



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

Research Article

January 2021 Vol.:20, Issue:2

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Efficacy of Metformin among Subjects Diagnosed with Gestational Diabetes Mellitus



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals



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Submitted: 05 December 2020
Revised: 26 December 2020
Accepted: 16 January 2021

Keywords: Gestation Diabetes Mellitus; Glycaemic control in Pregnancy; Metformin, Insulin

ABSTRACT

Gestational Diabetes Mellitus (GDM) refers to the unrecognized glucose intolerance, antedated or begun concomitantly with pregnancy. Indian women are considered to be the high risk population for developing Diabetes Mellitus during pregnancy. The prevalence of GDM is increasing worldwide with the dramatic increase in the prevalence of overweight and obesity in women of childbearing age. Poorly controlled blood sugar level in pregnant woman results in maternal and fetal morbidity and mortality. Diet, obesity, family history, and ethnicity are the important risk factors for the development of GDM. Improved outcome rely on early diagnosis and tight glycaemic control. However, management of diabetes in pregnancy remains controversial with conflicting guidelines. All antenatal pregnant women with 24-28 weeks of pregnancy attending the Obstetrics and Gynecology Department of a tertiary care referral hospital in South India based on inclusion and exclusion criteria were included in the study. The diagnosis of GDM was made confirmed according to the criteria recommended by the American Diabetes Association (ADA) guidelines. The results obtained from the study proved the effectiveness of Metformin in controlling elevated blood sugar level in GDM. It also found that Metformin caused significantly less weight gain during the pregnancy when compared with Insulin therapy.



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INTRODUCTION

Gestation Diabetes Mellitus (GDM) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy.^[1] It is defined by the American Diabetes Association (ADA) as the Glucose intolerance of any degree with onset or recognition during pregnancy.^[2] The prevalence of GDM is variable depending on the population was being studied and which screening strategies or diagnostic criteria were.^[3] As per the protocol of antenatal care, each woman usually undergo detailed clinical examination and fasting blood sugar test during the 24-28 weeks of gestation. A recent report from the International Diabetes Federation estimated that worldwide 16% of live births were complicated by hyperglycemia during pregnancy.^[4] 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% .^[5] Obesity, previous history of Pregnancy induced Diabetes Mellitus, family history of Diabetes Mellitus, ethnicity, increased maternal age, previous macrosomic baby, polycystic ovary syndrome and twin pregnancy are considered as main risk factors for developing gestational diabetes.^[6] Untreated hyperglycemia in pregnancy may lead to serious maternal complications including pregnancy induced hypertension, pre-eclampsia, increased risk caesarean delivery.^[7] Neonatal complication includes macrosomia, neonatal hypoglycemia, perinatal mortality, congenital malformations, hyperbilirubinemia, polycythemia, hypocalcemia and respiratory distress syndrome. These complications may be reduced either by appropriate diet, mild physical exercise or through proper medication management.^[8]

Subcutaneous Insulin administration is the standard treatment for achieving adequate glucose level in pregnancy induced diabetes which is not controlled by diet modification.^[9] 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. Also, insulin preparations are seemed to be costly for economically poor patients. Use of oral hypoglycemic agents in pregnancy has opened new vistas for management of Diabetes during pregnancy.^[10] Oral hypoglycemic agents falling in Insulin sensitizers group are the considerable alternative in treatment, since they are free from hypoglycemia, weight gain and are cost effective also. Metformin is such an oral biguanide may be a more logical alternative to Insulin for women with GDM who are unable to cope with the adverse effects of Insulin. Metformin is the most widely prescribed oral agent for the treatment of Diabetes Mellitus. It reduce the blood glucose level by inhibiting

gluconeogenesis and also reduce insulin resistance, particularly in liver and musco-skeletal tissue.^[11]

