ORIGINAL ARTICLE

Comparing effectiveness of metformin versus insulin in gestational diabetes mellitus

Khadija Bano, Shazia Naseeb, Shereen Zulfiqar Bhutta

Abstract

Objectives: To determine if metformin compared to Insulin is a safe and effective treatment option in the management of gestational diabetes mellitus.

Study Design: Randomized open label controlled trial

Study Setting: Department of gynecology and obstetrics, Ward 9(Unit II), Karachi, Pakistan

Duration of study: Six months (11th September 2012 till 10th March 2013)

Subject and methods: A total of 134 women with GDM diagnosed on single fasting blood sugar followed by confirmation by oral glucose tolerance test (OGTT) were included in the study. Patients were randomly allocated to two groups. 76 patients assigned each to Insulin and Metformin group. Demographic and clinical data were recorded at enrollment followed by OGTT. Informed consent was obtained . Effectiveness was seen in terms of maternal hyperglycemia (Fasting blood sugar>- 100mg/dl of Postprandial >-126 mg/dl), Gestational hypertension Blood pressure (BP > 140/90 mg /dl without proteinuria), preeclampsia (BP >- 140/90mg/dl with proteinuria of > 0.3mg/24 hours), preterm labor (28-less than 37 weeks gestation), polyhydramnios (AFI > 5), and mode of delivery. Neonataloutcome in terms of macrosomia (4000mg), Apgar score at 5 minand hypoglycemia at birth.

Results: Effectiveness of metformin treatment was 67.7% and insulin 70.1%, the difference was not significant (p-value=0.71)

Conclusion: We conclude that metformin and Insulin are equally effective and metformin is not associated with increased risk of maternal and neonatal complications.

Key Words: gestational diabetes mellitus, insulin, metformin

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Jinnah Postgraduate Medical Centre, Rafiqui Shaheed Road, Karachi.
K Bano
S Naseeb
SZ Bhutta

Correspondence:
Dr. Khadija Bano
Department Of Gynecology and Obstetrics, Ward 9 (Unit II), JPMC Karachi, Pakistan.
email:jpmc622003@yahoo.com
Cell: 0323-2277745
Tel: 021-99201300

Introduction:

Gestational diabetes mellitus (GDM) is characterized by hyperglycemia of varying severity diagnosed during pregnancy and usually, but not always, resolving within six weeks of delivery[1]. It is estimated that 3-10% of pregnancies are complicated by diabetes mellitus. Pakistan is a high prevalent area for diabetes with emerging obesity and increased insulin resistance[2]. Genetic variations exist and study on one population may not be applicable to another.The differences in screening programs and diagnostic criteria have made comparison frequencies of GDM difficult among various populations[3]. It is associatedwith complications to the pregnancy and a long term risk of diabetes in both the mother and neonate. The presence of GDM accompanies risk of preeclampsia, cesarean- section and increased risk of developing Type-II diabetes mellitus after pregnancy[4]. In addition there is increased risk of intrauterine death, still birth and congenital anomalies. Another major complication is macrosomia due to glucose transfer from mother to fetus resulting in problems at delivery like shoulder dystocia, instrumental delivery and cesarean-section and neonatal hypoglycemia at birth[5]. Interventions to change life style and useof insulin remains mainstay of treatment of GDM[6]. However, concerns of hypoglycemia, frequent pricks, weight gain, a high cost and storage problem requires to look for an alternative[7]. Oral hypoglycemic like metformin was found to be effective replacement of insulin and had almost similar efficacy in controlling hyper-

glycemia as insulin. Besides oral metformin improves insulin sensitivity probably by activating AMP kinase and is not associated with weight gain or hypoglycemia[8]. The role of metformin in a low-middle income country like Pakistan cannot be underscored. Unlike insulin, Metformin does not require refrigeration. Frequent power outage also hinders its storage and use. In addition, compliance to frequent injections may be low. In Gestational diabetes (MiG), the largest clinical trial conducted so far in this respect provide further evidence regarding the safety of metformin in pregnancy[9].

Since limited data are available at local level, this study would help guide to optimum choice of treatment which would be cost effective and easy to take. Thus raising compliance and better feto-maternal outcome.

Material and Methods:

This Study was carried out in department of Obstetrics and Gynaecology ward (ward-9), Unit-II, JPMC, Karachi. Duration of study: Six months (11th September 2012 to 10th march 2013). This study was randomized control trial. Sampling technique was Non probability consecutive.

