ORIGINAL ARTICLE

Comparison of Metformin and Insulin for Management of Gestational Diabetes Mellitus: A Randomized Control Trial

TAYYIBA WASIM[1], SHYSTA SHAUKAT[2], LUBNA JAVAID[3], SAIMA MUKHTAR[4], WASIM AMER[5]
[1]*Professor of Obstetrics & Gynaecology, Services Institute Of Medical Sciences, Lahore*
[2,3,4]*Services Institute Of Medical Sciences, Lahore*
[4]*Professor Medicine Lahore Medical & Dental College, Lahore*
Correspondence to Dr. Tayyiba Wasim Email: tayyibawasim@yahoo.com Cell: 0300-8400197

ABSTRACT

Aim: To compare maternal and fetal outcome of metformin and insulin in pregnant women with gestational diabetes mellitus.
Methods: A total of 278 pregnant patients fulfilling the eligibility criteria were randomized to therapy with insulin or metformin in this open labelled randomized control study. They were followed through pregnancy till 7 days' post-partum and fetomaternal outcomes were studied.
Results: Patients were comparable in maternal characteristics. 34(24.8%) patients in metformin group required additional insulin. Majority of patients tolerated metformin well in mean dose of 1500mg and intolerance to metformin in form of nausea, vomiting occurred in 4 women (2.8%). Mean age of delivery was 37.5±1.0 and 37.6±1.0 in both groups. Maternal glycemic control was significantly better with metformin ($p<0.05$). There was no significant difference in maternal outcomes of pre-eclampsia (12.4%vs19.8% p=0.092), maternal hypoglycemia (4.3%vs13.4% p=0.166), preterm delivery (9.2%vs 14.5% p=0.226) and operative delivery (55.4%vs65.9% p=0.073) in metformin and insulin group respectively. Most of babies were born with good APGAR score (8.2±0.1 vs 8.1±0.98; p=0.445) with average comparable birth weight of 3.0±1.0 kg vs 3.1±1.0 kg in both groups. Neonatal hypoglycemia, macrosomia and NICU admissions was significantly less in patients on metformin($p<0.05$). There was 1 perinatal death in metformin group against 3 in insulin group.
Conclusion: Metformin is associated with better maternal glycemic control and significantly lesser neonatal complications as compared to insulin in patients with gestational diabetes mellitus.
Keywords: GDM, metformin, insulin, glycemic control, maternal and fetal outcome

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the commonest medical disorders complicating pregnancy. Global prevalence is reported to be 16.9%with South Asian region showing prevalence of 25% versus 10.4% in North America & Caribbean[1]. Known risk factors for gestational diabetes include family history of diabetes, obesity, advanced maternal age and south Asian ethnicity[2].

Hyperglycemia and adverse pregnancy outcome (HAPO) study has shown that hyperglycemia in pregnancy is associated with poor fetomaternal outcome in terms of development of preeclampsia, polyhydramnios, macrosomia, increased operative delivery and neonatal morbidity of hypoglycemia, respiratory distress and NICU admission[3].GDM also poses increased risk of developing type-2 DM in later life both in the mother and the offspring if blood sugar levels are uncontrolled[4]. Maintaining adequate glycemic levels reduces serious perinatal morbidity and improves mother's quality of life[5,6].

Insulin is traditional treatment which has been in long use by patients with GDM. It does not cross placenta, hence there are no safety concerns for fetus. There are though issues with insulin administration as it requires sufficient education on the part of the patient to have skill for its monitoring, storage, self-administration and dose adjustment to maintain optimum glycemic control. Moreover, there is pain, discomfort, anxiety and fear of injections, maternal weight gain and chances of severe hypoglycaemia. Metformin, an oral hypoglycemic drug, is easy to administer, stored at room temperature and being relatively cheaper is a logical alternative option. It decreases hepatic glucose production, reduces intestinal absorption of glucose, improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin crosses placenta and its use in pregnancy was not considered safe due to fetal concerns. MIG trial was the first randomized control trial comprising of 751 pregnant patients, published in NEJM in 2008 which reported comparable fetal outcome in patients taking metformin and insulin and suggested less incidence of macrosomia and neonatal hypoglycemia. In the trial, patients preferred metformin treatment and tolerated it well[7]. Since the publication of MIG trial, more and more studies have reported safe perinatal outcomes with the use of metformin in pregnancy[8,9,10,11,12]. NICE guidelines recommend that metformin can be safely given in gestational diabetic patients up to doses of 2500mg per day[13]. Despite this, controversy still exists regarding metformin use in pregnancy as there is concern of crossing placenta and causing fetal hypoglycemia. ADA suggests insulin as a preferred treatment and does not endorse metformin use in pregnancy due to limited long term safety data[14].