Intestinal absorption of glucose and increased insulin sensitivity is enhanced by glucose uptake and utilization in peripheral tissues. Metformin improves glucose tolerance in diabetic patients, by lowering both basal and post-prandial blood sugar level. Additionally, Metformin does not cause a stimulation of insulin secretion and subsequently does not cause event of hypoglycemia and thereby is associated with weight loss when used in treatment of Diabetes Mellitus.^[12] Metformin consistently reduces HbA1c levels by 1.5% to 2%, fasting plasma glucose levels by 60 to 80 mg/dl and retains the ability to reduce fasting plasma glucose levels when they are extremely high (> 300 mg/dl). Metformin tablets are available all over the world in 500 mg, 850 mg and 1000 mg strengths and its extended release tablets of 500mg, 750 mg and 1000 mg strengths.^[13] Oral bioavailability of Metformin is approximately 50% to 60%. Food decreases the extent of Metformin absorption and sometimes slightly delays. Metformin is excreted unchanged in the urine through renal tubular secretion and glomerular filtration. The average half-life of Metformin is 6 hours though pharmacodynamically its anti-hyperglycemic effects last > 24 hours.^[14] About 1% – 30 % of patients taking Metformin may be affected with GI side effects like nausea, diarrhea, bloating and metallic taste in the palate.^[14] Taking Metformin with meals can help reduce these side effects. Long term use of Metformin has been associated with increased homocysteine levels and malabsorption of Vitamin B12. Even though Metformin crosses the placenta, it is not associated with teratogenicity.^[15] Several studies revealed the therapeutic use of Metformin is beneficial in maintaining blood sugar level in normal range; also as safe as insulin in the pharmacological management of gestational diabetes. The children of gestational diabetic women treated with Metformin are healthier in the neonatal period than that of Insulin treated.^[16] The main objective of the study was to explore the antidiabetic activity of Metformin among subjects diagnosed with GDM.

METHODOLOGY

This was a prospective observational study conducted in Obstetrics and Gynecology Department of a tertiary care referral hospital in South India. The study was initiated after obtaining the approval of proposal submitted to Institutional Ethics Committee (IEC). Women with 24-28 weeks of gestation, attending OBG department for antenatal care were considered for the study after detailed clinical examination and fasting blood sugar test. The

diagnosis of the GDM at the time of the study was established by two step approach according to American Diabetes Association (ADA) guidelines. Pregnant women visiting department of Gynecology and Obstetrics who satisfies the inclusion criteria underwent 50gm Glucose Challenge Test (GCT). If the value is greater than 139mg/dl, then they were for 75gm Oral Glucose Challenge Test (OGTT). Values of OGTT are considered normal were as follows: 95mg/dl at 0 minutes, 180mg/dl at one hour, 155mg/dl at second hour, 140mg/dl at third hour. When the patient presented 2 or more altered results on OGTT those were referred to a physician to start the appropriate treatment. Subjects with previous history of Diabetes Mellitus were excluded from the study. All the subjects were enrolled after obtaining written informed consent in vernacular language. Demographic and clinical data were collected during enrolment by patient direct interview and investigational reports were collected from medical records department. In this study 140 study subjects were treated with Insulin and 146 were with Metformin and they were followed up until delivery. The goal of the treatment was to achieve a mean glucose concentration of 90 to 105 mg/dl. Collected data were entered in Excel sheet and statistical analysis was carried out to explore the aim and objective of the study. All the parameters used in the study were expressed in Mean \pm Standard Deviation (SD) and comparison of two drug treatment was statistically analyzed by using Student's t-test using SPSS software.

RESULTS

During the study period, among pregnant women attended and diagnosed with GDM, 140 patients were treated with Insulin and 146 treated with Metformin. All the values are expressed in Mean \pm Standard Deviation (SD). The student's t-test was performed to compare the parameters between Metformin group and Insulin treatment groups. Table 1 explains the distribution of Body weight, Height, BMI and weight gain between the groups. The result shows the mean \pm SD of Body Mass Index is 26.287 ± 2.791 in Metformin group and 27.169 ± 3.906 in Insulin treatment. It says that the significance in Body Mass Index between two treatment is found to be statistically significant ($p < 0.05$). Interestingly the mean \pm SD of Body weight gain is 8.952 ± 1.65 in Metformin group and 10.043 ± 2.31 in Insulin treatment and shows high significance between two treatment groups ($p < 0.01$). A histogram of Body weight, height, Body Mass Index and weight gain is plotted in Figure 1.

