Comparison of Fetal Outcome in Patients of Gestational Diabetes Treated with Met Formin and Insulin

Fatima Amin, Shaheera Usman, Abeera Choudhry, Shaheen Aslam Baloch, Qurat Ul Ain Aslam, Ghana Shahid*

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi, Pakistan, *Pak Air Force Mianwali, Pakistan

ABSTRACT

Objective: To compare frequency of fetal outcome in patients of gestational diabetes being managed with Metformin and Insulin.

Study Design: Comparative prospective Study.

Place and Duration: Department of Obstetrics and Gynecology, Pak Emirates Military Hospital, Rawalpindi, from Apr to Dec 2016.

Methodology: This study involved 286pregnant women aged between 18-40 years presenting after 24 weeks of gestation and diagnosed with gestational diabetes which were randomly allocated into two treatment groups. Patients in Group-A were treated with met for min while those in Group-B were treated with Insulin. Outcome variables were various fetal outcome measures which were noted and compared between the study groups.

Results: The mean age of met for min group (32.71 ± 6.54 years) and Insulin groups (32.85 ± 6.10 years) was comparable. Mean APGAR score was similar between met for min and Insulin groups at 1 minute (7.56 ± 1.12 vs. 7.40 ± 1.13; *p*=0.229) and 5 minutes (8.34 ± 0.60 vs. 8.24 ± 0.67; *p*=0.231) after birth. The frequency of good APGAR (≥7) was significantly higher in met for min group at 1 minute (82.5% vs. 69.2%; *p*=0.009). Frequency of hyper-bilirubinemia (8.4% vs. 11.9%; *p*=0.327), respiratory distress syndrome (18.9% vs. 25.9%; *p*=0.156) and Neonatal Intensive Care Unit (NICU) admission (16.1% vs. 16.8%; *p*=0.873) showed no significant association with treatment method.

Conclusion: The efficacy of met for min and Insulin was found to be comparable in the management of pregnancy with diabetes. Metformin was as safe as Insulin in treating gestational diabetes considering the fetal outcome.

Keywords: Fetal Outcome, Gestational Diabetes, Insulin, Met for mine.

How to Cite This Article: *Amin F, Usman S, Choudhry A, Baloch SA, Aslam QUA, Shahid G. Comparison of Fetal Outcome in Patients of Gestational Diabetes Treated with Met Formin and Insulin. Pak Armed Forces Med J 2022; 72(Suppl-2): S195-199. DOI: https://10.51253/pafmj.v72iSUPPL-2.3872*

INTRODUCTION

Gestational diabetes mellitus (GDM) has become a major global health problem in recent years. The main source of increase in prevalence of this disease is epidemic of obesity and type 2 diabetes mellitus. GDM is emerging as most frequent medical complication of pregnancy worldwide. The prevalence of gestational diabetes mellitus is increasing with global prevalence range from 5.8% to 12.9%. GDM has severe risks for maternal and neonatal health.[1] The maternal risk factors include risks of preeclampsia development, cesarean section and increased chances of type 2 diabetes mellitus after pregnancy.[2]

Diabetes during pregnancy may be divided into clinical diabetes that is women with previously diagnosed with type 1 or type 2 diabetes or diagnosed during pregnancy by HbAlC and gestational diabetes.[3] Several adverse outcomes have been found to be associated with gestational diabetes mellitus. Maternal side effects mainly include risk of preeclampsia, cesarean section and type 2 diabetes mellitus after pregnancy. The severe hazards for neonatal health, related to GDM may include risk of fetal death, still birth and neonatal hypoglycemia immediately after birth.[4,5]

At initial stages gestational diabetes mellitus is tried to manage by lifestyle modifications but if required control of glucose level is not achieved by exercise and dietary changes then medical treatment is initiated. Conventionally Insulin is considered as treatment of choice for gestational diabetes mellitus and type 2 diabetes. However, there are some disadvantages and doubts associated with usage of Insulin. Which produce hesitation in use of Insulin during pregnancy. The main disadvantages related to Insulin use include exertion of multiple injections, risk for maternal hypoglycemia and higher weight gain in pregnancy.[6]