GDM is on a rise in South Asia and it is estimated that Pakistan will be the 8th most prevalent country for diabetes mellitus in 2030[1]. The choice of Metformin is particularly attractive in developing countries like Pakistan where insulin is not preferred by patients for issues like cost, injection administration and storage issues. On the other

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hand, doctors are reluctant to use metformin due to fear of fetal & neonatal hypoglycaemia. There is sparsity of local data and obstetricians are sceptical about the dosage recommended by NICE.

No national guideline is available for GDM in Pakistan. We planned this study with the hypothesis that metformin is comparable to insulin in its effects and an acceptable alternative in patients with GDM. The rationale of this study is to compare the fetomaternal outcome in patients of GDM using metformin or insulin for glycemic control.

The objective of the study was to compare the fetomaternal outcomes in women with GDM treated with insulin or metformin.

MATERIAL AND METHODS

This open label randomized control study was conducted in the Department of Obstetrics &Gynecology, Services Institute of Medical Sciences, Services Hospital Lahore from Feb 2016 to Dec 2017. Services Hospital Lahore is a tertiary care hospital attached to public sector medical college, catering the needs of a large population. It is adjacent to Diabetes Management Center (DMC) so pregnant patients with diabetes are managed in close collaboration with diabetic physician. Ethical approval for the study was taken by the Institutional Review Board (IRB) SIMS, Services Hospital Lahore on 29.1.2016 number IRB/2015/211/SIMS.

After calculation of sample size, pregnant patients presenting in antenatal clinic at 22-34 weeks of gestation with singleton pregnancy were subjected to 75gm oral glucose tolerance test (OGTT). Gestational diabetes mellitus (GDM) was diagnosed according to international association of pregnancy study group(IADPSG) criteria with fasting glucose level > 5.1mmol/l (92mg/dl),1 hour $\geq$ 10 mmol/L (180mg/dl) or 2 hour post prandial glucose level was >8.5mmol/l (153mg/dl)[15]. The women who had any other systemic disorder including type 1 & type 2 diabetes, known hypertensive & fetal malformation diagnosed on ultrasonography were excluded from the study.

After diagnosis of GDM, all women were counseled regarding diet, exercise and life style modification in liaison with a nutritionist. Daily caloric allotment was based upon Body Mass Index (BMI). Carbohydrate intake was restricted to 45% of calories, protein 20% & fat 35%. They were advised 30 minutes' walk daily. Patients was called after two weeks and their blood glucose was checked, fasting blood glucose level< 95mg/dl and 1 hour post prandial <140mg/dl were taken as normal. If blood glucose level exceeded these limits, they were enrolled in the study after explaining & taking informed written consent. The enrolled patient was randomized in two groups by lottery method. Their demographic features including age, parity, gestational age, BMI, family history of diabetes was noted and all baseline investigations including BSF, BSR, HbA1c and ultrasound were carried out at enrollment.

Group 1 was started with Metformin at a dose of 500mg twice daily for the first week and then increased till maximum dose of 2500mg daily in divided doses to achieve the glycemic control (fasting blood glucose level < 95mg/dl and 1 hour post prandial < 140mg/dl). Insulin was added if glycemic control was not achieved despite maximum dose of metformin. Those assigned to insulin group were admitted after counseling for adjusting the dose of insulin and educating them regarding administration of insulin, storage and symptoms of hypoglycemia. Dose of total insulin required was calculated by multiplying maternal weight with 0.7 in second and 0.8 in third trimester. Insulin was prescribed as a combination of three doses of short acting (Humulin R) before each meal & single dose of intermediate acting (NPH) at bed time. Increment in units of insulin was done according to response to achieve glycemic control. Total calories were distributed into three meals and three snacks per day. Women were discharged once normoglycemia was achieved. They were asked to record their fasting and 3 post prandial blood glucose levels. Patients were then followed up in antenatal clinics fortnightly till 36 weeks and then weekly till delivery.

