ORIGINAL ARTICLE

Efficacy and Safety of Metformin in Gestational Diabetes Mellitus

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ABSTRACT

Background: Gestational Diabetes Mellitus (GDM) is a sequence of serious unfavorable maternal and perinatal outcomes specially if uncontrolled. Although insulin is a standard therapy, Metformin can be used as an alternative medication to insulin. This study aimed to establish the efficacy, safety, and other metabolic effects of metformin in GDM due to limited studies in the local population.

Methods: This quasi experimental trial was conducted on pregnant female at 24 weeks of gestation and above, presenting to Ziauddin Hospital. A total of 361 patients who were diagnosed with GDM were enrolled. Patients were divided into three groups: diet control, metformin, and metformin with insulin. The Chi Square and ANOVA were used to compare the maternal and neonatal outcomes. Further post hoc analysis of significant parameters was done using Tukey HSD test.

Results: Weight gain in pregnancy and gestational age at delivery gives significant mean differences across three study groups (p=<0.01). In diet control group, weight was significantly gained as compare to metformin group. Similarly, the gestational age in diet control group was significantly higher as compare to metformin and metformin with insulin group (p=<0.01). The higher gestational age was found in patients treated with metformin as compared to metformin with insulin group (37.25±1.41).

Conclusion: Metformin alone as well as in combination with insulin, is a safe, effective treatment option and more acceptable to women with GDM. Metformin has shown to cause less weight gain during pregnancy with minimal risk of maternal and neonatal hypoglycemia.

Keywords: Gestational Diabetes Mellitus; Metformin; Insulin.

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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is a condition of carbohydrate intolerance associated with hyperglycemia of variable severity, which first develops or initially diagnosed in pregnancy that is not clearly overt diabetes[1,2]. Approximately 85-90% of diabetic cases in pregnant women are diagnosed as gestational diabetes mellitus and in 50% of women with polycystic ovary (PCO)[3-5].

It has been noticed in women who are overweight before pregnancy with body mass index >25kg/ m^2, family history of diabetes, gestational diabetes in previous pregnancy, previous large for date ormacrosomicfetus>4.5 kg, suspected macrosomia, polyhydramnios, high risk ethnicity i.e., south Asian countries like India, Pakistan, Bangladesh, Black Caribbean and Middle East[2].

Other traditional risk factors are parity related to maternal age, polycystic ovaries, multiple pregnancy, pregnancy induced hypertension, glycosuria, previous still birth, recurrent miscarriage, congenital anomalies and unexplained fetal death[6]. International Diabetes federation estimates that GDM affects approximately 16%of pregnancies with an incidence of >200,000 cases per year[6,7]. The incidence of gestational diabetes mellitus varies widely, according to the characteristics of the studied population such as ethnicity, screening

strategies and criteria used for diagnosis defined by each country[6,8]. The prevalence is increasing on the whole, mostly in low, middle income countries, related to the increment in the prevalence of obesity and type 2 diabetes mellitus (T2DM) [9,10].

Insulin resistance usually diagnosed late at the end of second trimester (24-28 weeks gestation) and persists throughout the pregnancy due to gradually rising secretion offeto-placental hormones such as estrogen, progesterone, cortisol, growth hormone, prolactin, and particularly human placental lactogen[11-13]. GDM occurs when pancreatic β-cell function is insufficient to overcome insulin resistance due to a limited ability of cells to increase insulin secretion specifically in obese women in whom insulin resistance already exist[11,14].

It is associated with numerous short and long-term complications during pregnancy and higher risk of diabetes in both mother and off spring[15,16]. The most common complications are miscarriages, congenital malformation, preterm delivery, infections, polyhydramnios, gestational hypertension, preeclampsia, as well as intrauterine death or growth retardation[11,17].

Macrosomia (birth weight more than 4,000g or above the 90th percentile for gestational age) is an extra important fetal complication which is a risk factor for induction of labor, higher caesarean rate, instrumental delivery, shoulder dystocia, birthtrauma, bone fracture, Erb's palsy, birth asphyxia and perinatal death[7,13,18,19]. Risk of neonatal complications like hypoglycemia, hypocalcemia, polycythemia, hyperbilirubinemia requiring phototherapy, idiopathic respiratory distress syndrome, still birth and neonatal death are increased because of the adverse metabolic effect of excessive transfer of glucose from mother to fetus during the third trimester[19].

