as GDM . HbA1C was done for all women whose blood sugar level (BSL) was > 140mg/dl and was managed with joint care with Endocrinologist. If BSL is normal, the screening criteria will be repeated in between 24 and 28 weeks of gestation again . Subjects has been followed through out their index pregnancy and blood glucose level monitored. Blood Glucose monitoring by a Glucometer was encouraged. Target blood sugar levels was aimed at FBS equal or less than 92 mg/dl and 1 hour postprandial level equal or less than 140 mg/dl and 2 hour less than 120mg/dl. Initially GDM has been managed by diet and exercise for two weeks. If blood glucose was not controlled, pharmacotherapy has been instituted. These women were enrolled for the study and randomization process was done and given insulin and metformin.

In the Metformin group, the starting does of Metformin was 500 mg once a day and increased gradually over time according to blood sugar values up to 1500mg/day. Insulin was added if targets are not achieved with Metformin alone at maximum doses. Insulin doses was adjusted by Diabetologist as per BSL (blood sugar level) frequency of monitoring will be decided based on BSL. ACOG recommends insulin be considered in women with 1 hour post prandial levels that persistently exceeds 140 mg/dl or those with 2 hours level more than 120mg/dl. Insulin starting dose is 0.7-1 unit/kg/day and is given in divided doses. A combination of intermediate acting and short acting insulin is used. Total daily insulin requirement is given as two-third in the day and one third at night. Patient needs to be taught self administration of insulin and to be warned against hypoglycaemia .The total dose of insulin titrated for each patient to achieve the above Glycaemic targets. The women asked to follow up regularly and USG was done. More frequent visits were advised if necessary. The dose of Metformin or Insulin required for optimal glycaemic control in each patient has been noted. Onset of labour as spontaneous or induced and its outcome has been evaluated. Gestational age at delivery and mode of delivery has been recorded. Maternal complications like Preeclampsia, Cesarean Section, Maternal infections, Fasting hyperglycaemia etc has been documented. Neonatal complication like Hypoglycaemia ,Polycythaemia , Prematurity , Birth trauma etc has been documented and neonatal intensive care unit admissions has been noted.

RESULTS AND OBSERVATION:

In our study, maximum participants of metformin group and insulin group belonged to age group of 20-30 years respectively. The difference between participants according to age group was statistically not significant. The mean FBS was 99.4 mg/dL with 5.1 SD and 100.7 mg/dL with 4.1 SD of participants of metformin and insulin group respectively. The difference between mean FBS was statistically significant. Mean PPBS was 143.1 mg/dL with 5.5 SD and 141.9 mg/dL with 5.9 SD of participants of metformin and insulin group respectively and was statistically significant. Maximum participants of metformin group and insulin group had parity of 2. This difference according to parity was statistically not significant. In both the groups, participants were enrolled at 28-34 weeks and it was statistically not significant.Maximum participants of metformin group and insulin group had weight gain during pregnancy between 10 to 12 kg. Mean FBS was 136.4 mg/dL with 39.6 SD and 139.9 mg/dL with 27.3 SD of participants of metformin and insulin group respectively. Mean PPBS was 187.1 mg/dL with 33.4SD and 203.9 mg/dL with 19.4 SD of participants of metformin and insulin group respectively. The difference between mean FBS and PPBS was statistically not significant.

Weight Gain (in kg)	Metformin [n=52]	Insulin [52]	P value
<10 10-12 >12	7 (13.5%) 38 (73.1%) 7 (13.5%)	5 (9.6%) 42 (80.8%) 5 (9.6%)	0.64
Mean Weight (Mean ± SD)	10.1 ± 5.4	11.4 ± 4.5	0.03

Distribution of study participants according to mean FBS and mean PPBS throughout pregnancy (N=104)			
Parameter	Metformin [n=52]	Insulin [52]	P value
Mean FBS (in mg/dl) (mean ±SD)	99.4 ±5.1	100.7 ±4.1	0.01
Mean PPBS (in mg/dl) (mean ±SD)	143.1 ±5.5	141.9 ±5.9	0.03

Both participants of metformin group and of insulin group delivered at gestational age of 37 to 40 weeks , maximum had normal vaginal delivery and polyhydramnios was present in both the groups. The difference between participants according to gestational age, mode of delivery and polyhydramnios was statistically not significant .One stillbirth occurred in metformin group which was a post dated pregnancy with oligohydramnios and meconium stained liquor .In our study, 19.2% participants of metformin group and 26.9% of insulin group had 'large for gestational age' baby respectively, this difference between participants according to presence of large for gestational age' baby was statistically not significant. 1 IUFD was noted in insulin group, who had Gross oligohydramnios.

Distribution of study participants according to 'Neonatal Mean blood glucose level at birth' (N=104)			
Mean blood glucose level at birth (in mg/dl)	Metformin [n=52]	Insulin [52]	P value
RBS<40mg/gl RBS>40mg/dl	50 (96.2%) 2 (3.8%)	44 (84.6%) 8 (15.4%)	0.05
Mean ± SD	38.6 ± 8.1	41.8 ± 11.8	0.04

Mean birth weight was 2.8 kg with 0.8 SD and 3.1 kg with 0.6 SD of babies of metformin and insulin group respectively and this difference was statistically significant. Mean APGAR score was 7.5 with 1.5 SD and 8 with 0.7 SD of babies of metformin and insulin group respectively. The difference between mean APGAR score was statistically significant. Mean blood glucose level at birth was 38.6 mg/dL with 8.1 SD and 41.8 mg/dL with 11.8 SD of babies of metformin and insulin group respectively and was statistically significant. 23.1%,17.3%,38.5% and 23.1% of babies of metformin group and 26.9%,21.2%,55.8% and 26.9% of insulin group had Transient Tachypnoea of New born ,Respiratory Distress Syndrome ,required NICU admission and had hypoglycaemia, respectively.