Metformin can be considered as excellent alternate of Insulin treatment for the patients presented with pregestational diabetes mellitus or gestational diabetes mellitus. It is treatment modality with less side effects and complications for fetus and better compliance for

Correspondence: Dr Fatima Amin, Department of Obstetrics & Gynecology, Pak Emirates Military Hospital, Rawalpindi

Received: 15 Feb 2020; revision received: 08 Jun 2020; accepted: 17 Jun 2020

mother. In a randomized clinical trial comparing use of Insulin and Metformin it was noted that Fasting blood sugar level was controlled among more patients in Metformin group as compared to Insulin group after 1 month of treatment.[7,8]

In another study comparing Insulin and Metformin, no significant difference was noted in fetal outcome. A higher rate of macrosomia (birth weight >4kg) neonates was noted in Insulin group as compare to Metformin group. The rate of large for gestational age (LGA) was also observed higher (24% vs. 16%) in Insulin group as compared to Metformin group. Similarly,there was no significant difference in Apgar score of first and 5th min and neonatal hypoglycemia, between both groups. Neonatal respiratory distress (15% vs. 6%), Neonatal jaundice and hyper biliru-binemia (13% vs. 4%) and NICU admission (33% vs. 14%) were significantly more common in Insulin as compare to Metformin group.[9]

Literature review revealed that Insulin treatment has a disadvantage of weight gain but treatment with Metformin did not show any association with weight gain or hypoglycemia. Probably Metformin activates AMP kinase to improve Insulin sensitivity without disturbing the wight of patient. However, local trails and data on the same is insufficient in our population.[10] So, this current study has been planned to compare the efficacy of Metformin with Insulin in the management of gestational diabetes and pre-gestational DM type II and fetal outcome of both drugs in our target population.

METHODOLOGY

This was a comparative prospective study carried out on 286 women at Department of Obstetrics and Gynecology, Pak Emirates Military Hospital, Rawalpindi, from April to December 2016.

Inclusion Criteria: All the patients visiting to Department of Obstetrics and Gynecology, Pak Emirates Military Hospital, Rawalpindi, having singleton pregnancy and diagnosed with gestational diabetes were included in the study.

Excluison Criteria: Women having known diabetes mellitus type 2 or any other disease which can affect fetal outcome like IUGR, placenta previa, eclampsia and preeclampsia were excluded from the study.

Approval of the study was taken from the Hospital Ethical Committee prior to start of the study. Informed written consent was taken from each patient by researcher herself.

Sample size was calculated by using WHO sample size calculator, taking Level of 5% significance level, 80% power of test, and rate of control of blood sugar level of 79.4% in Metformin group and 64.5% in Insulin group.[10] A total of 286 patients of gestational diabetes were taken and were divided into two groups of 143 women in each group.

These women were divided into two groups randomly by lottery method. One group included women who were treated by Met formin. The second group consisted on women who were treated with Insulin. The patients on Metformin might be given Insulin during late 3rd trimester if they required to achieve target values of plasma glucose.

Fasting blood sugar levels of < 95 mg/dl and blood sugar level at hours < 120 mg/dl was taken as required target level for plasma glucose.[11] The dose of Met formin was started with 500 mg/d and adjusted up to 1500mg/d by monitoring the blood sugar levels of the patient. Insulin dose was adjusted according to sliding scale by 2 IU for each difference of 50 mg/dl glucose level. The patients were followed up after every 2 weeks. Specifically, in the antenatal period the baby growth was monitored at 32 and 36 weeks.[12]

Data related to demography, first and 5th min Apgar, NICU admission (> 24hrs.), Respiratory Distress Syndrome (RDS), and hyper-bilirubinaemiawas recorded on pre-design proforma.