Sample was selected following the underlying criteria. Our inclusion criteria is following:

•age ranging from 18 to 40 years of age

•GDM diagnosed for GDM according to International association diabetes study group (IADPSG criteria : Fasting blood sugar ≥ 120mg/dl or RBS ≥ 126mg/dl followed by confirmation through oral glucose test (OGTT) with (75 gm glucose load).

Single fetus between 24 and 33 weeks of gestational age confirmed by history, clinical exam and dating ultrasound

Our exclusion criteria was as following:

Known case of insulin dependent diabetes mellitus (IDDM), strong family history of diabetes mellitus, a contraindication to metformin, Known case of severe PIH, Pre-eclampsia, fetal anomaly or fetal growth restriction, ruptured membranes

Data Collection Procedure:

Patients presenting in the antenatal clinic, were included in the study after inclusion criteria has been met. Informed consent was taken. Demographic and clinical data were recorded at enrollment followed by OGTT. Patients were randomly allocated in two groups. Blinding was not possible because of different routes of administration. Patients were advised for dietary modification and nutritional instructions of three meals and three snacks daily with predesigned diets according to body weight. Metfformin (Glucophage) (Merck, Pakistan) was started at a dose of 500 mg/day orally up to 1500 mg in divided doses as tolerated by patients and till glycemic control was achieved.

Insulin (Humulin N (Lilly) was prescribed as a combination of short acting and intermediate acting as twice daily injections before breakfast and before dinner for the cover up of three meals and three snacks a day or as multiple injections of short acting insulin before meals and intermediate acting insulin at bed time depending on individual patient requirement to achieve glycemic control. Dose of insulin was calculated according body weight and gestational age. Both the groups were treated for three days. They were taught self, blood glucose monitoring using home glucose monitors and were advised to maintain a written record of the levels. Those meeting the criteria were discharged. Both groups were followed up in the OPD with report of fasting andpostprandial blood sugars fortnightly. Patient compliance with treatment was checked by history of symptoms, clinical examination and the blood sugar levels. If blood glucose levels were notachieved in the first follow up, patients were readmitted and revaluated thoroughly. Patients in metformin group, if not achieving normal glycemic levels despite readmission or those developing adverse symptoms like pre-eclampsia were taken off from metformin and were shifted to insulin. Performa was filled with relevant information.

Statistical Analysis:

All collected data were entered into SPSS version 16.0. Data on continuous variables e.g.

age of mother, weight, gestational age in weeks, werepresented as Mean ± SD and data on categorical variables e.g. gravida, parity, mode of delivery, maternal and baby outcome as well as effectiveness was calculated as frequency and percentage.

Comparison of effectiveness between the two treatment groups, chi-square test was applied. Stratification was executed to control the effect of age, parity, diabetic family history of GDM in previous pregnancy. In all statistical analysis p-value ≤0.05 was considered as significant.

Results:

The effectiveness of metformin treatment versus insulin was not statistically significant (p-value = 0.71). The average age of woman in the study was (30.09 ± 8.05yrs). The average age, weight, gestational age (in weeks) and GDM diagnosed at weeks were comparable. (Table 1) Maternal outcome with respect to treatment is shown in (Table 2) Preeclampsia was significantly less in metformin treated group (p-value =0.0023). There was no significant difference in modes of delivery (p-value=0.244), preterm labor (p-value=0.701) and polyhydramnios (p-value=0.071). (Table-3) Birth weights more than 4 Kg were more in the Insulin group (p-value=0.036). There was no significant difference in Apgar scores (1.000) and neonatal hypoglycemia (0.745). There were no perinatal deaths in either group.

Discussion:

This study was conducted in a setting where patients presenting belonged to low socioeconomic background and high prevalence of diabetes.

In the current study, out of 134 patients t metformin treatment was effective in 67.7% and insulin was 70.1%.This difference was not significant (P = 0.71). Patients enrolled for study were between 24-33 weeks with a viable fetus. Mean gestational age at delivery was the same, around 37 weeks. No statistical difference was observed between the rates of vaginal deliveries and cesarean-section (P value= 0.244)[10]. This is consistent to other studies[11]. A study by Jehan Ara et al showed cesarean section rate was much lower in metformin treated patients[12].

