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Association of glycaemic control and maternal outcome in women with gestational diabetes mellitus on anti-diabetic therapy: A prospective observational study

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Abstract
Aim: The aim of the study was to compare the glycemic control and maternal outcome among gestational diabetic women treated with metformin versus insulin.
Methodology: A prospective observational study conducted in the obstetrics and gynecology department of post graduate teaching hospital, after obtaining approval from Institutional Ethics Committee. The diagnosis of the GDM was confirmed by two step approach according to American Diabetes Association (ADA) guidelines. Participants who diagnosed with GDM were given with dietary counselling and advised for moderate physical exercise. Repeated the Fasting Blood Sugar (FBS) and Post Prandial Blood Sugar (PPBS) after two weeks. Those with FBS greater than 120 mg/dl and PPBS greater than 140 mg/dl, were referred to a physician to confirm the diagnosis and to start with appropriate drug treatment.
Result: Among 3972 pregnant ladies visited in the obstetrics and gynecology department during the study period, 286 were diagnosed to have GDM. Out of 286 GDM patients, 140 were treated with insulin and 146 were treated with metformin. The overall result from the study says that metformin was found as effective as insulin in controlling glycemic status in GDM women; also metformin was found to be effective in reducing maternal complications when compare to that of insulin treated group.
Conclusion: The study conclude that metformin is a cost-effective oral hypoglycemic agent, which may be a more logical alternative to insulin for women with GDM.

Keywords: pregnancy, gestation diabetes mellitus, drug therapy, glycemic control, maternal outcome

Introduction
Gestational Diabetes Mellitus (GDM) is a condition in which women without previously diagnosed diabetes exhibit elevated blood sugar level during pregnancy. GDM can be defined as glucose intolerance that begins or is the first recognized during pregnancy [1]. The American Diabetes Association (ADA) defines GDM as the Glucose intolerance of any degree with onset or recognition during pregnancy [2]. Uncontrolled blood sugar complicates about 1-4% of all pregnancies, which may range from mild degree of hyper glycaemia to insulin dependent diabetes. GDM may be caused by reduced pancreatic β cell function, which results from the full spectrum of causes of β cell dysfunction in young women or it may considered as an insulin resistant state, possibly due to the placental production of progesterone, cortisol, prolactin and other hormones which interfere with normal glucose metabolism [3]. Obesity, previous history of GDM, family history of diabetes mellitus, racial origin, increased maternal age, previous macrosomic baby, polycystic ovary syndrome and twin pregnancy are considered as main risk factors for developing gestational diabetes [4]. GDM is one of the most occurring metabolic diseases of pregnancy and the prevalence of GDM is variable depending on the population was being studied and which screening strategies or diagnostic criteria were used. A study conducted in 2013 by the International Diabetes Federation estimated that worldwide 16% of live births were complicated by hyperglycemia during pregnancy [5]. The prevalence of GDM is increasing worldwide with the dramatic increase in the prevalence of overweight and obesity in women of childbearing age. The prevalence of GDM in Indian population varies from 3.8 to 21% in different parts of the country and prevalence in South India has increased dramatically recently to 16% [6]. The high prevalence of GDM in South India may be due to obesity, family history of Diabetes Mellitus, sedentary lifestyle, genetic predisposition and dietary habits.

Untreated hyperglycemia in pregnancy may lead to serious maternal complications such as pregnancy induced hypertension, pre-eclampsia and increased risk of caesarean delivery. Neonatal complication includes macrosomia, neonatal hypoglycemia, perinatal mortality, congenital malformations, hyperbilirubinemia, polycythemia, hypocalcaemia and respiratory distress syndrome. These complications may be reduced either by appropriate diet, mild physical exercise or through proper medication management. Insulin has pivotal role in the management of GDM since many years, due to its efficacy to control elevated blood sugar level [7].

Insulin can be administered according to the pattern of glucose concentration in order to control the rising blood sugar. An initial dose of subcutaneous administration of NPH insulin (4 units) could be used, if the fasting blood glucose concentration is greater than 90 mg/dl, or when the 1-hour postprandial blood glucose concentration is greater than 120 mg/dl and the dose can be titrated on the following visits according to the glycemic status. However, the difficulty in medication administration with multiple daily injections, potential for hypoglycemia, increase in appetite and weight gain make this therapeutic option cumbersome for many pregnant patients [8].

Materials and Methods

A prospective observational study was conducted in the Department of Obstetrics and Gynecology in a super specialty teaching hospital during January 2015 to December 2019. A research proposal was submitted to the Institutional Ethics Committee of MES Medical College Hospital and the study was initiated after IEC approval (No: IEC/MES/51/2014 dated 29-09-2014). The diagnosis of the Gestational Diabetes Mellitus at the time of enrolment was confirmed by two step approach according to American Diabetes Association (ADA) guideline [9]. All pregnant women visited the OBG department during the study period, who satisfied with the inclusion criteria underwent 50gm Glucose Challenge Test (GCT).