After birth majority of women become normoglycemic, 10% of women with GDM were diagnosed as type 2 diabetes mellitus soon after delivery[20]. The main objective of treatment is to minimize the risk of fetal hyperinsulinemia and macrosomia in the current pregnancy by controlling maternal glucose level, reducing the risk of recurrence in further pregnancies and in future without pregnancy[14,21].

After diagnosis the initial management of GDM typically involves self-glucose monitoring, nutritional counseling, and lifestyle modification. Pharmacotherapy should be considered after 1-2 weeks when normal glycemic control is not achieved by diet and exercise intervention[18]. In clinical practice insulin therapy had been considered as an optimal treatment option for women with GDM, which is uncontrolled by dietary intervention and lifestyle modification to prevent adverse pregnancy outcome[22].

Metformin is a biguanide (oral hypoglycemic drug) that improve peripheral insulin resistance, decrease hepatic gluconeogenesis, intestinal glucose absorption, and plasma triglyceride concentration, whereas enhances peripheral glucose utilization in the skeletal muscles and adipose tissue. It does not stimulate insulin production and not associated with risk of hypoglycemia[23,24]. It easily transfers through the placenta but it seems to be safe and no increased rate of congenital malformation or other adverse fetal outcome reported[14].

Insulin therapy can be difficult for pregnant women due to multiple injection requirements, risk of hypoglycemia and weight gain. Recent trial has reported that tablet Metformin can be used as alternative to insulin and is an effective, economical, and convenient therapy for the treatment of GDM in reducing maternal and perinatal morbidity[24]. The usual starting dose is 500mg-1000mg/ day that can be increases gradually up to 2500 mg/ day in divided doses[11]. Metformin was easily tolerated by most of the women throughout pregnancy but few patients may tolerate despite minimum dose at initiation[25]. Therefore, the study aimed to establish the efficacy, safety, and other metabolic effects of metformin in GDM due to limited studies in the local population.

METHODS

All pregnant women above 20 years of age attending the antenatal clinic with singleton pregnancy beyond 24 weeks of gestation were included in the study. The samples were collected by consecutive sampling technique after approval from ERC of Ziauddin University (Ref. Code 0120415HMGYN). The calculated sample size was 300 in three groups Calculated from Gehan E tables at a 0.05 power 0.80 and one sided (Ref. Leon Gordin). Patients were divided into three groups: diet control, metformin, and metformin with insulin. The women with BMI 20-30 kg/m^2, previous history of GDM, macrosomia, still birth or intrauterine device (IUD) birth and those had family history of GDM were screened using a 50g glucose challenge test (GCT). If the result was high i.e., >140mg/dl, women were advised for oral glucose tolerance test (OGTT). GDM was diagnosed when at least one of the following three plasma glucose level was met or exceeded (fasting 92mg /dl, 1-hour 180mg/dl and 2-hour 153mg/dl). Patients with systemic underlying disease, autoimmune, cholestasis, preeclampsia, intrauterine growth restriction (IUGR), major fetal malformation, Diabetes mellitus, twin pregnancy, previous caesarean section, and placenta previa were excluded from the study.

Women with high blood sugar levels and those who were not controlled on diet and exercise within 1-2 weeks, metformin started from 500mg twice a day

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and gradually increased in divided doses as tolerated until glycemic target was achieved. If blood glucose levels were remaining high than we used cut off values, 1-2 weeks after therapy or at any time with maximum doses of metformin, insulin was adjusted as additional treatment along with diet and exercise advice.

Self-sugar records or laboratory investigation during antenatal visits, monitored blood glucose control initially. It was also done after admission for delivery till discharge. A mean value of 3-4 readings of each fasting and random blood sugar was taken. Maternal weight gain was recorded at each visit and serial monitoring of the fetal abdominal circumference (AC) on ultrasound every 4 weeks assessed fetal growth. Any maternal complications like hypoglycemia, weight gain, caesarean section or prenatal complications like preterm delivery, prenatal mortality (still birth, IUD), macrosomia, shoulder dystocia, respiratory distress syndrome, hypoglycemia as mentioned above and were documented on performa.