All the collected data was entered and analyzed through SPSS version 21. Numerical variables were presented by mean ± SD.Categorical variables were presented as frequency and percentage. Chi-square test was applied to compare the frequency of 1st and 5th minutes APGAR, NICU admission (>24 hrs.), Respiratory Distress Syndrome (RDS), and hyperbili rubinaemia between the two groups taking p-value ≤0.05 as statistically significant.

RESULTS

There were two groups of patients of diabetes on the basis of treatment with Metformin and Insulin. The mean age of Met formin group (32.71 ± 6.54) years was comparable (p-value=0.859) with mean age (32.85 ± 6.10 years) of Insulin group. There was no significant (p-value=0.935) difference in both groups with respect to-mean gestational age (29.52 ± 2.91 weeks) in Met formin group versus (29.55 ± 2.87 weeks) in Insulin group. The mean parity was also comparable (2.62 ± 1.22 vs. 2.71 ± 1.27, p-value = 0.537) in Met formin and Insulin groups. Similarly, there was no significant (p-value=0.200) diffe-

rence in mean BMI of Metformin group (31.83 ± 2.06) as compared to Insulin group (32.14 ± 2.06) as elaborated in Table-I.

Table-I: Basic demographic characteristics of the patients.

Characteristics	Metformin (n=143)	Insulin (n=143)	*p*-value
Age of the Patients (years)			
Mean ± SD	32.71 ± 6.54	32.85 ± 6.10	0.859
Gestational Age (weeks)			
Mean ± SD	29.52 ± 2.91	29.55 ± 2.87	0.935
Parity of the Patients			
Mean ± SD	2.62 ± 1.22	2.71±1.27	0.537
Primiparas	33 (23.1%)	29 (20.3%)	0.120
Multiparas	104 (72.7%)	99 (69.2%)	
Grand-multiparas	6 (4.2%)	15 (10.5%)	
Body Mass Index (BMI) of the Patients			
Mean ± SD	31.83 ± 2.06	32.14 ± 2.06	0.200
25-30 Kg/m²	24 (16.8%)	21 (14.7%)	0.626
30-35 Kg/m²	119 (83.2%)	122 (85.3%)	

There was no significant difference in the mean APGAR score between Metformin and Insulin at 1 minute (7.56 ± 1.12 vs. 7.40 ± 1.13; *p*=0.229) and 5 minutes (8.34 ± 0.60 vs. 8.24 ± 0.67; *p*=0.231) after birth. The frequency of good APGAR (≥7) was significantly higher in Metformin group at 1 minute (82.5% vs. 69.2%; *p*= 0.009). However, there was no significant difference at 5 minutes (97.9% vs. 97.9%; *p*=1.000) in APGAR score of the babies.Frequency of hyperbilirubinemia (8.4% vs. 11.9%; *p*=0.327), respiratory distress syndrome (18.9% vs. 25.9%; *p*=0.156) and NICU admission (16.1% vs. 16.8%; *p*=0.873) showed no significant association with treatment methods that is no difference was observed in rate of hyperbilirubinemia, respiratory distress syndrome and NICU admission in Metformin or Insulin groups as shown in Table-II.

Table-II: Comparison of Feta outcome between both groups.

APGAR Score	Metformin (n=143)	Insulin (n=143)	*p*-value
APGAR Score at 1 minute			
Mean ± SD	7.56 ± 1.12	7.40 ± 1.13	0.229
Good	118 (82.50%)	99 (69.20%)	0.009
Poor	25 (17.50%)	44 (30.80%)	
APGAR Score at 5 minutes			
Mean ± SD	8.34 ± 0.60	8.24 ± 0.67	0.231
Good	140 (97.90%)	140 (97.90%)	1.00
Poor	3 (2.10%)	3 (2.10%)	
Hyperbilirubinemia			
Yes	12 (8.40%)	17 (11.90%)	0.327
No	131 (91.60%)	126 (88.10%)	
Respiratory Distress Syndrome			
Yes	27 (18.90%)	37 (25.90%)	0.156
No	116 (81.10%)	106 (74.10%)	
Neonatal Intensive Care Unit (NICU) Admission			
Yes	23 (16.1%)	24 (16.8%)	0.873
No	120 (83.9%)	119 (83.2%)	