The results of our study showed statistical difference between rates of hypertensive complications 16% in the metformin group as compared to 33% in insulin group consistent to study by Hellmuth et al in metformin treated patients[13,14]. However other studies showed no significant difference in rates of hypertensive complications[15,16]. Premature labour occurs in approximately 20% of diabetic pregnancies[17]. A study at Jinnah hospital, Lahore reported 38% of diabet-

Table 1: *Comparison of Maternal Characteristics between groups*

Variables	Group A n=67		Group B n=67		P-Values
	Mean	Std. Deviation	Mean	Std. Deviation	
Age (Years)	30.18	7.91	30	8.25	0.89
Weight (kg)	68.54	5.35	69.39	5.59	0.37
Gestational Age (Weeks)	37.63	1.26	37.64	1.41	0.94
GDM diagnosed at gestational age (weeks)	27.97	2.98	28.3	3.06	0.53

Table 2: *Maternal Outcome between groups*

Variables	Insulin (n=67)	Metformin (n=67)	Total (n=134)	
Mode of Delivery				
Normal Vaginal Delivery	36 (53.7%)	37 (55.2%)	73 (54.5%)	
Assisted Delivery	11 (16.4.7%)	05 (7.5%)	16 (11.9%)	
Caesarian Section	20 (29.9%)	25 (37.3%)	45 (33.6%)	0.244
Gestational Hypertension				
Yes	40 (59.7%)	22 (32.8%)	62 (46.3%)	
No	27 (40.3%)	45 (67.2%)	72 (53.7%)	0.0018
Pre-eclampsia				
Yes	33 (49.3%)	16 (23.9%)	49 (36.6%)	
No	34 (50.7%)	51 (76.1%)	85 (63.4%)	0.0023
Preterm labor				
Yes	20 (29.9%)	18 (26.9%)	38 (28.4%)	
No	47 (70.1%)	49 (73.1%)	96 (71.6%)	0.701
Polyhydramnios				
Yes	21 (31.3%)	12 (17.9%)	33 (24.6%)	
No	46(68.7%)	55 (82.1%)	101 (75.4%)	0.071

Table 3: *Neonatal Outcome between groups*

Variables	Insulin (n=67)	Metformin (n=67)	Total (n=134)	P value
Birth Weight				
< 4000gm	32 (47.8%)	44 (65.7%)	76 (56.7%)	
> 4000gm	35 (52.2%)	23 (34.2%)	58 (43.3%)	0.036
Apgar Score at 5 Minutes				
< 7	14 (20.9%)	14 (20.9%)	28 (20.9%)	
> 7	53 (79.1%)	53 (79.1%)	58 (43.3%)	1.000
Hypoglycemic				
Yes	9 (13.4%)	12 (12.9%)	21 (15.7%)	
No	58 (86.6%)	55 (82.1%)	113 (84.3%)	0.745

ic pregnancies ended up in premature labour[18].

The association of polyhydramnios with diabetes is a common complication with reported incidence of 3-32%. This reason of preterm delivery may be because of this association and patients belonging to low socioeconomic class. However, no significant difference was observed in our study in preterm delivery (P value =0.701) and polyhydramnios(P value = 0.071). This is consistent to other studies19.In the Metformin Gestational Diabetes (MIG) trial thelargest study so far conducted, preterm birth was found to be increased in the metformin group but the cause of preterm birth was not documented[9].

There was no difference in neonatal composite endpoint like Apgarscore, NICUadmission. No perinatal death occurred partly because congenital anomalies were excluded.in this study, 52.2% of babies born in the insulin group had higher mean birth weight > 4Kg as compared to the metformin group 34.2 %, comparable to study by Shirin, Nironmanesh[20]. This may be because of better glycemic control in the metformin group. The frequency of neonatal hypoglycemia in the insulin treated group 13.4% and in the group treated with metformin12.9% was not statistically significant. This percentage is similar to that reported by Coetzee and Jackson (28.6 %)[21] but differs to rates reported by Rowen et al (46.3%) Teri et al (18%)[22] and Moore et al (34.7%)23. The published results of hyperglycemia and adverse pregnancy outcome (HAPO) study showed strong continuous association between hyperglycemia and excessive size at birth24. In our study, despite of having similar rates of hyperglycemia and utilizing similar definitions of macrosomia, the macrosomia rate was lower. This probably can be explained by differences in genetic and metabolic factors affecting fetal growth.

Limitations of the study was that this was a single center study and like all single Centre trials, the results cannot be widely generalized. Since data was collected only for six months and there has been no long term follow up large randomized control studies are required to fully evaluate short and long term effects of metformin therapy.

Conclusions:

The findings of this study suggest that metformin is equally effective in achieving glycemic targets I the management of diabetes in pregnancy. However large sample size randomized control studies are required to fully evaluate short and long term effects of metformin therapy.

Conflict of Interest: None

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