If the value was greater than 139mg/dl, then they were send for 75gm Oral Glucose Challenge Test (OGTT).The values of Oral Glucose Challenge Test were considered as normal: 95mg/dl at 0 minutes, 180mg/dl at one hour, 155mg/dl at second hour, 140mg/dl at third hour. If the participant presented 2 or more altered results on OGTT, the diagnosis of GDM was confirmed. Women with GDM were given with counselling and advised for Medical Nutrition Therapy (MNT) along with moderate physical exercise. Then they were repeated the Fasting Blood Sugar (FBS) and Post Prandial Blood Sugar (PPBS) after two weeks. Those with FBS greater than 95 mg/dl and PPBS greater than 120 mg/dl, were referred to a physician to confirm the diagnosis of GDM and to initiate pharmacotherapy [10].

The selection of participant for the study was based on the following,

Inclusion Criteria

- The patients who were diagnosed with Gestational Diabetes Mellitus (GDM) according to the diagnostic criteria recommended by the American Diabetic Association (ADA) guidelines.
- 18-40 years old with singleton pregnancy and gestational age between 20-34 weeks, Who did not maintain fasting blood glucose level less than 95 mg/dl or 2 hour post prandial blood glucose less than 120 mg/dl by medical nutritional therapy during one week.

Exclusion Criteria

- History of underlying diseases like renal, cardiovascular, liver, and autoimmune diseases or other terminal diseases, substance abuse and major malformations.
- Subjects with contraindication to metformin, foetal anomaly, essential hypertension, gestational hypertension, pre-eclampsia, foetal growth restrictions and ruptured membranes, Intra uterine growth retardation, abnormal glucose tolerance before pregnancy, twin pregnancy, treatment initiated before 12 weeks or after 34 weeks of gestation.

The study was explained to each participants and written informed consent in vernacular language was obtained from each participants before enrolment. Demographic and clinical data were collected by patient direct interview and investigational repots were collected from medical records department. The Demographic data includes age, Body weight, height, body mass index, history of Diabetes mellitus, history GDM, number of pregnancies were collected from medical records and by patient direct interview. Baseline values of GCT, OGTT recorded. FBS, PPBS and Hb1Ac were recorded at the starting and end of the study. The maternal variables such as parity, total weight gain during pregnancy, shoulder dystonia, mode of delivery, gestational week at delivery and pre term delivery also were recorded. The collected data from each patient were recorded in data collection form and were entered into an excel sheet. The mean ± SD values of the each variable was calculated. The data were analyzed using appropriate software to find out the statistical significance. Parameters with $P<0.05$ was considered as significant and those with $P<0.01$ was considered as statistically highly significant.

Results and Discussion

Among 3972 pregnant ladies visited the Obstetrics and Gynecology Department during the study period, 286 were diagnosed to have GDM. During the study period, prevalence Gestational Diabetes Mellitus was found to be 7.2% in the study center. Out of 286 GDM patients, 140 were treated with Insulin and 146 were treated with Metformin.

Out of 140 patients in the Insulin Group, 44 were in the age group 20-25 years, 56 were in the age group 26-30 years, 25 were in the age group 31-35 years and 15 were in the age group 36-40 years. Whereas in the Metformin group 61 were in the age group 20-25 years, 71 were in the age group 26-30 years, 9 were in the age group 31-35 years and 5 were in the age group 36-40 years. Based on Body Mass Index (BMI), patients in the insulin group were with ideal body weight, 50 were overweight and 36 were found to be obese. In the Metformin group 36 were with ideal body weight, 91 were overweight and 19 were obese. In the Insulin Group 31 had family history of Diabetes Mellitus; whereas in the Metformin group 19 had family history of Diabetes Mellitus. 60 participants in the insulin group had family history of GDM, whereas in the Metformin group 17 had family history of GDM.

It is observed that all participants in both group achieved the goal of drug therapy. The effect of two drug treatment on FBS, PPBS are given in Table-2 and Table 2 and respectively.

The mean FBS value of insulin group during 24-28 gestational weeks was found to be 122.31 ± 26.14 mg/dl and that of metformin group was 108.99 ± 8.11 mg/dl. The difference in the mean FBS value between two groups was statistically significant ($p<0.001$). In 36 to 38 gestational weeks the mean FBS value in of Insulin group was 90.20 ± 6.37 mg/dl and that Metformin group was 94.68 ± 16.06 mg/dl. The difference in the mean FBS value between two groups was statistically significant ($p<0.001$).

In 24 to 28 gestational weeks the mean PPBS value weeks in Insulin group was 151.80 ± 30.62 mg/dl and PPBS value in Metformin group is 136.21 ± 10.05 mg/dl. The difference in the mean PPBS value between two groups was statistically significant (p<0.001). In 36 to 38 gestational weeks the mean PPBS value weeks in Insulin group was 126.91 ± 33.25 mg/dl and PPBS value in Metformin group was 116.06 ± 9.86 mg/dl. The difference in the mean PPBS value between two groups is statistically significant (p<0.001).