Table No. 1: Distribution of Body weight, Height, BMI and weight Gain between the Groups

Parameters	Metformin (n=146)	Insulin (n=140)	t	p
Body Weight (Kg)	64.219 ± 7.176	65.957 ± 8.85	-1.828	0.069
Height (m)	1.562 ± 0.043	1.558 ± 0.049	0.589	0.556
BMI (Kg/m ²)	26.287 ± 2.791	27.169 ± 3.906	-2.203	<0.05*
Weight Gain (Kg)	8.952 ± 1.65	10.043 ± 2.31	-4.610	<0.01**

All Values are mean ± standard Deviation. n=Total Number of subjects.

Statistical test used t test. *Significant at <0.05 and ** Highly Significant at <0.01

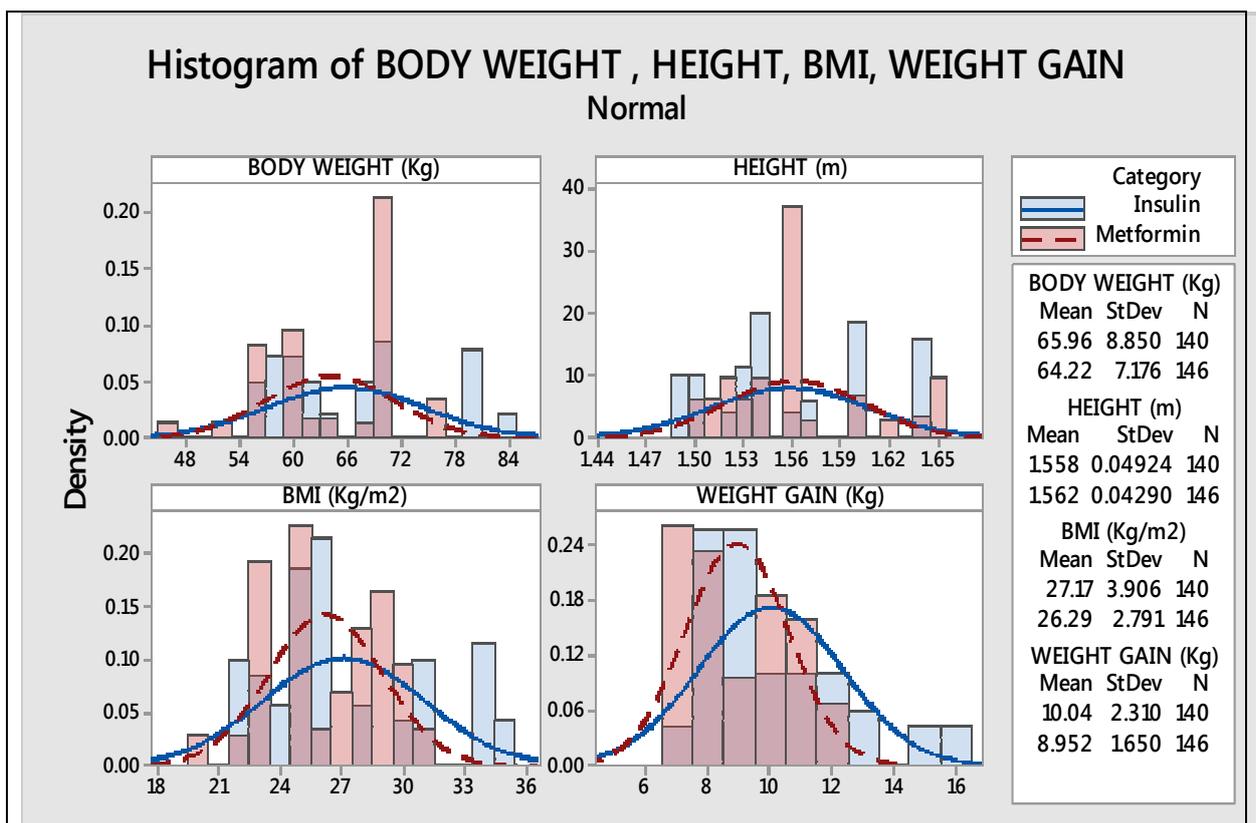


Figure No. 1: Distribution of Body weight, Height, BMI and weight Gain between the Groups

