Original Article

Comparison of the Fetal Outcome between Metformin and Insulin in Gestational Diabetes Mellitus

Joveria Sadaf, Anbreen Abbas, Sana Ara and Aslam Mahmood Malik

ABSTRACT

Objective: To compare the fetal outcome in patients taking metformin and insulin for control of gestational diabetes mellitus.

Study Design: Randomized Controlled trial study.

Place and Duration of Study: This study was conducted at the Department of Obstetrics & Gynaecology, Shahida Islam Teaching Hospital, Lodhran from 1st January 2020 to 31st December 2020.

Materials and Methods: Total 134 pregnant women with gestational diabetes mellitus of gestational age >20 weeks of age 18-40 years were selected. Patients with multiple pregnancies, hypersensitivity to metformin or insulin, IUGR, known diabetics and CRF were excluded. Patients in the group A were given tablet metformin 500mg orally and group B were given insulin by subcutaneous route. Serum sugar levels were done regularly for glycemic control and dose adjustment. Patients were followed regularly by the researcher herself till delivery at which fetal outcome (preterm birth, NICU admission and neonatal hypoglycemia) was noted.

Results: The mean age of women in group A was 27.52 ± 6.02 years and in group B was 26.70 ± 6.56 years. Majority of the patients 95 (70.90%) were between 18 to 30 years of age. The mean gestational age of women in group A was 28.02 ± 3.45 weeks and in group B was 28.43 ± 3.52 weeks. In this study, there were 05 (7.46%) had preterm birth with metformin while 15 (22.39%) had preterm birth with insulin (p-value = 0.015). There were NICU admission in 12 (17.91%) neonates with metformin and 20 (29.85%) neonates with insulin. Neonatal hypoglycemia was seen in 08 (11.94%) neonates with metformin and 20 (29.85%) neonates with insulin.

Conclusion: This study concluded that fetal outcome is better with metformin use in gestational diabetes mellitus as compared to insulin use.

Key Words: gestational diabetes, metformin, preterm birth, insulin

Citation of article: Sadaf J, Abbas A, Ara S, Malik AM. Comparison of the Fetal Outcome between Metformin and Insulin in Gestational Diabetes Mellitus. Med Forum 2021;32(5):2-5.

INTRODUCTION

Diabetes in pregnancy can be divided into two broader types. One is pre-conceptional that can either be type 1 or type 2 and second is gestational diabetes(GDM). It is called gestational when hyperglycemia is first recognized during the pregnancy.[1] Diabetes is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretions, action or both.[2] Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity that is first detected during pregnancy, which may or may not revert to normal after delivery.[3]

Department of Obstetrics and Gynaecology Department Shahida Islam Teaching Hospital Lodhran.

Correspondence: Dr. Joveria Sadaf, Assistant Professor Obstetrics and Gynaecology Department Shahida Islam Teaching Hospital Lodhran
Contact No: 03001280960
Email: joveriasadaf@gmail.com

Received: January, 2021
Accepted: March, 2021
Printed: May, 2021

Diabetes mellitus is responsible for almost 2-7% of pregnancies that are complicated with diabetes are associated with increased risk of complications and perinatal mortality.[4] When gestational diabetes mellitus is detected and treated timely, it reduces or eliminates the risks for the fetus. It also has a strong positive effect on the woman's quality of life related to health.[5]

Therefore, it is very important that the patient with diagnosed diabetes mellitus should have pre-pregnancy evaluation and counseling. Poor glycemic control in the pregnancy later on leads to macrosomia and its related complications by two to four folds.[9] Perinatal mortality rates (stillbirths and first-week neonatal deaths) in diabetic population is almost 2-4 times higher than non-diabetic population., and perinatal morbidity (neonatal hypoglycemia, macrosomia, LGA, birth asphyxia) is also very high in diabetics.[4,6]