Both drug treatment has shown efficacy in bringing down blood glucose level to normal range, but the Insulin treatment caused a larger decrease in fasting blood sugar level with a 27.63 ± 19.12 mg/dl in Insulin group and 18.80 ± 6.83 mg/dl. The details regarding the change made with drug treatment on fasting blood sugar level is given Table-3. The effect of the drug treatment on the PPBS of participants are given as Table-4. The both drugs found to be effective in bringing the post prandial blood sugar level to normal range. Even though insulin treatment found to be made the decrease in a better way.

The mean weight gain value in Insulin group was 10.04 ± 2.31 kg and mean weight gain value in Metformin group is 8.95 ± 1.65 kg. The difference in the mean weight gain value between two groups is statistically significant (p<0.001). In this study out of 140 patients in the Insulin Group 25 (17.9%) were gestational age less than 37, whereas in the Metformin group 10 were gestational age more than 37. It is statistically significant (p=0.005). In the study, 140 patients in the Insulin Group 29had done Normal delivery, 34 had done assisted delivery and 36 had done LSCS which accounts for 20.7%, 24.3% and 55.0% respectively. Whereas in the Metformin group 70 (47.9%) were Normal, 61 (41.8%) were assisted and 159 (10.3%) were LSCS. It is statistically significant (p<0.001).

Table 1: Fasting blood sugar level (FBS) of Gestational Diabetic Woman in different treatment groups at enrolment and end of the study

Groups	N	FBS(mg/dl)			Mann Whitney U Value	p Value
		Mean	SD	Median (IQR)		
24-28 weeks (at enrolment)						
Insulin	140	122.31	26.14	113 (105-124)	6257	<0.001
Metformin	146	108.99	8.11	105 (104-112)		
36-38 weeks (end of the treatment)						
Insulin	140	90.20	6.37	90 (88-95)	9530	<0.001
Metformin	146	94.68	16.06	90 (87-98)		

Table 2: Post Prandial blood sugar level (PPBS) of Gestational Diabetic Woman in different treatment groups at enrolment and end of the study

Groups	N	PPBS(mg/dl)			Mann Whitney U Value	p Value
		Mean	SD	Median (IQR)		
24-28 weeks(at enrolment)						
Insulin	140	151.80	30.62	144 (135-150)	4471	<0.001
Metformin	146	136.21	10.05	135 (130-140)		
36-38 weeks (end of the treatment)						
Insulin	140	116.06	9.86	115 (110-120)	8326	<0.001
Metformin	146	126.91	33.25	118 (112-124)		

Table 3: The Difference in fasting blood sugar level of different treatment groups from baseline to end of the study

Groups	N	Change in FBS(mg/dl)			Mann Whitney U Value	p Value
		Mean	SD	Median (IQR)		
Insulin	140	27.63	19.12	25 (34.0-18.0)	5282	<0.001
Metformin	146	18.80	6.83	16 (25.0-15.0)		

Table 4: The effect of the drug treatment on the PPBS of participants

Groups	N	PPBS: Difference from baseline to end of the study			Mann Whitney U Value	p Value
		Mean	SD	Median (IQR)		
Insulin	140	24.89	34.94	28 (35.0-18.0)	7090	<0.001
Metformin	146	20.14	9.14	20 (25.0-15.0)		

Table 5: Comparison of Weight Gain values in Gestational Diabetic Woman treated with Metformin versus Insulin

Groups	N	Weight Gain during gestation in kg			Man Whitney U Value	p Value
		Mean	SD	Median (IQR)		
Insulin	140	10.04	2.31	9 (8-9)	7472	<0.001
Metformin	146	8.95	1.65	9 (7-10)		

Table 6: Effect of drug treatment on gestational age of GDM women

Gestational Age	Groups				$\chi 2$ Value	p Value
	Insulin		Metformin			
	n=140	%	n=146	%		
< 37	25	17.9	10	6.8	8.063	0.005
≥ 37	115	82.1	136	93.2		

Table 7: Effect of drug treatment on mode of delivery

Mode of Delivery	Groups				$\chi 2$ Value	p Value
	Insulin		Metformin			
	n=140	%	n=146	%		
Normal	29	20.7	70	47.9	66.339	<0.001
Assisted	34	24.3	61	41.8		
LSCS	77	55.0	15	10.3		

Conclusion

The overall result from the study says that Metformin was found as effective as Insulin in maintaining normal glycemic status in GDM woman. Metformin was found to be effective in reducing maternal complications when compare to that of Insulin treated group. Also the affordable cost and convenience of oral administration make Metformin more patient friendly and thus to increase adherence with drug therapy can bring better patient compliance. There for Metformin may be prescribed for pregnant women with Gestational Diabetes Mellitus in order to bring down the elevated blood glucose level to normal range so that the further complications of GDM can be minimized.

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