DISCUSSION

The women having tendency of Insulin resistance prior to pregnancy, are at higher risk of developing gestational diabetes. The requirement of Insulin secretion increases during pregnancy enhancing the burden on pancreatic b-cells by increasing demand of Insulin, which causes the development of gestational diabetes. The impaired pancreatic b-cell compensation for Insulin resistance during pregnancy is main cause of gestational diabetes development. Several severe consequences related to pregnancy outcome are associated with gestational diabetes mellitus with an increased chance of development of type 2 diabetes mellitus. The development of gestational diabetes increases the chance of type 2 diabetes later in life and 14-60% of these women develop type 2 diabetes mellitus. The occurrence of GDM in any pregnancy will indicate a 30-50% chance of gestational diabetes in consecutive pregnancy.[9]

The rising trend of industrialization and sedentary life style is increasing the incidence of diabetes mellitus globally. Due to severe adverse effects of diabetes mellitus on pregnancy outcome, the identification and proper management is very important. The medical management protocol of gestational diabetes is evolving and randomized controlled trials for better management plan are improving our knowledge regarding optimum medical treatment with fewer adverse effects. Insulin treatment has been considered treatment of choice for diabetes mellitus due to its effectiveness and safety in comparison to other available pharmacological treatments.[10,11]

In the present study, the mean age of the patients was 32.78 ± 6.32 years. Ainuddin *et al,*[12] reported similar mean age of 30.6 ± 2.9 years at Lyari General Hospital Karachi, and Munshi *et al*,[13] reported it to be 30.0 ± 4.23 years in India, among pregnant women diagnosed with gestational diabetes.

According to the results of this present study the mean gestational age was 29.54 ± 2.88 weeks at the time of GDM diagnosis. Our observation is in line with that of Ainuddin *et al,*[12] who also reported similar mean gestational age of 29.9 ± 1.1 weeks at the time of diagnosis of gestational diabetes in women presenting at Lyari General Hospital Karachi.Similar mean gestational age of 30.18 ± 3.71 weeks has been reported by Spaulonci *et al,*[14] in Brazil while Munshi *et al,*[13] reported it to be 28.12 ± 4.29 weeks in India.

The mean parity of the patients in the present study was 2.66 ± 1.24. Ainuddin *et al,*[12] reported results parallel to this study with mean parity of 2.7 ± 1.1 in

local pregnant population with gestational diabetes while Munshi *et al*,[13] reported it to be 2.52 ± 1.83 in India. There were 62 (21.7%) primiparas, 203 (71.0%) multiparas and 21 (7.3%) grand-multiparas. Our observation is in line with that of Qadir *et al*,[15] study, who also reported similar frequency of primiparas (24.0%), multiparas (70.0%) and grand-multiparas (6.0%) in women with gestational diabetes presenting at Alhada Military Hospital, Taif, KSA. Similarly, Beyuo *et al,* [16] also reported similar frequency of primiparas (16.3%), multiparas (76.7%) and grand-multiparas (7.0%) in African women with gestational diabetes mellitus.

The results of this present study showed a mean BMI of 31.98 ± 2.06 kg/m^2 among these patients. Our observation is in line with that of Rowan *et al*,[17] who also observed a similar mean BMI of 32.2 ± 8.2 kg/m^2 among such women and Beyuo *et al*,[16] who reported it to be 33.47 ± 6.95 Kg/m^2 in African such women.