IBM SPSS version 23.0 was used for data collection and analysis, mean and standard deviation were noted for all base line characteristics quantitative maternal and neonatal parameters like maternal age, parity, Body Mass Index (BMI), weight gain, Fasting Blood Sugar (FBS), Random Blood Sugar (RBS), birth weight, gestational age, and Apgar Scores at first and fifth minute. Count and percentages were reported for all qualitative maternal and neonatal outcomes. One-way ANOVA was used to compare the means of quantitative maternal and neonatal outcomes across diet control, metformin, and metformin with insulin groups, further post hoc analysis of significant parameters was done using Tukey HSD test. Pearson Chi Square test was applied to observe the association of qualitative maternal and neonatal outcomes with treatment group, *p*-values less than 0.05 were considered significant.

RESULTS

In the current study (Table 1) showed the enrollment of total 361 patients, having mean maternal age 28.86±4.94 years, the median of parity was 1.00, BMI was 25.48±.02 kg/m^2, average weight gain in pregnancy was 4.73±3.16 kg and FBS was found 96.38±25.19. Whereas, RBS was found 124.42±20.68, weight of babies at birth was 3.05±0.53 kg, the gestational age of samples was 37.38±1.5 weeks, and Apgar scores at first minute was 6.79±1.14 and at fifth minute it was 8.53±1.03. This study required 49.6% pharmacological intervention (Figure 1) with metformin and 9.7% required additional insulin to target the standard sugar levels.

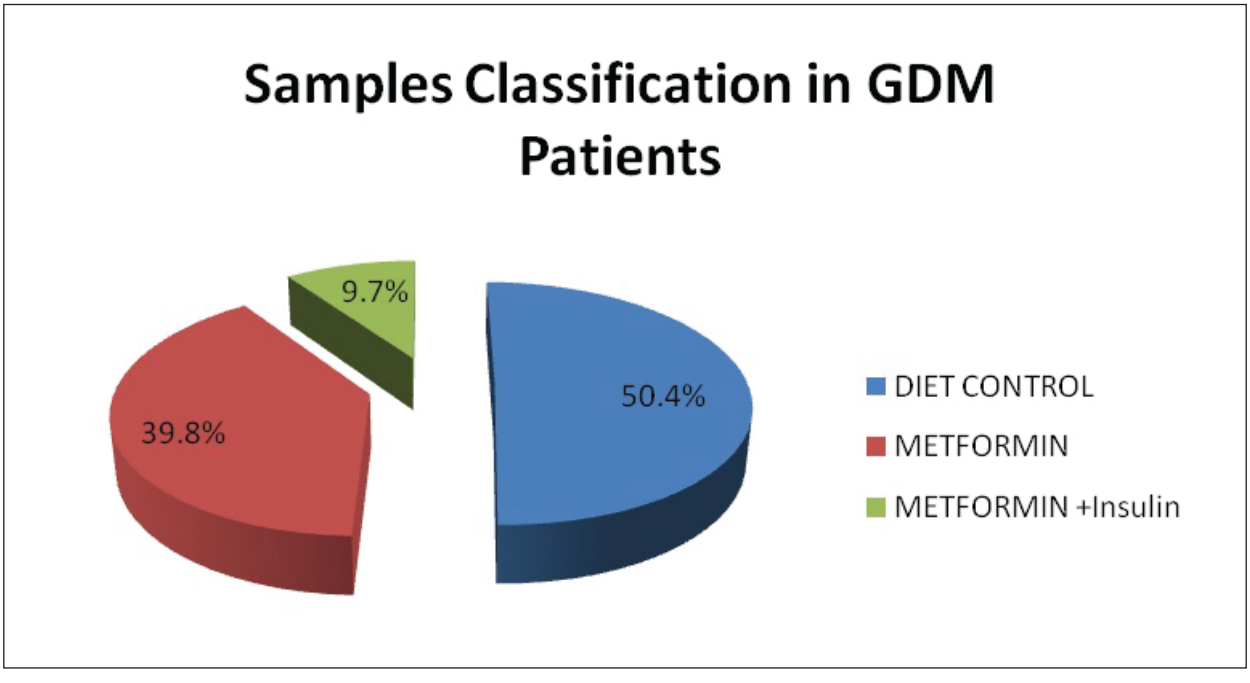

Figure 1: Sample classification in gestational diabetes mellitus (GDM) patients.