At each antenatal visit patients were enquired about symptoms of hypoglycemia. Hypoglycemia was defined as symptoms of sweating, lethargy, palpitations and blood glucose reading of less than 60mg/dl. Their BP, and weight were recorded and abdominal examination was done for fetal growth. They were admitted if blood glucose level was uncontrolled or any complications developed. All patients had ultrasonography for fetal biometry, growth and was repeated every two weeks. Glycosylated hemoglobin (HbA1c) was measured at entry to the study and was repeated again at the 36 – 37 weeks of gestation. Time and mode of delivery was decided according to obstetrical indications. All patients were received and assessed by pediatrician. Blood glucose was checked and if it was normal, babies were sent back to the mother after short stay in nursey. Patients were followed for 7 days after delivery.

Maternal and perinatal outcomes were recorded on a predesigned proforma. Primary outcome was maternal glycemic control which was assessed by HbA1c, mean FBG and mean RBG at delivery. Optimum glycemic control was declared when HbA1C was ≤6, FBG≤ 95md/dl and RBG at one hour was ≤140mg/dl. Other maternal outcomes included gestational age at delivery, maternal hypoglycemia (2 or more drops in blood glucose levels <60 mg/dl or symptoms of light headedness, palpitations, sweating), preeclampsia (BP of 140/90mmhg with proteinuria >3g/24 hours), preterm delivery (<37 weeks) and mode of delivery.

Perinatal outcomes were APGAR score at 5 minutes of birth, neonatal hypoglycemia (BSR < 40 mg/dl on two consecutive occasions) perinatal mortality, birth weight, macrosomia (birth weight ≥4kg), transient tachypnea of newborn (TTN), respiratory distress syndrome (RDS), neonatal sepsis and NICU (Neonatal intensive care unit) admission.

Data analysis: SPSS version 22.0 was used for data analysis. Quantitative variables like patient's age, BSL, GTT and neonatal birth weight are presented by mean and standard deviation. Qualitative variables like apgar score, still birth and congenital anomalies are presented by calculating frequency and percentages. Chi square and t-test was used to analyse the qualitative and quantitative variables, respectively. P value ≤ 0.05 is considered significant.

RESULTS

During the study period, 343 patients were diagnosed with GDM and 312 met the inclusion criteria. Out of these, 304 agreed to participate and were enrolled and randomized in two groups. Of randomised patients, 278 were included in the analysis (137 patients in metformin group and 141 in insulin group). 34(24%) of patients on metformin required additional insulin(fig1). Baseline characteristics including age, parity and gestational age at enrolment were comparable in two groups (table1). Family history was seen in 53.9% of total patients, more significantly in patients of metformin group (63.5 vs 44.7; p=0.002). BMI of 26.5±5.1 and 27.1±5.3 was in metformin and insulin group respectively. HbA1C, FBG and RBG were comparable in both groups at enrolment (p=0.235, 0.215,0.117). The median daily dose of metformin to maintain normoglycemia was 1500mg. Intolerance to metformin in form of nausea, vomiting occurred in 4 women (2.8%). Gestational age at delivery was comparable in both groups; 37.5+1.0 vs 37.6+1.0 weeks(p=0.226).

Maternal pregnancy outcomes are shown in table 2. Maternal glycemic control as assessed by FBG and 1 hour RBG was significantly better in women on metformin then those on insulin (p=0.001). Most of the patients achieved glycemic control within one week in both groups. Although maternal hypoglycaemia, preeclampsia and pre-term birth were more in insulin group but they were not statistically significant (p=0.092, 0.166 and 0.226). Caesarean sections were performed in 60.7% of patients. There was no statistical difference in caesarean deliveries in both groups(p=0.073).

Table 1: Demographic & maternal characteristics

Parameters	Metformin n=137 mean± SD	Insulin n=141 mean± SD	P-value
Age	29.5 ± 4.8	29.7 ±4.8	0.781
Parity	2.5± 1.2	2.7± 1.1	0.148
Education			
Illiterate / Elementary	76(56)	72(51)	0.404
Secondary	55(40)	63(44)	0.500
Higher secondary	06(4.3)	06(4.1)	0.933
Family history	87(63.5)	63(44.7)	0.002
Gestational Age at Enrolment	28.9± 2.9	28.6± 3.1	0.359
HBAIc at enrolment	6.99±7.5	7.1±0.79	0.235
FBS at enrolment	117±18.1	120± 22.4	0.215
RBS at enrolment	181 ±28	185± 25	0.117
Dose of Drug			
Metformin	1.48± 0.44	N.A	0.928
Insulin	N.A	30.8±8.6	0.303
Gestational age at delivery	37.5±1.0	37.6±1.0	0.226