In the present study, there was no significant difference in the mean APGAR score between Metformin and Insulin at 1 minute (7.56 ± 1.12 vs. 7.40 ± 1.13; p= 0.229) and 5 minutes (8.34 ± 0.60 vs. 8.24 ± 0.67; p=0.231) after birth. The frequency of good APGAR (≥7) was significantly higher in Metformin group at 1 minute (82.5% vs. 69.2%; p=0.009). However, there was no significant difference at 5 minutes (97.9% vs. 97.9%; p= 1.000). There was no statistically significant difference in the frequency of hyperbilirubinemia (8.4% vs. 11.9%; p=0.327), respiratory distress syndrome (18.9% vs. 25.9%; p=0.156) and NICU admission (16.1% vs. 16.8%; p=0.873) between Metformin and Insulin. Similar insignificant difference was noted across all age, gestational age, parity and BMI groups.

Spaulonci *et al*,[14] reported similar insignificant difference in the frequency of hyperbilirubinemia (8.70% vs. 10.70%; p>0.05) and NICU admission (15.22% vs. 15.22%; p=1.000) between Metformin and Insulin. Moore *et al*,[17] (7.99% vs. 8.38%; p>0.05) and Niromanesh *et al*,[18] (8.18% vs. 9.35%; p>0.05) also observed similar insignificant difference in the frequency of neonatal hyperbilirubinemia between Metformin and Insulin. Hassan *et al*,[19] reported similar insignificant difference in the frequency of RDS between Met formin (18.67% vs. 25.33%; p>0.05) and Insulin. Rowan *et al*,[20] also observed similar insignificant difference in the frequency of RDS between these two groups (18.73% vs. 21.08%; p>0.05) while Munshi *et al*,[13] reported similar difference in mean APGAR score between Metformin and Insulin at 1 (7.2 ± 1.03 vs. 6.76 ± 1.52; p>0.05) and 5 (7.8 ± 1.11 vs. 7.44 ± 1.71; p>0.05) minutes after birth. Saleh *et al*,[21] also reported insignificant difference in the frequency of NICU admission (14.9% vs. 17.1%; p>0.05) and good APGAR score between Metformin (98.6% vs. 98.5%; p=0.59) and Insulin at 5 minutes after birth.

The present study is first of its kind in local population and has found Met formin as safe as Insulin in treating gestational diabetes considering the fetal outcome. We also observed Metformin to be associated with significantly higher frequency of good APGAR score at 1 minute after birth. Considering the convenience of oral dosage and better patient compliance, it appears to be a good alternative to Insulin. Though on the basis of this short-term data available, it can be considered that Metformin could be as safe and effective treatment for GDM, as Insulin with better fetal outcome. However, clinicians should pay attention to the relative lack of long-term offspring data with GDM patients treated with Metformin. Compared with Insulin treatment which has risk of increasing neonatal hypoglycemia.[22]

CONCLUSION

The efficacy of Metformin and Insulin was found to be comparable in the management of pregnancy with diabetes. Metformin was as safe as Insulin in treating gestational diabetes considering the fetal outcome. Metformin was associated with significantly higher frequency of good APGAR score at 1 minute after birth. Considering the convenience of oral dosage and better patient compliance, it appears to be a good alternative to Insulin.

Conflict of Interest: None.

Authors' Contribution

FA: Main idea, concept, data collection, SU: data collection, AC: supervisor, SAB: data collection, QUAA:, GS: literature review.

REFERENCES

1. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep 2016; 16(1): 7.
2. Guo L, Ma J, Tang J, Hu D, Zhang W, Zhao X. Comparative efficacy and safety of metformin, glyburide, and insulin in treating gestational diabetes mellitus: A meta-analysis. J Diabetes Res 2019; 2019: 9804708. doi: 10.1155/2019/9804708. eCollection 2019.
3. Barda G, Bar J, Mashavi M, Schreiber L, Shargorodsky M. Insulin treatment is associated with improved fetal placental vascular circulation in obese and non-obese women with gestational diabetes mellitus. Front Endocrinol 2019; 10(1): 84.
4. Zhu B, Zhang L, Fan YY , Wang L, Li XG , Liu T, et al. Metformin versus Insulin in gestational diabetes mellitus: a meta-analysis of randomized clinical trials. Ir J Med Sci 2016; 185(2): 371-381.
5. Rowan JA, Rush EC, Plank LD. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): Body composition and metabolic outcomes at 7-9 years of age. BMJ Open Diabetes Res Care 2018; 6(1): e000456.