Distributions of GCT at diagnosis and OGTT Fasting, 1st, 2nd and 3rd Hour between the Groups are given in Table 2. The result shows the mean ± SD of GCT at diagnosis is 157.9 ±

17.255 in Metformin group and 166.54 ± 35.223 in Insulin treatment shows the difference is significant ($p < 0.01$). The mean \pm SD of OGTT fasting is 108.295 ± 15.695 in Metformin group and 105.814 ± 19.2827 in Insulin treatment and the difference is found be not significant. The mean \pm SD of OGTT in 1st hour is 195.95 ± 18 in Metformin group and 105.814 ± 19.2827 in Insulin treatment and the difference is found be significant ($p < 0.01$). The mean \pm SD of OGTT 2nd hour is 164.18 ± 13.298 in Metformin group and 172.82 ± 42.177 in Insulin treatment and the difference is found be significant ($p < 0.05$). The mean \pm SD of OGTT 3rd Hour 101.42 ± 12.331 in Metformin group and 124.46 ± 33.07 in Insulin treatment and the difference is found be highly significant ($p < 0.01$). A histogram of GCT at diagnosis and OGTT Fasting, 1st, 2nd and 3rd Hour between the Groups is presented in Figure 2.

Table No. 2: Distribution of GCT at diagnosis and OGTT between the Groups				
Parameters	Metformin (n=146)	Insulin (n=140)	t	p
GCT at Diagnosis (mg/dl)	157.9 ± 17.255	166.54 ± 35.223	-2.648	<0.01**
OGTT Fasting (mg/dl)	108.295 ± 15.695	105.814 ± 19.2827	1.195	0.233
OGTT 1 st Hour (mg/dl)	195.95 ± 18.1	206.26 ± 35.98	-3.08	<0.01**
OGTT 2 nd Hour (mg/dl)	164.18 ± 13.298	172.82 ± 42.177	-2.355	<0.05*
OGTT 3 rd Hour (mg/dl)	101.42 ± 12.331	124.46 ± 33.071	-7.865	<0.01**
All Values are mean \pm standard Deviation. n=Total Number of subjects. Statistical test used t test. *Significant at <0.05 and ** Highly Significant at <0.01				