Regarding perinatal outcome, most of babies were born with good APGAR score in both groups (8.2 vs 8.1; p=0.445) with average comparable birth weight of 3.0±1.0 kg vs 3.1±1.0 kg. (Table 3). Neonatal hypoglycaemia, macrosomia and NICU admission was seen significantly less in patients on metformin (9.4 vs 26.9; p=0.001, 5.1 vs 13.4; p=0.017 and 6.6 vs14.2 p=0.038). There were 1 perinatal death in metformin group as compared to 3 in insulin group (P=0.267). All three babies in insulin group had pre-term birth at 31, 33 and 34 weeks and died due to RDS and neonatal sepsis. Fetal death in metformin group was still birth at 36 weeks with birth weight of 3.9 kg. This patient did not have regular follow up and came with intrauterine death at 36 weeks. All of these patients had deranged blood glucose levels. Although TTN, RDS and sepsis were seen more in patients with insulin but difference was non-significant in two groups (p<0.05).

Table 2: Maternal outcomes

Parameters	Metformin n=137 mean± SD	Insulin n=141 mean± SD	P-value
HbAIc at 36 /37wk	6.0±0.9	6.1±1.1	0.408
FBS at delivery	92.1±6.0	96.6±6.2	0.001
RBS at delivery	120±13.6	128±10.0	0.001
Pre Eclampsia	17(12.4)	28(19.8)	0.092
Maternal hypoglycemia	06(4.3)	19(13.4)	0.166
Preterm delivery	13(9.2)	20(14.5)	0.226
SVD	61(44.5)	48(34.0)	0.086
LSCS	76(55.4)	93(65.9)	0.073

Table 3: Perinatal outcomes

Parameters	Metformin n=137 mean± SD	Insulin n=141 mean± SD	P-value
Alive	136(99.3)	138(97.4)	0.047
Perinatal death	1(0.7)	3(2.1)	0.122
Birth weight	3.0±0.4	3.1±0.44	0.204
Macrosomia	07(5.1)	19(13.4)	0.017
Neonatal hypoglycemia	13(9.4)	38(26.9)	0.001
APGAR score	8.2±1.0	8.1±0.98	0.445
NICU Admission	09(6.6)	20(14.2)	0.038
TTN	05(3.6)	10(7)	0.204
RDS	02(1.4)	06(4.2)	0.163
Neonatal sepsis	04(2.9)	8(5.6)	0.259

DISCUSSION

Diabetes complicating pregnancy is an important health problem in Pakistan with reported prevalence of 3.3%[16]. This study was done to compare the effectiveness and safety of metformin's use in pregnancy as compared to insulin. Maternal characteristics of age, parity and education were matched in both groups.

GDM is generally more prevalent in obese patients, yet BMI of our patients at enrolment was 26.5±5.1and 27.1±5.3 in both groups, lower than reported in MIG Trial (32.2±8.2 and 31.9±7.6) and other western studies[7,17]. Comparable BMI though has been reported by studies from adjoining countries i.e. Iran[18] and India[19]and other Asian contries[2].Therefore, it can be assumed that in addition to obesity; ethnicity and genetic predisposition are also important in the development of GDM.

Family history is a significant risk factor predisposing women to develop GDM and was found in 53.9% of patients in our study as well. Therefore, early OGTT is recommended for those having positive family history.

We found metformin to be significantly more effective in achieving glycemic control at 36/37 weeks. Fasting and random blood glucose levels were significantly better controlled at the time of delivery in patients who were taking metformin, although HBA1c levels were comparable. Better acceptance and compliance with metformin, being an oral drug, contributed a lot in achieving this. Blood glucose control in insulin group was low, attributable to illiteracy and inability to administer insulin properly. Adequate glycemic control in patients taking metformin has been reported in other studies as well[7-12,18].

Tolerability with metformin was also good and 97.2%of our patients continued to take the drug in a mean dose of 1500mg/day till delivery. Only 4 patients discontinued the drug due to gastrointestinal upsets of nausea and vomiting. MIG trial[7]and Jahan Ara[20] have also reported good tolerability with metformin with 92% of patients taking the drug till delivery. Insulin had to be added in 24.8% of our patients in whom glycemic control was not achieved on metformin in 2weeks.Kitwee P in metanalysis of 8 randomised trials have reported supplemental insulin requirement in 14-46% of patients[21]. Most of our patients needing supplemental insulin were those who had highly deranged blood sugar levels on OGTT and high BMI at time of enrolment, or those who were booked late in pregnancy. Another observation made in the study was few hypoglycemic incidents reported in metformin group as compared to insulin group (3.3% vs 13.4%), making it a feasible option in our patients where intense monitoring is not routinely possible.