6. Zhen XM, Li X, Chen C. Metformin versus Insulin for gestational diabetes: the reporting of ethnicity and a meta-analysis combining English and Chinese literatures. Obesity Med 2018; 11(3): 48–58.
7. Waheed S, Malik FP, Mazhar SB. Efficacy of Metformin versus Insulin in the Management of Pregnancy with Diabetes. J Coll Physicians Surg Pak 2013; 23(12): 866-869.
8. Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S et al. Treatment for gestational diabetes: a systematic review and meta-analysis. BMJ Open 2017; 7(6): e015557.
9. Hanem LGE, Stridsklev S, Juliusson PB, Salvesen, Roelants M, Carlsen SM et al. Metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age; follow-up of two RCTs. J Clin Endocrinol Metab 2018; 103(4): 1612-1621.
10. Lv S, Wang J, Xu Y. Safety of Insulin analogs during pregnancy: a meta-analysis. Arch Gynecol Obstet 2015; 292(4): 749–756.
11. Song R, Chen L, Chen Y. Comparison of glyburide and Insulin in the management of gestational diabetes: a meta-analysis. PLoS One. 2017; 12(8): e0182488.
12. Ainuddin J, Karim N, Hasan AA, Naqvi SA. Metformin versus Insulin treatment in gestational diabetes in pregnancy in a developing country: a randomized control trial. Diabetes Res Clin Pract 2015; 107(2): 290-299.
13. 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(2): 357-361.
14. Gamal HE, Elaleem MA, Sadek S. Insulin versus Metformin in treatment of gestational diabetes mellitus (rando-mized control-led clinical trial). Egypt J Hospital Med 2018; 72(1): 3753-3761.
15. Qadir SY, Yasmin T, Fatima I. Maternal and foetal outcome in gestational diabetes. J Ayub Med Coll Abbott 2012; 24(3): 175-181.
16. Beyuo T, Obed SA, Adjepong-Yamoah KK, Bugyei KA, Oppong SA, Marfoh K. Metformin versus Insulin in the management of pre-gestational diabetes mellitus in pregnancy and gestational diabetes mellitus at the Korle Bu Teaching Hospital: a rando-mized clinical trial. PLoS ONE 2015; 10(5): e0125712.
17. McGrath RT, Glastras SJ, Hocking S, Fulcher GR. Use of Metformin earlier in pregnancy predicts supplemental Insulin therapy in women with gestational diabetes. Diabetes Res Clin Pract 2016; 116(1): 96-99.
18. Ghomian N, Vahed SHM, Firouz S, Yaghoubi MA, Mohebbi M. The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: A randomized clinical trial. J Cell Physiol 2019; 234(4): 4695-4701.
19. Hassan JA, Karim N, Sheikh Z. Metformin prevents macrosomia and neonatal morbidity in gestational diabetes. Pak J Med Sci 2012; 28(3): 384–389.
20. van Weelden W, Wekker V, de Wit L, Limpens J, Ijas H, van Wassenaer-Leemhuis AG, et al. Long-Term Effects of Oral Antidiabetic Drugs During Pregnancy on Offspring: A Systematic Review and Meta-analysis of Follow-up Studies of RCTs.Diabetes Ther 2018; 9(5): 1811-1829.
21. Saleh HS, Abdelsalam WA, Mowafy HE, Abd ElHameid AA. Could Metformin manage gestational diabetes mellitus instead of Insulin? Int J Reprod Med 2016; 2016(1): 3480629.
22. Huhtala MS, Tertti K, Pellonpera O, Ronnemaa T. Amino acid profile in women with gestational diabetes mellitus treated with Metformin or Insulin. Diabet Res Clin Practice 2018; 146(1): 8–17.