The mean comparison of quantitative maternal and neonatal outcomes (Table 1) across three study group, age, parity, BMI, FBS, RBS, birth weight, and Apgar scores at 1st and 5th minutes were found same on average across all three study groups. However, GCT, OGTT (1hour, 2hour), weight gain in pregnancy and gestational age gives significant mean differences across three study groups. The post hoc analysis (Table 1) gives the evidence that, in diet control group weight was significantly gain as compare to metformin group. Similarly, gestational age in diet control group was significantly higher as compare to metformin and metformin with insulin group. The gestational age was also found significantly higher in metformin group as compare to metformin with insulin patients.

Table 1: Comparison of maternal and neonatal parameters among three groups.

Maternal Parameters	Diet Control (n=181)		Metformin (n=143)		Metformin +Insulin(n=35)		*p*-Value
	Mean	S.D	Mean	S.D	Mean	S.D	
Age (Years)	27.98	4.82	29.23	4.94	30.06	5.15	0.058
Parity (Median, Range)	1.00	8.00	1.00	4.00	1.00	5.00	0.20
Body Mass Index (kg/m^2)	25.11	3.00	25.84	3.08	26.08	2.85	0.17
Weight gain (Kg)	6	4	4	2	4	2	<0.01*
Glucose Challenge Test (mg/dl)	165.69	23.07	178.98	28.96	205.57	61.62	<0.01*
Oral Glucose Tolerance Test (OGTT)	94.59	11.90	101.98	22.48	100.07	13.21	0.089
OGTT Fasting 1 hour	174.69	27.58	197.19	27.60	195.73	20.96	<0.0 1*
OGTT Fasting 2 Hour	150.06	25.50	166.08	26.94	173.56	33.06	<0.01*
Fasting Blood Sugar	92.34	19.36	97.90	27.02	109.67	37.25	0.07
Random Blood Sugar	121.81	20.82	123.90	18.86	137.73	23.36	0.06
Neonatal Birth Weight (kg)	3.04	.52	3.08	0.53	3.03	0.69	0.81
Gestational Age (weeks)	37.67	1.39	37.25	1.41	36.43	1.90	<0.01*
Apgar Score 1 min	6.75	1.27	6.83	0.97	6.89	1.11	0.71
Apgar Score 5 min	8.55	1.08	8.49	1.09	8.63	0.55	0.75

**p<0.05 was considered significant using one-way ANOVA.*

The comparison of qualitative maternal and neonatal parameters (Table 2) across three study groups, results showed that, metformin with insulin group have 17.1% associated risk factors, metformin group has 8.4% cases of pre-ruptured of membrane/preterm, 48.6% elective sections delivery (Figure 2) were done in metformin with insulin group. Only 0.7% maternal complications were recorded from metformin group, however there was no significant association of these parameters with treatment. In addition, results showed that 48.6% Neonatal Care Unit (NCU) babies obtained metformin with insulin group and 28.6% neonatal complications were recorded from Metformin with insulin patient, and NCU and neonatal complication gives significant association with treatment.

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Table 2: Comparison of maternal and neonatal parameters after treatment.