Variable	Metformin [n=52] (Mean ±SD)	Insulin [52] (Mean ±SD)
Age (years)	29.4 ± 3.4	31.4 ± 3.5
Parity	2.5 ±1.3	2.8 ± 1.3
Gestational age at enrolment (weeks)	31.9 ± 4.8	31.4 ± 5.5
Weight gain during pregnancy (kg)	10.1 ± 5.4	11.4 ± 4.5

FBS at enrolment (mg/dl)	136.4 ± 39.6	139.9 ± 27.3
PPBS at enrolment (mg/dl)	187.1 ± 33.4	203.9 ± 19.4
FBS throughout pregnancy(mg/dl)	99.4 ±5.1	100.7 ±4.1
PPBS throughout pregnancy (mg/dl)	143.1 ±5.5	141.9 ±5.9
Gestational age at delivery (weeks)	36.6 ± 1.9	37.5 ± 1.6
Birth weight (kg)	2.8 ± 0.8	3.1 ± 0.6
APGAR score at 5 minutes	7.5 ± 1.5	8.0 ± 0.7
Neonatal Mean blood glucose level at birth (mg/dl)	38.6 ± 8.1	41.8 ± 11.8

The difference between babies according these parameters were statistically not significant.23.1%, 5.8% and 1.9% babies of metformin group and 19.2%, 7.7% and 7.7% of insulin group had neonatal jaundice ,neonatal sepsis and shoulder dystocia respectively and was statistically not significant.

DISCUSSION:

Present study found non-significantly higher mean FBS and mean PPBS among participants of insulin group compare to metformin group at the time of enrolment in the study . But during the progress of study and pregnancy, present study found significantly almost similar mean FBS and lower mean PPBS among participants of insulin group when compared to metformin group.Patients were advised for dietary modifications and nutritional instructions of three meals and three snacks daily with predesigned diets according to body weight. Metformin was started at dose of 500 mg/day orally and increased up to 1500 mg/day as tolerated by the patient and till glycemic control was achieved.If target blood glucose levels were not maintained anytime during treatment, insulin was added as supplementary treatment with metformin. These findings are correlating with to similar study done by Ainuddin JA et al[16].

One stillbirth occurred in metformin group which was a post dated pregnancy with oligohydramnios and meconium stained liquor. IUFD which occurred in Insulin group was due to Gross oligohydraminos. No incidence of congenital malformation were noted among both the groups. GDM, is associated with several short and long term adverse outcomes in both mother and the offspring. First, the presence of GDM always accompanies an increased maternal risk for preeclampsia, cesarean section, and with an increased risk for developing type 2 diabetes (T2DM) after pregnancy.

Present study observed statistically significant higher mean birth weight in insulin group than metformin treated group. These findings correlate with similar study done by Ainuddin JA et al[16], Rowan JA et al[17],but are not comparable with similar study done by Munshi S et al[18]and Syngelaki A et al[19]. It may be due to insulin which has anabolic effect. Hyperglycaemia in the foetus resuts in stimulation of insulin, insulin like growth factors, growth hormone, and other growth factors, which is in turn stimulate foetal growth and deposition of fat and glycogen. Mean 'APGAR score at 5 minutes' was significantly lower among the participants of metformin group when compare to insulin group, similar results were obtained by Syngelaki A et a[19], Ainuddin JA et al[16] , Rowan JA et al[17], and but are not comparable with study done by Munshi S et al[18].Present study observed statistically significant and slightly higher mean blood glucose level at birth in insulin group than metformin group. Same observations were found in similar study done by Ainuddin JA et al[16]. It may be due to Metformin crossing the placenta and its concentrations in the umbilical cord have been found to be comparable with concentrations in the maternal circulation and insulin cannot cross the placenta.Age of the mother, parity, gestational age of enrolment, weight gain during pregnancy, mode of delivery, incidence of polyhydramnios in mother were statistically not significant, similarly in neonate incidence of TTN, RDS, hypoglycaemia, sepsis, shoulder dystocia and jaundice were statistically not significant.

CONCLUSION:

Gestational diabetes continues to be an important etiological factor for maternal and foetal morbidity and mortality. The present randomised control study was conducted with the objective to study the efficacy of insulin over metformin on blood sugar control and to compare maternal and foetal outcomes in patients treated with Metformin and Insulin. Current study concluded that Metformin when compared with Insulin was showing similar efficacy and safety in terms of variables like Fasting and Post Prandial blood glucose control. Blood glucose level control during pregnancy is the prime factor which affects maternal and neonatal outcomes. Thus Metformin is also an optimum treatment for blood glucose control.Metformin significantly reduces the incidence of polyhydramnios, fasting hypoglycaemia, post prandial hyperglycaemia and excessive weight gain during pregnancy. In the foetus, Metformin use was found to have reduced incidence of large for gestational age babies and indirectly preventing its related complications like need for LSCS, occurrence of shoulder dystocia at labour and neonatal hypoglycaemia. Insulin use in Gestational diabetes showed better neonatal outcome in terms of APGAR score and neonatal hypoglycaemia. But comparative efficacy of Insulin to Metformin in terms of post prandial blood glucose control was better, thus reducing the incidence of complications of poor glycaemic control in Gestational diabetes. The above inferences suggest that compared with Insulin, Metformin also can be used as an effective treatment of Gestational Diabetes but efficacy of Insulin is more than Metformin. Further larger trials are needed to confirm.

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