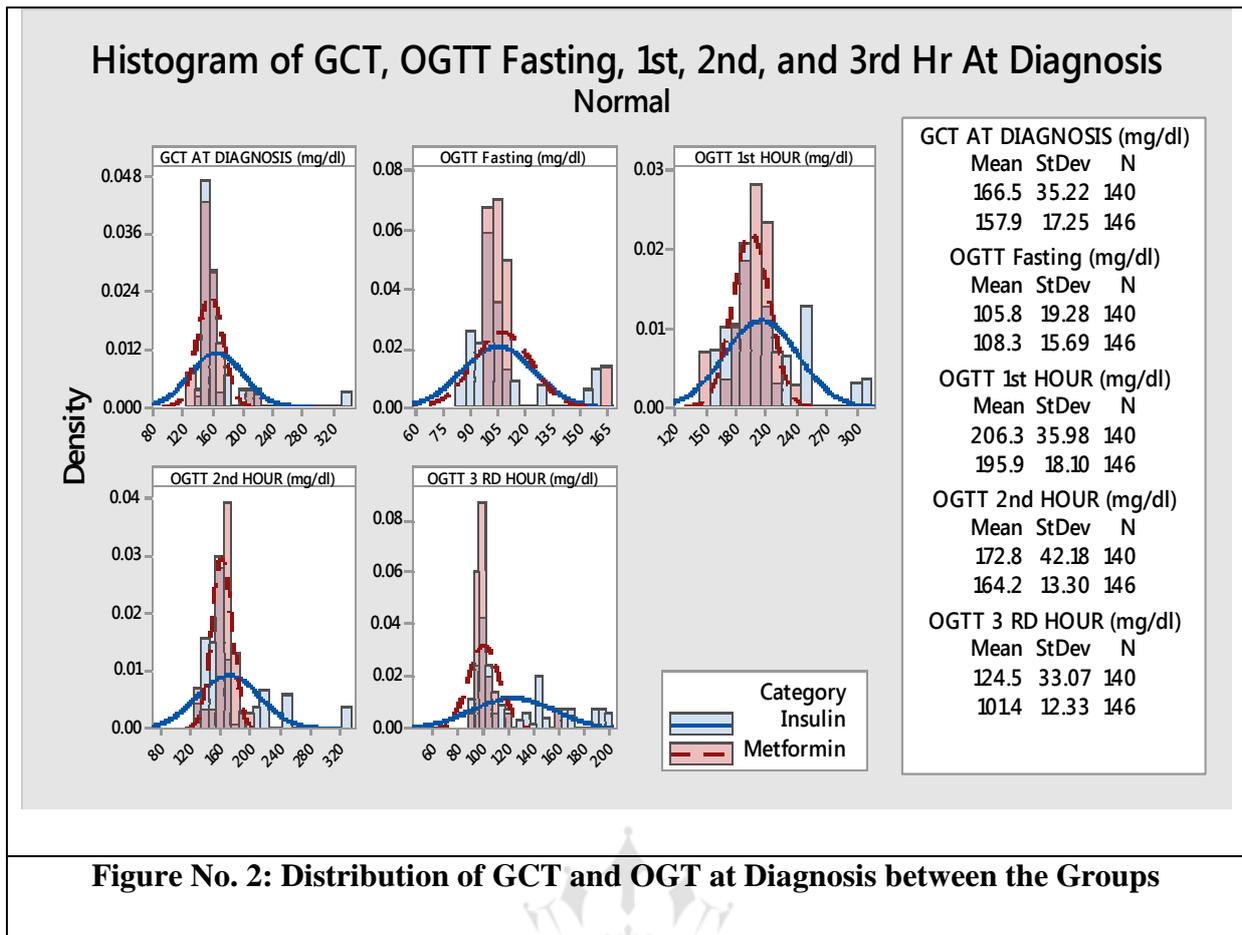


Figure No. 2: Distribution of GCT and OGT at Diagnosis between the Groups

Distributions of Fasting Blood Sugar at enrolment and at 36th Week between the groups are given in Table 3. The result shows the mean \pm SD of FBS at Enrolment is 109.05 ± 8.078 in Metformin group and 122.31 ± 26.14 in Insulin treatment and the mean \pm SD of FBS at 36 Weeks is 90.2 ± 6.368 in Metformin group and 94.68 ± 16.062 in Insulin treatment and the difference is found to be highly significant ($p < 0.01$). A histogram of FBS at enrolment and FBS at 36 Weeks between the groups is presented in Figure 3.

Table No. 3: Distribution of Fasting Blood Glucose/Sugar at enrolment and at 36th Week between the Groups

Parameters	Metformin (n=146)	Insulin (n=140)	t	p
FBS at Enrolment (mg/dl)	109.05 ± 8.078	122.31 ± 26.14	-5.843	<0.01**
FBS at 36 Weeks (mg/dl)	90.2 ± 6.368	94.68 ± 16.062	-3.124	<0.01**

All Values are mean \pm standard Deviation. n=Total Number of subjects.

Statistical test used t test. ** Significant at <0.01.