3-5% of pregnancies are complicated by gestational diabetes mellitus and the incidence is higher in obese and older age women.[7] GDM not only increases the risk of developing complications for example pregnancy induced hypertension and adverse perinatal outcome, it also carries the risk of type 2 diabetes mellitus (DM) (75%) later in her life.[8] The purpose of treatment of diabetes in pregnancy is to reduce fetal hyper-

insulinemia by reducing maternal serum sugar levels.[9] Prospective randomized controlled trials have recently concluded that effective control of high sugar levels in GDM can reduce adverse outcomes in the neonates.[10] Traditionally, treatment of gestational diabetes is diet control alone or diet control and insulin. Insulin therapy though in use for decades has its drawbacks. It requires multiple injections per day, patient education and is related with hypoglycemia and weight gain. That why it seems necessary to adopt some oral medications in place of insulin that is not only safe for the mother but also for the neonate. Many studies suggest that metformin is an acceptable replacement for glycemic control in gestational diabetes that has fewer fetal and neonatal complications.[11]

Diabetes mellitus is an important medical problem in pregnancy and associated with adverse effects on mother and fetus both, so its proper and timely diagnosis and management is mandatory. We have decided to conduct this study to compare the fetal outcome of insulin versus metformin in gestational diabetes mellitus. Then based on this empirical evidence, some recommendations can be made in our routine clinical practice for using the better approach towards gestational diabetes mellitus to reduce perinatal mortality and morbidity.

MATERIALS AND METHODS

Study design: Randomized Controlled trial study.

Place and duration of study: Department of Obstetrics & Gynaecology, Shahida Islam Teaching Hospital, Lodhran from 1st January 2020 to 30th December 2020.

Sample Technique: Non-probability, consecutive sampling.

Sample Selection: All the patients presented to Gynaecology and Obstetrics Department Shahida Islam teaching Hospital Lodhran in a period of one year between ages 18-40 with singleton pregnancy and diagnosed as having gestational diabetes were included in the study. Patients with known diabetes mellitus, multiple pregnancy, intrauterine growth restriction, and renal failure (having serum creatinine ≥1.5 mg/dl) were excluded from the studies. Patients having history of hyper-sensitivity to either metformin or insulin were also excluded.

Data Collection Procedure: After permission from the ethical review committee of the Shahida Islam Medical Complex, total 134 women who fulfill the Inclusion criteria were selected. Informed consent was taken from each patient. After this, all patients were divided into two groups by lottery method. All patients were offered to pick up a slip from total mixed up slips (half-slips having letter 'A' and other half-slips having letter 'B') and she was placed in that respective group. Patients in the group A were given tablet metformin 500mg orally (dose depending on their sugar levels) and group B were given insulin by subcutaneous route (dose adjusted to their glycemic controls). Serum sugar levels were done regularly for glycemic control and dose adjustment. Patients were followed regularly by the researchers themselves till delivery at which fetal outcome (preterm birth, NICU admission and neonatal hypoglycemia) was noted. This all data was recorded on a proforma.

Data Analysis Procedure: Statistical analysis was performed using SPSS version 20.0. Age, gestational age, body mass index (BMI) and parity were presented as mean and standard deviation. Place of living (rural/urban) and preterm birth (yes/no), NICU admission (yes/no) and neonatal hypoglycemia (yes/no) were presented as frequency and percentage. The fetal outcome in both groups was compared by Chi Square test and p-value ≤0.05 was considered as significant. Effect modifiers like age, gestational age, parity, BMI, place of living were controlled through stratification and chi square was applied to see their effect on fetal outcome. P-value ≤ 0.05 was taken as significant.

RESULTS

Distribution of patients according to age is shown in Table I. Distribution of patients according to gestational age is shown in Table 2. Distribution of patients according to parity is shown in Table lll. Distribution of patients according to BMI of women is shown in Table 4. Distribution of patients according to place of living & lifestyle is shown in Table 5.

In this study, there were 05 (7.46%) had preterm birth with metformin while 15 (22.39%) had preterm birth with insulin (p-value = 0.015). There were NICU admission in 12 (17.91%) neonates with metformin and 20 (29.85%) neonates with insulin. Neonatal hypoglycemia was seen in 08 (11.94%) neonates with metformin and 20 (29.85%) neonates with insulin (Table 6).

