



1. FCPS
Senior Registrar
Department of Gynaecology and
Obstetrics
Bahawal Victoria Hospital
Bahawalpur.
2. MCPS, FCPS
Associate Professor
Department of Gynaecology and
Obstetrics
Bahawal Victoria Hospital
Bahawalpur.
3. FCPS
Senior Registrar
Department of Gynaecology and
Obstetrics
Bahawal Victoria Hospital
Bahawalpur.
4. MBBS
House Officer
Department of Gynaecology and
Obstetrics
Bahawal Victoria Hospital
Bahawalpur.

Correspondence Address:
Dr. Khiaynat Sarwar Hashmi
FCPS
Department of Gynaecology and
Obstetrics
Bahawal Victoria Hospital Bahawalpur.
ksarwar61@gmail.com

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GESTATIONAL DIABETES MELLITUS; TO COMPARE METFORMIN AND REGULAR INSULIN IN BLOOD SUGAR CONTROL AND NEONATAL OUTCOME IN PATIENTS WITH GESTATIONAL DIABETES MELLITUS.

Khiaynat Sarwar Hashmi¹, Tasneem Akhtar², Sidrah Batool³, Kokab Saleem⁴

ABSTRACT... Objectives: To Compare metformin and regular insulin in blood sugar control and neonatal outcome in patients with gestational diabetes mellitus. **Material and Method:...** **Study Design:** Randomized control trial. **Place of the Study:** Department of Gynecology and Obstetrics, Bahawal Victoria hospital Bahawalpur. Duration of the study. 1 year 1st January 2017- 31st December 2017. **Sample Size:** N=200, one half (group A) receiving Metformin and other half (group B) receiving regular insulin. **Results:** Blood sugar control depicted by fasting, 2 hr post prandial levels and HbA1c % was similar in both group. coexisting hypertensive complications were seen more in insulin group. Weight gain was also significantly more in insulin group 17 kg on an average as compared to metformin group where average weight gain was 13 kg. Convenience and satisfaction regarding their treatment, more number of patients were satisfied in metformin group. There were significant increase in the mean birth weight of the newborns, need for admission in NICU and Neonatal hypoglycemia in insulin group as compared to metformin group. **Conclusion:** Metformin when compared to insulin has equal efficacy in controlling maternal blood sugar levels but better neonatal outcome, patient satisfaction and convenience in treatment of gestational Diabetes Mellitus.

Key words: Gestational Diabetes, Metformin, Insulin, Macrosomia, Neonatal Hypoglycemia.

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INTRODUCTION

Gestational Diabetes is labeled at any level of glucose intolerance during pregnancy or even if first time diagnosed in pregnancy.¹ South Asia specifically is experiencing a rise of pregnancy complications. Owing to rise in number of diabetes mellitus patients and early onset of type 2 diabetes mellitus [T2DM] in India.² Pregnancy makes a state of insulin resistance at tissue level which is compensated by increase in insulin synthesis but whenever this compensation is insufficient or in cases where there is defect in beta cells of pancreas gestational diabetes mellitus occurs.³ In GDM maternal hyperglycemia drives more glucose to the fetus resulting in fetal hyperinsulinemia which in turn is responsible for increased fat deposition in tissues. this results in exaggerated unbalanced fetal growth i.e, macrosomia which in turn is a risk factor for birth trauma, shoulder dystocia and increased

perinatal mortality and morbidity. GDM not only puts fetus at risk but simultaneously increases the risk of hypertension, pre-eclampsia, more chance of cesarean delivery and increased risk of developing type 2 diabetes later in life of the mother.^{4,5}

Dietary control was the first step in management of diabetes followed by insulin therapy over a long period in the past. Insulin has a wide safety data, controls blood sugar efficiently but is not devoid of side effects. It is associated with maternal hypoglycemia and weight gain. Then came oral agents like metformin that lowered blood sugar equally good and were safe both for mother and fetus. Metformin has an added advantage over insulin as it improves insulin sensitivity, by activating AMP kinase, still it doesn't cause maternal hypoglycemia and weight gain.⁶ Not only this metformin is easily available, easily

administered and cost effective which makes it superior over insulin specially in resource-poor populations like ours. Further limitations of insulin are requirement of cold chain, painful administration daily and it also enhances the appetite and weight of the mother. Metformin dose can be easily be adjusted by obstetrician whereas titrating the insulin dose needs multidisciplinary management. Placenta permeates the metformin but metformin is not found to be teratogenic. neither it causes hypoglycemia in mothers.⁷ Insulin although effective in controlling blood sugar levels but due to its inability to increase insulin sensitivity fails at improving insulin resistance, a hall mark of pregnancy. Metformin on the other hand is an insulin sensitizer and reduces the insulin resistance without making more insulin. Thus controlling blood sugar levels. It was found that metformin was better at controlling blood sugar levels as compared to insulin, in our poor population were people were not prone to daily blood sugar monitoring.^{7,8} When GDM was optimally managed it reduced the incidence of macrosomia and perinatal morbidity. Various studies have shown more convenience of patients along with better fetal and maternal outcome with oral antidiabetic agents. Balani *et al.*, showed that birth weight percentile in the metformin group was lower when compared to the insulin group. In the similar study neonatal hyperbilirubinemia and NICU admission were more in the insulin group.^{14,17,18}

Owing to the question whether insulin or metformin to be preferred in patients with gestational diabetes a study was conducted to compare metformin and regular insulin in blood sugar control and neonatal outcome in patients with gestational diabetes mellitus who were not controlled on diet therapy. No such study has been done in our centre before. So it will generate local data and better of the two drugs will be used in future.