Characteristics	Diet Control (n=181)		Metformin (n=143)		Metformin +Insulin (n=35)		*p*-Value
	n	%	n	%	n	%	
Associated Risk Factors	28	15.5	36	25.2	6	17.1	0.08
Pre-ruptured of Membrane/ Preterm	13	7.2	12	8.4	3	8.6	0.90
Maternal Complication	8	4.4	1	0.7	2	5.7	0.09
Neonatal Care Unit	43	23.8	57	39.9	17	48.6	<0.01*
Neonatal Complication	23	12.7	19	13.3	10	28.6	0.04*
**p<0.05 was considered significant using Pearson Chi Square test.*							

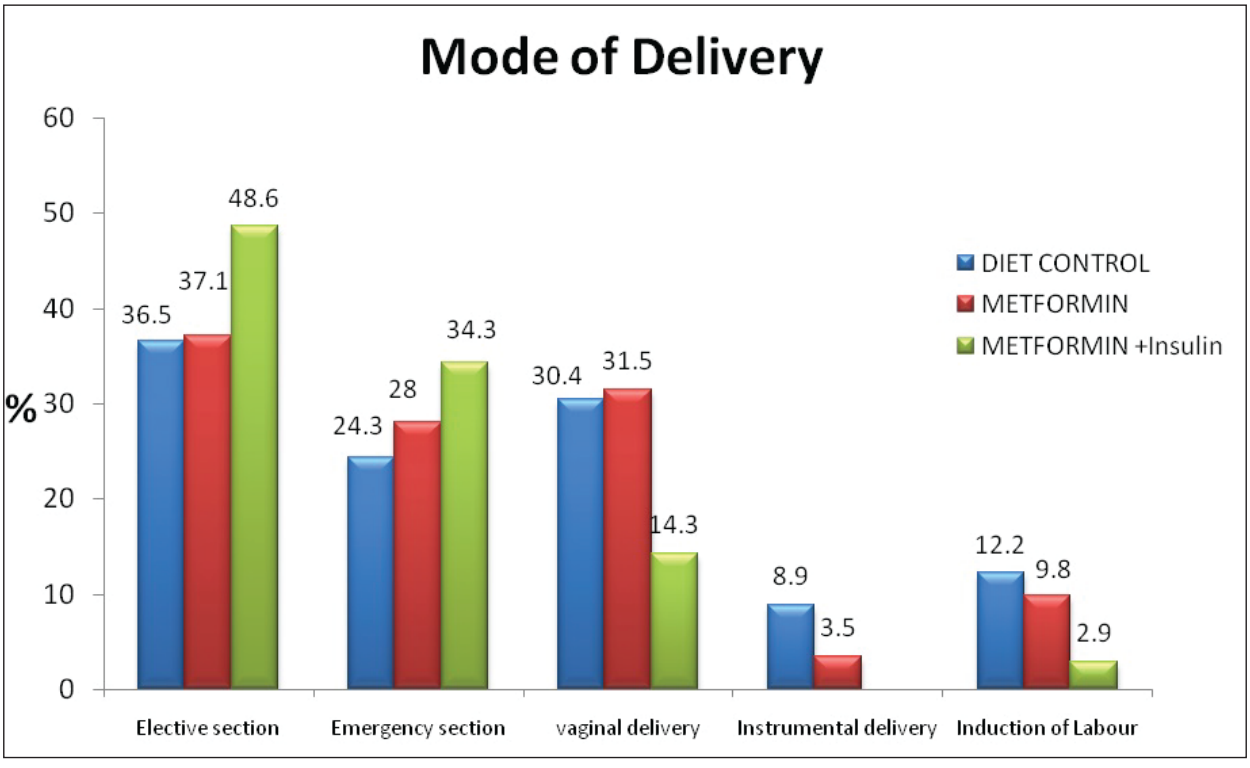

Figure 2: Mode of delivery in gestational diabetes mellitus (GDM) patients.

The analysis of logistic regression model (Table 3) was applied to estimate the risk for treatment with Metformin. The binary logistic regression model suggested patients with higher GCT more likely to be treated with Metformin as compared to diet control samples, oral glucose tolerance test fasting 1-hour and 2-hours also gives positive association with treatment group; samples with NCU were found 2.28 times more likely for treatment Metformin. Neonatal complication also gives positive association with treatment group however, it was found statistically insignificant. The model also suggested, weight gain and gestational age (weeks) gives negative association with treatment group, samples with an increase in weight and gestational age will be at lower risk to treated with Metformin and found statistically significant (<0.05).

Table 3: Effect of metformin treatment on maternal and neonatal parameters using binary logistic regression model.