Table No.1: Age distribution for both groups (n=134)

Age (years)	Group A (n=67)		Group B (n=67)		Total (n=134)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
18-30	20	29.85	28	41.79	48	35.82
31-40	47	70.15	39	58.21	86	64.18
Mean ± SD	32.0 ± 6.0		30.0 ± 5.0		31.0 ± 6.0	

Table No.2: Distribution of patients according to gestational age (n=134)

GA (weeks)	Group A (n=67)		Group B (n=67)		Total (n=134)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
21-30	44	65.67	40	59.70	84	62.69
>30	23	34.33	27	40.30	50	37.31
Mean ± SD	28.02 ± 3.45		28.43 ± 3.52		28.24 ± 3.50	

Table No.3: Distribution of patients according to parity in both groups

Parity	Group A (n=67)		Group B (n=67)		Total (n=134)	
	Frequency	%age	Frequency	%age	Frequency	%age
0-2	55	82.09	52	77.61	107	79.85
3-5	12	17.91	15	22.39	27	20.15

Table No.4: Distribution of patients according to BMI

BMI (kg/m^2)	Group A (n=67)		Group B (n=67)		Total (n=134)	
	Frequency	%age	Frequency	%age	Frequency	%age
≤ 27	35	52.24	26	38.81	61	45.52
> 27	32	47.76	41	61.19	73	54.48
Mean ± SD	29.40 ± 3.58		29.42 ± 3.59		29.44 ± 3.58	

Table No.5: Distribution of patients according to place of living

Place of living	Group A (n=67)		Group B (n=67)		Total (n=134)	
	Frequency	%age	Frequency	%age	Frequency	%age
Rural	30	44.78	35	52.24	65	48.51
Urban	37	55.22	32	47.76	69	51.49

Table No.6: Comparison of fetal outcome between both groups

		Group A (n=67)		**Group B (n=67)**		**P-value**
		Frequency	%age	Frequency	%age	
Preterm Birth	Yes	05	7.46	15	22.39	0.015
	No	62	92.54	52	77.61	
NICU Admission	Yes	12	17.91	20	29.85	0.105
	No	55	82.09	47	70.15	
Neonatal Hypoglycemia	Yes	08	11.94	20	29.85	0.011
	No	59	88.06	47	70.15	

DISCUSSION

The main goal of treatment of gestational diabetes mellitus is to maintain normal blood sugar levels to control peri-natal mortality and morbidity. The used diagnostic criteria to diagnose gestational diabetes will decide that how many patients will require treatment. However, if we keep the diagnostic threshold at those low levels that are currently in use, the proportion of patients with GDM requiring medications is less than in the days where insulin has been the gold standard treatment for GDM after dietary and lifestyle modifications have failed to maintain normal sugar levels. Keeping in view the pathophysiology of GDM, insulin sensitizers would be the first choice of treatment but due to fetal concern it was not practically applied and insulin was remained the main stay of treatment in gestational diabetes. Oral hypo-glycemic agents are cost-effective, easy to take, improves compliance and also more physiological, because the insulin resistance is likely to be the main mechanism in GDM.[12] For decades Metformin has been in used for patients of type II DM and now in insulin-resistant polycystic ovarian syndrome (PCOS) patients for many years.[13] However, its use in pregnancy has been restricted due to fetal concerns.

In a meta-analysis [13] of 5 RCTs involving 1270 participants, in metformin group incidence of preterm birth was significantly more but the incidence of pregnancy induced hypertension was significantly less. The fasting blood sugar levels of OGTT were significantly lower in the patients using metformin alone than in the patients using metformin supplemented with insulin.

Two meta-analysis conducted by Su et al[13] (involving six RCTs) (2014), concluded a significantly better maternal outcome in patients using metformin as compared to patients using insulin in terms of less pregnancy induced hypertension, less weight gain, and pre-eclampsia.as well as neonatal outcomes were also significantly better in patients treated with metformin than insulin when neonatal hypoglycemia was compared in two groups. However, these meta-analyses showed significantly higher preterm birth in the metformin group, compared to insulin group. The results of our study is matching their results however in our study pre-term birth was also lesser in the metformin group.