MATERIAL AND METHOD

Study Design

Randomized control trial.

Place and Duration of the Study

Department of Gynecology and Obstetrics, Bahawal Victoria hospital Bahawalpur.

Duration of the study. 1 year 1st January 2017- 31st December 2017.

Sample Size

n=200, there will be two groups of patients, one half (group A) i.e., 100 patients receiving Metformin and other half (group B) i.e., 100 receiving insulin therapy

SAMPLE TECHNIQUE

Inclusion Criteria

1. Patients having diabetes first time diagnosed during pregnancy between 24 wk to 34 weeks of gestation.
2. BMI 30-35 kg/m²

Exclusion Criteria

1. Patients who have their blood sugars controlled on dietary modifications.
2. Fetal anomalies.
3. Contra indication to metformin use i.e., liver/renal impairment and sepsis.
4. Pre-eclampsia
5. Essential Hypertension requiring antihypertensive medication

Data Collection Procedures

Approval was taken from the ethical committee, an informed and written consent was taken from the patients. Lottery method was used to segregate patients into group A i.e., who will be given metformin and group B i.e., who will be given insulin. Liver and renal function tests and glycosylated haemoglobin (HbA1c) were conducted before starting study. Patients were admitted in ward and their whole day profile was monitored i.e. fasting, pre and post meals levels (total of six levels). Dose of metformin was 500 mg three times a day increasing to a maximum of 2000 mg/day based on glycemic profile. Regular Insulin was similarly started and adjusted according to plasma glucose levels.

Glycemic profile was done prior to initiation of therapy, during normalization of levels and weekly

after that to monitor the effect of therapy.

The goal of therapy was to have Fasting Glucose around <100 mg/dl and 2 hours postprandial of <130 mg/do. After control of blood sugar was achieved patients were discharged and followed up in opd every month till 32 wks, fortnightly till 36 weeks and then once or twice a week till 39 weeks.

They were advised to check their daily profile of capillary glucose concentration twice a week and record it to be brought to hospital on follow up and to report earlier if levels were not within optimal range. Maternal weight gain and fetal growth assessed by ultrasound examination were recorded at every prenatal visit. Glycosylated haemoglobin was measured again 4 weeks after the initiation of medication and monthly thereafter. After delivery patients were called back after 6-8 weeks for follow up.

The primary outcome was the incidence of macrosomia, defined as a birth weight of over 4000g. Secondary outcomes included neonatal complications, such as admission to neonatal intensive care unit (NICU), neonatal hypoglycaemia requiring intravenous glucose treatment. Maternal outcomes included maternal weight gain, hypertensive complications of pregnancy, weight gain during pregnancy and patient satisfaction.

Data Analysis

Data was analyzed by computer software SPSS version 16. The blood sugar levels were calculated for both groups A and B and compared marking the differences and subjecting them to statistical analysis. Level of significance used was < 0.05.

RESULTS

During the study period 453 patients presented to Gynae OPD of Bahawal Victoria Hospital for medical management of GDM. Of these, 225 women were eligible for the study, and 200 of them were randomized. 14 patients had to be shifted to insulin after randomization and they were withdrawn from the study and 14 more participants were selected for metformin group.

The women needing supplemental insulin had greater BMIs, higher fasting capillary glucose concentrations and needed pharmacological treatment at earlier gestational age than women who were normoglycaemic with metformin. The mean dose of insulin needed at the end of gestation was 35 iu.

The baseline characteristics of the women did not differ between the study groups (Table-I).

Regarding maternal outcomes (Table-II) blood sugar control was more or less the same among both groups. HbA1c % was not different in both groups. The incidence of pregnancy induced hypertension was seen more in insulin group. Weight gain was also significantly more in insulin group 17 kg on an average as compared to metformin group where average weight gain was 13 kg. when patients were asked about the convenience and satisfaction regarding their treatment, more number of patients was satisfied in metformin group (83 %) which was statistically greater than insulin group (72 %)The mean gestational age at delivery was almost the same between the study groups (Table-II).

There was greater mean birth weight of the newborns, increased need for admission in NICU and Neonatal hypoglycemia (defined as blood sugar level of baby less than 36mg/dl and requiring intravenous glucose) in the insulin group as compared to metformin.