Parameters	Odds Ratio (OR)	95% C.I for OR	*p*-Value
Glucose Challenge Test (mg/dl)	1.02	(1.0 – 1.03)	<0.01*
Oral Glucose Tolerance Test Fasting (mg/dl) 1-Hour	1.03	(1.01 – 1.05)	<0.01*
Oral Glucose Tolerance Test Fasting (mg/dl) 2-Hour	1.04	(1.01 – 1.04)	<0.01*
Weight Gain(kg)	0.74	(0.61 – 0.88)	<0.01*
Gestational Age (weeks)	0.75	(0.64 – 0.88)	<0.01*
Neon atal Care Unit	2.28	(1.45 – 3.59)	<0.01*
Neonatal Complication	1.33	(0.74 – 2.41)	0.33

*Dependent variable: treatment (Metformin, Metformin+ Insulin), *p<0.05 was considered statistically significant for odds ratio.*

DISCUSSION

Metformin reduces the total weight gain of women with GDM. In our study, total weight gain was significantly less in metformin treated group as compared to diet and in metformin supplemental insulin group. Different scientist has been noticed that weight gain in insulin group was significantly higher than metformin group[17,16]. In this study metformin showed a higher average gestation age at delivery as compared to insulin added group. Jiang et al. reported the average gestational age at delivery were significantly lower in the metformin as compared to insulin group[4].

The present study showed the same result as other studies in those no significant risk of preterm birth was found among three groups, in contrast to the MIG trial by Rowan et al., reported that the preterm birth to be more in women treating with metformin[16]. The cesarean section results of diet, metformin and plus insulin groups were in accordance to the other studies by Rowan, Tertti, and Ainuddin in Pakistan [14,16,27]. The rate of cesarean section found higher mainly due to other obstetrical indication or a high-risk pregnancy.

Metformin was well accepted and tolerated by GDM patients selected in this study. Only 0.01% women required dose limitation because of gastrointestinal upset, compared to 2% in MiGTrial and 5% in the trial by Gandhi et al[23]. In our study we observed only 9.7% of patients in the metformin group eventually needing additional insulin to target normoglycemia. The study by Rowen et al. had the highest number of patients required additional insulin 46% in compared to the study other studies that found 10%), 14% and 18%[14,16,22]. In our observation the rate of macrosomia (birth weight more than 4 kg) was equal among three groups. 2.8% in diet, 2.2% in metformin group and no significant differences were observed. Newborns of the additional insulin group had extremely higher mean birth weights than metformin group[24].

In addition to this, we observed that NCU admission were higher in insulin added groups as compared to diet and metformin group. Similarly, in another study they found NCU admission higher 48.6% in supplemental insulin, 39.9% in metformin and 23.8% in diet group [25]. The authors reported less episodes of neonatal hypoglycemic in infants of women in the metformin than in the insulin group[26]. The current study also revealed that other neonatal outcomes including IUD, macrosomia did not differ significantly between these groups. Thus, neonatal hyperbilirubinemia, respiratory distress, hypoglycemia and IUGR are same in diet and metformin group than additional insulin provided group[27].

CONCLUSION

Metformin, alone as well as in combination with insulin, is a safe, effective treatment option and more acceptable to women with gestational diabetes mellitus. However, metformin treatment in gestational diabetes has shown to cause less total maternal weight gain during pregnancy with minimal risk of maternal and neonatal hypoglycemia. For that reason, it is economical, acceptable oral therapy with good compliance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

ERC Ziauddin University reviewed this project on 9-9-2015 (Ref. Code 0120415HMGYN).

PATIENT CONSENT

Necessary information about the study protocol provided and written consent of the patients were taken.

AUTHORS' CONTRIBUTION

HM collected, analyzed, and interpreted the patient data and prepared the research article. SC helped in manuscript writing. NS also proofread the manuscript and RH supervised the whole research study.