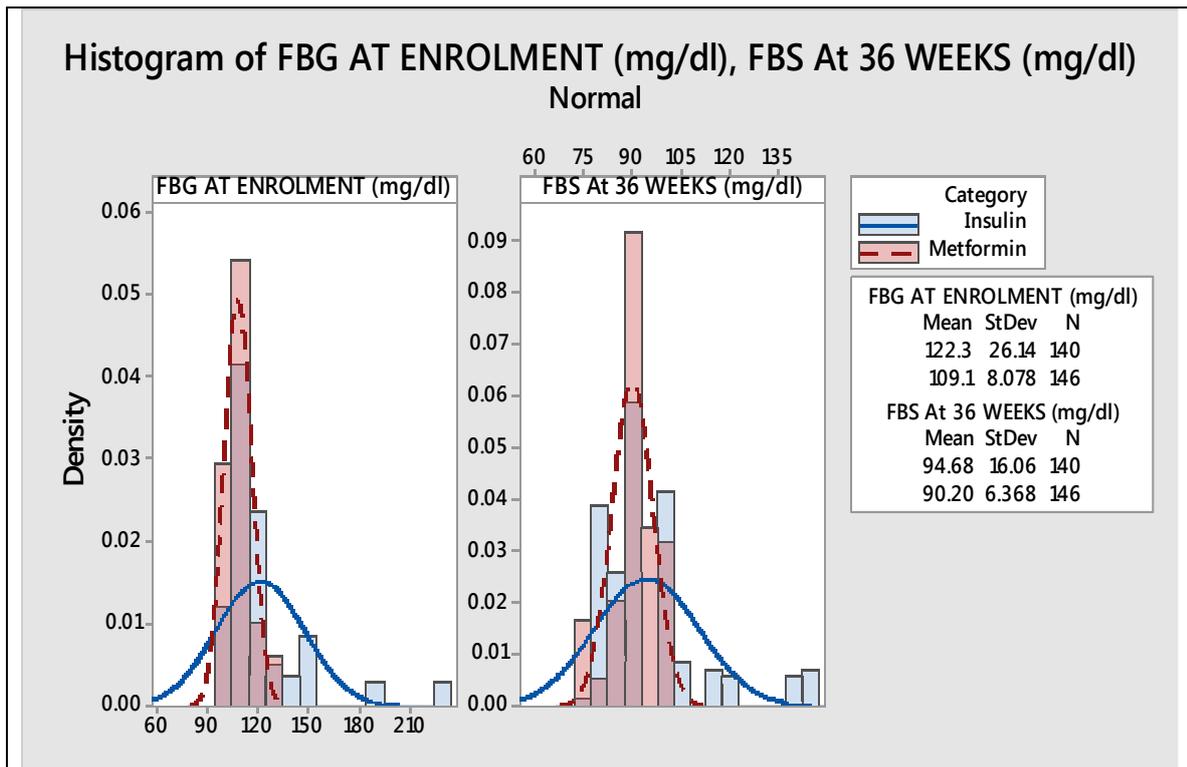


Figure No. 3: Distribution of Fasting Blood Sugar at enrolment and at 36th Week between the Groups

DISCUSSION

Metformin is an acceptable treatment option in management of type 2 Diabetes Mellitus worldwide. It is used as a first line agent in dietetic of any age group, and is really interesting to learn its ability to body weight as well as fasting blood sugar level. In Gestational diabetes Mellitus, the problem with insulin treatment observed is it might cause troublesome hypoglycemia; also the increased fetal weight could lead to increased rate of Cesarean section. The increased birth weight and neonatal hypoglycemia are considered to be the predicting tool of future development of Type 2 Diabetes Mellitus in future. Also, both Metformin and Insulin treatment was found to effective in reducing blood sugar level to normal range. The overall result obtained from this study points that Metformin caused less weight gain during pregnancy period; that means insulin resistance is at minimum level in diabetic pregnant woman treated with Metformin. The health condition of pregnant woman will definitely reflect the health of the health of child also. The unique quality of Metformin in reducing blood sugar level with minimal weight gain will make a positive trend in the use of metformin in pharmacotherapy of GDM.

CONCLUSION

The study points that Metformin is as effective as Insulin in blood sugar control of Gestational Diabetes Mellitus. Apart from the excellent control on blood sugar, Metformin caused less weight gain during the entire study period. Result from this study suggests that Metformin can be considered as a safe and effective alternative to Insulin therapy in medical management of Gestational Diabetes Mellitus.

ACKNOWLEDGEMENT

We would like to express our sincere thanks and deep gratitude to Central research Laboratory, MES Academy of Medical Sciences, Perinthalmanna, Kerala for providing their infrastructure and their co-operation during this study.

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