Characteristics	Metformin (Group A)	Insulin Use (Group B)
Age (years)	31.7 ± 6.1	32.3 ± 5.6
BMI kg/m ² (avg.)	30.8	31.5
FBS (mmol/l)	5.4 ± 0.6	5.6 ± 0.9
2 hr after OGTT (mmol/l)	8.1 ± 1.8	8.2 ± 1.9
HbA1c % at randomization	5.9 ± 0.4	5.9 ± 0.4

Table-I. Maternal baseline characteristics:

Maternal Outcomes	Metformin (Group A) N=100	Insulin Use (Group B) N=100
Gestational age at time of delivery	39 ± 0.3	38 ± 6
FBS (mmol/l)	94 ± 13	95 ± 16
2 hr after post parental (mmol/l)	111 ± 22	112 ± 15
HbA1c %	5.5 ± 0.7	5.6 ± 0.6
Pregnancy induced hypertension	9 (9%)	15(15%)
Weight gain (kg)	13 kg	17 kg
Patient satisfaction	83%	72%

Table-II. Maternal outcomes:

Neonatal Outcome	Metformin (Group A) N=100	Insulin Use (Group B) N=100
Birth weight > 4000 g	19 (19%)	24 (24%)
Admission to NICU	15 (15%)	28 (28%)
Neonatal hypoglycemia	18 (18%)	23(23%)

Table-III. Neonatal outcome:

DISCUSSION

We found the glycemic control was almost the same for both insulin and metformin group while treating women with GDM. Whereas 2 similar studies showed lower 2 hr post parandial blood glucose levels in metformin group as compared to the insulin group.^{9,10} This was because of the increasing insulin sensitivity and more peripheral glucose uptake properties of metformin.¹¹

Glycosylated hemoglobin HbA1c was also not found to be much different among both groups in our study at time of delivery. This was supported by Elahe Mesdaghinia at el. In their study, metformin group although had better glycemic control but mean values of both groups were normal, showing metformin to be equally effective to insulin in controlling blood sugar level.¹²

It is a common observation that women having diabetes are more prone to develop gestational hypertension as compared to the non diabetics. In our study there was increased association of hypertensive complications in gestational diabetics being treated with insulin as compared to metformin group that was supported by another study by Hijas at ell. This might have been due to

interaction of metformin at endothelial level thus releasing reactive oxygen species.²⁰

Macrosomia defined as birth weight of > 4000gm was 19% in the metformin and 24% in the insulin group that was statistically significant. Another study had similar findings.¹³ Whereas this finding was not supported by earlier cohort studies and MiG Trial¹⁴⁻¹⁶, those showed no statistical difference in neonatal birth weight in both groups.

Neonatal ICU admission was seen in 28 % in insulin group that was almost double than the 15 % neonates requiring NICU admission, whose mothers were treated with metformin. Elahe Mesdaghinia¹² and Balani *et al.*, reported similar results¹⁴, but Rowan *et al.*, showed no statistical significance between both groups related to admission in NICU.¹⁶

Respiratory distress of newborns among infants of the insulin group were more than the metformin group infants in the current study and revealed a statistical significant difference between groups. Similar findings were observed by Elahe Mesdaghinia at el.¹²

Patients treated with metformin had lesser chance of Neonatal hypoglycemia as compared to insulin group in our study. In the MiG trial and in the Finnish cohort study the occurrence of severe neonatal hypoglycaemia was higher in the insulin-treated group than in the metformin-treated group.^{15,16} In yet another study¹³, the frequency of neonatal hypoglycaemia and the need for treatment in NICU were slightly higher in the insulin group, which is in line with Balani J at el,¹⁴ but not all previous studies overall. Metformin treatment may decrease the risk of neonatal hypoglycaemia as compared with insulin.

Patient satisfaction and convenience were by far more with metformin making it a suitable and acceptable alternative to insulin. The MiG trial also concluded metformin as better and more acceptable option to women with GDM.^{16,13} Major setbacks of insulin therapy were need for multiple injections daily, risk of maternal hypoglycemia, increased propensity towards maternal weight

gain, increased appetite and last but not the least, increased cost of treatment.¹⁹

CONCLUSION

We conclude that metformin when compared to insulin has equal efficacy in controlling maternal blood sugar levels but better neonatal outcome, patient satisfaction and convenience in treatment of gestational Diabetes Mellitus. Thus in patients without any maternal or fetal complications or significant obesity, who need treatment must be started with metformin rather than embarking directly on insulin.

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KNOWLEDGE
WILL GIVE YOU POWER, BUT
CHARACTER
RESPECT.

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“Bruce Lee”

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Khiaynat Sarwar Hashmi	Writing the manuscript.	<i>Kainat</i> <i>Kainat</i>
2	Tasneem Akhtar	Supervision and correction.	<i>Tasneem</i> <i>Tasneem</i>
3	Sidrah Batool	Reivew of literature.	<i>Sidrah</i> <i>Sidrah</i>
4	Kokab Saleem	Data collection.	<i>Kokab</i> <i>Kokab</i>