REFERENCES

1. Luesley DM, Kilby M, editors. Obstetrics and gynecology: an evidence-based text for MRCOG. CRC Press; 2016. p.3.
2. Bain E, Crane M, Tieu J, Han S, Crowther CA, Middleton P. Diet and exercise interventions for preventing gestational diabetes mellitus. Cochrane Data Sys Rev. 2015(4):CD010443.
3. Landon MB, Gabbe SG. Gestational diabetes mellitus. Obstet Gynecol. 2011;118(6):1379-1393.
4. Jiang YF, Chen XY, Ding T, Wang XF, Zhu ZN, Su SW. Comparative efficacy and safety of OADS in management of GDM: network meta-analysis of randomized controlled trials. Clin Endocrinol Metab. 2015;100(5):2071-2080.
5. Rojas J, Chávez-Castillo M, Bermúdez V. The role of metformin in metabolic disturbances during pregnancy: polycystic ovary syndrome and gestational diabetes mellitus. Int J Reprod Med. 2014:1-15.
6. Bortolon LNM, Triz LDPL, Faustino BDS, Sa LBCD, Rocha DRTW, Arbex AK. Gestational diabetes mellitus: new diagnostic criteria. Open J Endocr Metab Dis. 2016;6: p.13.
7. Saleh HS, Abdelsalam WA, Mowafy HE, Abd ElHameid AA. Could metformin manage gestational diabetes mellitus instead of insulin? Int J Reprod Med. 2016:1-9.
8. Marques P, Carvalho MR, Pinto L. Metformin safety in the management of gestational diabetes. Endocr Pract. 2014;20(10):1022-1031.
9. Koning SH, Hoogenberg K, Lutgers HL, Van den Berg PP, Wolffenbuttel BH. Gestational diabetes mellitus: current knowledge and unmet needs: Gestational diabetes: current knowledge and unmet needs. J Diabetes. 2016; 8(6):770-781.
10. 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(6):640-647.
11. Ryu RJ, Hays KE, Hebert MF. Gestational diabetes mellitus management with oral hypoglycemic agents. Semin Perinatol. 2014;38(8):508-515.
12. Alam AT, Ahmed S. Metformin: A Drug of choice for gestational diabetes mellitus in near future-hope or despair? Chattagram Maa-O-Shishu Hosp Med Coll J. 2015;14(2):70-77.
13. Kamana KC, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab. 2015;66(suppl 2):14-20.
14. Tertti K, Ekblad U, Vahlberg T, Rönnemaa T. Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective, case-control study. Rev Diabet Stud. 2008; 5(2): 95-101.
15. Horvath K, Koch K, Jeitler K, Matyas E, Bender R, Bastian H, *et al.* Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. BMJ. 2010;340:c1395.
16. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358(19):2003-2015.
17. Poolsup N, Suksomboon N, Amin M. Efficacy and safety of oral antidiabetic drugs in comparison to insulin in treating gestational diabetes mellitus: a meta-analysis. PloS one. 2014;9(10):e109985.
18. Reece SW, Parihar HS, LoBello C. Metformin in gestational diabetes mellitus. Diabetes Spectr. 2014;27(4):289-295.
19. Stewart A, Malhotra A. Gestational diabetes and the neonate: challenges and solutions. Res Rep Neonatol. 2015;5:31-39.
20. 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;185:371-381.
21. Abolfazal M, Hamidreza TS, NargesM, Maryam Y. Gestational diabetes and its association with unpleasant outcomes of pregnancy. Pak J Med Sci. 2008;24(4):566-570.
22. Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: A randomized clinical trial. Diabetes Res Clin Pract.2012;98:422-429.
23. Gandhi P, Bustani R, Madhuvrata P, Farrell T. Introduction of metformin for gestational diabetes mellitus in clinical practice: has it had an impact? Eur J Obstet Gynecol Reprod Biol.2012;160:147-150.
24. Ijäs H, Vääräsmäki M, Morin-Papunen L, Keravuo R, Ebeling T, Saarela T, *et al.* Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. BJOG. 2011; 118(7):880-885.
25. Carroll DG, Kelley KW. Review of metformin and glyburide in the management of gestational diabetes. Phar Pract. 2014;12(4):528-535.
26. Najafian M, Barati M, Masihi S, Fardipor A, Shajirat Z. Investigation the effects of metformin versus insulin on neonatal and maternal outcomes in women with gestational diabetes mellitus. Glob J Health Sci. 2017:9(4):272-278.
27. 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;107:290-299.