A small, RCT by Spaulonci et al[5] who compared the control in sugar levels in two groups one taking metformin and other taking insulin, and he found better control in metformin group maternal outcome like les weight gain was observed however no differences in other maternal outcomes such as preeclampsia, prematurity, and caesarean section were noted. The frequency of neonatal hypoglycemia was also lower in the metformin group and there was no increase in preterm birth. One-minute Apgar score and five-minute Apgar score, birth weight and umbilical artery pH at birth were having no statistical difference in two groups. However, the drawback of the study was that the sample size was small, and similar studies with larger sample sizes may strengthen the results of this study.

Study of Arshad R et al[14] also showed better glycemic control in patients having metformin than the patients having insulin for control in gestational diabetes. But neonatal NICU admission was more in metformin group that is less in our study however the difference is no significant. Another RCT by Ashoush S that dealt with identification of poor responders to metformin for gestational diabetes claimed that metformin is superior for glycemic control.[15] Another study by Saleh HS strongly favors the results of our study and recommends

that metformin is equivalent to insulin if not superior in patients with gestational diabetes.[16]

CONCLUSION

This study concluded that the fetal outcome is better with metformin use in gestational diabetes mellitus as compared to insulin use. So, it is recommended that metformin can be an excellent alternative to insulin for treating gestational diabetes mellitus and can help in reducing fetal and maternal morbidity and mortality in such group of patients.

Author's Contribution:

Concept & Design of Study:	Joveria Sadaf
Drafting:	Anbreen Abbas, Sana Ara
Data Analysis:	Sana Ara, and Aslam Mahmood Malik
Revisiting Critically:	Joveria Sadaf, Anbreen Abbas
Final Approval of version:	Joveria Sadaf

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Ali S, Dornhorst A. Diabetes in pregnancy: health risks and management. Postgrad Med J 2011;87: 417–27.
2. Evensen AE. Update on gestational diabetes mellitus. Prim Care 2012;39:83–94.
3. Padayachee C, Coombes JS. Exercise guidelines for gestational diabetes mellitus. World J Diabetes 2015;6(8):1033-44.
4. Mesdaghinia E, Samimi M, Homaei Z, Saberi F, Moosavi S, Yaribakht M. Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin of insulin: a randomized blinded trial. Int J Prev Med 2013;4: 327-33.
5. Spaulonci C, Bernardes L, Trindade T, Zugaib M, Francisco R. Randomized trial of metformin vs insulin in the management of gestational diabetes. Am J Obst Gynecol 2013;208:(13)00296-2.
6. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339–48.
7. Blumer I, Hadar E, Hadden DR. Diabetes and pregnancy: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2013;98(11): 4227-49.
8. Munshi S, Khandaker S. Evaluation of metformin versus insulin in the management of gestational diabetes mellitus: a prospective comparative study. Int J Reprod Contracept Obstet Gynecol 2014;3:357-61.
9. Bano K, Naseeb S, ZulfiqarBhutt S. Comparing effectiveness of metformin versus insulin in gestational diabetes mellitus. Pak J Surg 2015;31(4):260-4.
10. Mesdaghinia E, Samimi M, Homaei Z, Saberi F, Moosavi SG, Yaribakht M. Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: a randomised blinded trial. Int J Prev Med 2013;4:327–33.
11. Sivalingam VN, Myers J, Nicholas S, Balen AH, Crosbie EJ. Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications. Human Reprod Update 2014;20(6):853–68.
12. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ 2015;350:h10
13. Su DF, Wang XY. Metformin vs insulin in the management of gestational diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract 2014;104:353-7
14. Arshad R, Khanam S, Shaikh F, Karim N. Feto-maternal outcomes and glycemic control in metformin versus insulin treated gestational diabetics. Pak J Med Sci 2017;33(5):1182–7.
15. Ashoush S, El-Said M, Fathi H, Abdelnaby M. Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus. J Obstet Gynaecol Res 2016;42:640–7.
16. Saleh HS, Abdelsalam WA, Mowafy HE, AbdElHameid AA. Could metformin manage gestational diabetes mellitus instead of insulin? Int J Reprod Med 2016;2016:3480629.