Preeclampsia is a known complication in diabetic pregnancies. Recent meta-analysis of 8 RCT's comparing metformin and insulin showed a reduced risk of preeclampsia in patients taking metformin[22].We also found lower incidence of preeclampsia in patients taking metformin (12.4% vs 19.8%). It is now believed that metformin may reduce preeclampsia by reducing endothelial activation and inflammatory response of insulin resistance.

Complications caused by elevated blood sugar levels can lead to preterm birth which is an important determinant of neonatal morbidity. Our study reports less pre-term deliveries (9.2%)in metformin group vs 14.5% in insulin group although not statistically significant, with mean gestational age at delivery of 37.5±1.0 and 37.6±1.0 weeks. Increased preterm birth has been reported in Mig trial [7]and Shirin et al[18] in patients taking metformin while Balani[8] found significantly less pre-term birth in metformin group. The variation may be related to glycemic control or induced preterm births due to additional complications like pre-eclampsia.

The greatest concerns with metformin use have been fetal development and subsequent complications as it crosses placenta. Our study has shown that neonatal outcomes are significantly better in patients taking metformin in terms of macrosomia, neonatal hypoglycemia and NICU admissions. Macrosomia is a feared complication of diabetic pregnancies as it is associated with increased labor complications like shoulder dystocia, birth trauma, increased caesarean section and birth asphyxia. Average birth weight of babies was 3.0±0.4kg and 3.1±0.44 kg in metformin and insulin group respectively. Macrosomia developed in 13.4% of patients who were on insulin and 5.1% of patients who were taking metformin. Prevention of macrosomia is main target in management of GDM. Similarly, neonatal hypoglycemia is responsible for severe neonatal morbidity if not corrected timely. Development of all these complications is linked to glycemic control. In our study, glycemic control was significantly better in patients taking metformin which resulted in better neonatal outcomes. Moreover, it is postulated that metformin crosses placenta and it has direct effect on fetal physiology which leads to better neonatal profile including less hypoglycemia and decreased macrosomia. Majority of RCTs have shown similar results with lesser incidence of neonatal morbidity in patients taking metformin[17,18,20,23]. Some of the studies have shown comparable outcome in term of neonatal outcome in patients taking metformin or insulin[7,9-12,24].

Our study reports 4 perinatal deaths with 1 stillbirth in metformin group at 36 weeks and 3 early neonatal deaths in insulin group who were born prematurely at 31,33 and 34 weeks of gestation. All these mothers had poor glycemic control during pregnancy thereby emphasizing the importance of good glycemic control during pregnancy. The three babies who had early neonatal death had complications of prematurity of TTN, RDS and neonatal sepsis. NICU facilities in developing countries are overburdened with higher rate of neonatal sepsis. Moreover, patients are unable to bear cost of surfactant and antibiotics, hence prematurity remains leading cause of neonatal mortality. These mishaps can be avoided by optimizing blood sugar levels, hence minimizing complications which can lead to preterm birth. Western studies do not report any perinatal death due to good antenatal follow up and excellent neonatal facilities[7,10,17,18].

Metformin is reported to be safe as regards short term neonatal outcomes in almost all studies reported so far. The follow up study for long term safety data was published for 751 babies, 2 years following Mig trial regarding anthropometric measurements in children has revealed that there was no difference in total body fat percentage and total fat mass distribution in both group[25].

Strengths of the study: Our study is a randomized control study. It has good follow up of patients with fewer number of drop outs. The results can contribute to forming protocol of management of GDM in local population in routine practice.

Limitations of study: It was a randomized control study but blinding was not possible due to different routes of administration of drugs. There is no long term follow up of children although short term data has less neonatal complications in metformin group.

Conflict of Interest: There is no conflict of interest.

Details of Ethical Approval:

Funding: No funding was required for this study as the patients were provide medicines from the hospital during their stay and had to purchase own their own when managed as outdoor patients.

CONCLUSION

Metformin use in pregnancy is associated with better maternal glycemic control. The drug is well tolerated by

patients with good compliance. There were lesser neonatal complications of hypoglycaemia, macrosomia and NICU admission with metformin use as compared to insulin in patients with gestational diabetes mellitus.

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