ORIGINAL ARTICLE

Neonatal outcomes in women with gestational diabetes mellitus treated with metformin in compare with insulin: A randomized clinical trial

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Background: The objective of this study was to compare neonatal outcomes in women with gestational diabetes mellitus (GDM) treated with either metformin or insulin. **Materials and Methods:** A randomized clinical trial carried out on year 2011 on 109 women with GDM who did not adequately control by dietary measures. They received metformin 500 mg once or twice daily or insulin 0.2 IU/kg/day initially. The dose was titrated to achieve target blood glucose values. Neonatal outcomes such as hypoglycemia, birth weight, Apgar score, umbilical artery pH, and hyperbilirubinemia in the 50 women who remained exclusively on metformin were compared with 50 women who treated with insulin. **Results:** Two groups were similar in mean fasting blood sugar (P = 0.7) and postprandial measurements (P = 0.8) throughout GDM treatment. Pregnancy complications or preterm labor were not different significantly between two groups. Considering neonatal outcomes between insulin and metformin groups, such as hypoglycemia (2 [4%] and 0 [0%], respectively), birth weight (3342 ± 506 mg and 3176 ± 438 mg, respectively), 5th min Apgar score <7 (no one in either group), umbilical artery pH <7.05 (no one in either group) and hyperbilirubinemia (1 [2%] and 0 [0%], respectively), no significant statistical differences were seen. **Conclusion:** Based on these preliminary data, considering neonatal outcomes, metformin appears to be a safe as insulin in the treatment of GDM.

Key words: Gestational diabetes mellitus, insulin, metformin, neonatal outcome

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INTRODUCTION

Gestational diabetes mellitus (GDM) complicates a substantial number of pregnancies; it remains a major cause of perinatal morbidity and mortality, as well as maternal morbidity. GDM is classically defined as "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy."[1] The new diagnostic criteria being put to use are all set to increase the incidence owing to increased detection; and the overall incidence of 3-7% has steadily increased over time.[2] Incidence in Iran now is estimated about 10.2%.[3] In normal pregnancies, insulin sensitivity decreases as the pregnancy advances and this predisposes to the development of GDM.[4] Maternal hyperglycemia, which is typical of GDM, causes a greater transfer of glucose to the fetus, causing fetal hyperinsulinemia which causes excessive and unbalanced fetal growth, causing more trauma at birth, shoulder dystocia and perinatal deaths. Hyperinsulinemia can also cause numerous neonatal metabolic complications, such as hypoglycemia, hyperbilirubinemia, hypocalcemia, hypomagnesemia, polycythemia, respiratory distress syndrome (RDS), and a greater longterm risk of diabetes mellitus and obesity in the child.[5,6] GDM is related to maternal complications too, such as hypertension, preeclampsia, greater need for cesarean and a greater risk of developing diabetes mellitus later on.[5,7] Prospective randomized studies have demonstrated that effective treatment of hyperglycemia in women with GDM can reduce adverse perinatal out comes.[8,9] This is initially attempted by dietary and exercise counseling, but women often require additional treatment (from 20% to 60%).[6,10] Historically, insulin has been the therapeutic agent of choice for controlling hyperglycemia in pregnant women. It still is the treatment of choice in many situations, however, difficulty in medication administration with multiple daily injections, and increase in appetite and weight make this therapeutic option cumbersome for many pregnant patients. Moreover, hypoglycemia occurs in approximately 71% of women who take insulin at some time during their pregnancy.[11,12] Studies have shown that an oral hypoglycemic drug may not only have better maternal and fetal consequences but also could bring patients'

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acceptance.[13,14] Oral metformin is an alternative to insulin in the treatment of women with GDM. Metformin is a biguanide that improves insulin sensitivity and reduces both fasting and postprandial plasma glucose.[11] It does not induce hypoglycemia and it is not associated with increased weight gain.[15,16] Although it crosses the placenta, there is no evidence of adverse fetal effects or increased risk of major malformations when metformin is used in pregnant women.[17,18] Metformin has been used by women throughout pregnancy, but the concern is that whether this drug can reduce adverse perinatal out comes as well as insulin and would complicate the pregnancy or not.

The results of previous studies for differences in glycemic control or pregnancy and neonatal outcomes between insulin and metformin are contradictory. Some investigators showed that pregnancy complications or neonatal outcomes such as preterm labor, neonatal hyperbilirubinemia, small for gestational age neonates (SGA), and neonatal hypoglycemia were more in either insulin or metformin group significantly. Some also showed that the differences were not of significant statistical concern.[19-30]

In this study, we aimed to compare neonatal outcomes such as hypoglycemia, birth weight, Apgar score, umbilical artery pH, need for intensive care treatment and hyperbilirubinemia in women with GDM treated with either metformin or insulin.

MATERIALS AND METHODS

Study design and participants

This study used a randomized, double-blind controlled clinical trial design with two active medication conditions, which was carried out on year 2011 and posted on Iranian Registry of Clinical Trials (www.irct.ir) with identifier Number IRCT201306057841N4. The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee from the Isfahan University of Medical Sciences. All participants provided written informed consent.

Subjects were selected from patients who referred to the Alzahra and Shahid beheshti Hospitals (Isfahan, Iran). All subjects met the following inclusion criteria:

1. 18-45 years aged;
2. Pregnancy with a single fetus between 24 and 33 weeks of gestation;
3. Current diagnosis of GDM according to the criteria of the Australasian Diabetes in Pregnancy Society;[31]
4. No response to lifestyle modification (diet and exercise) after 1 week;[15]
5. Written informed consent.

Subjects also met none of the following exclusion criteria:

1. Any contraindication for receiving metformin (renal or hepatic failure);
2. Any history or documented diagnosis of diabetes prior to pregnancy;
3. History of sever drug reaction to the drugs in study;
4. Any serious medical condition that may interfere with safe study participation.

A total of 156 individuals screened. At the screening visit, after providing demographic data, blood pressure, and body mass index, blood samples were obtained after an overnight fast to assess baseline glycemia and to ensure that the results of renal and liver function tests did not preclude the use of metformin. Finally, 119 met all inclusion and no exclusion criteria. Eligible subjects were assigned to insulin or metformin groups with simple randomization by a third party physician using tables of random numbers. Two patients in metformin group (3.3%) did not achieve the target of glycemic control and needed insulin, so excluded. Ten patients in insulin group and seven patients in metformin group excluded because of pregnancy complications (pregnancy induced hypertension [PIH] and preeclampsia) or preterm labor [Figure 1].

Procedures and variables assessment

Metformin was started at a dose of 500 mg once or twice daily with food according to blood sugar (BS) level and increased, generally over a period of 1-2 weeks, to meet glycemic targets up to a maximum daily dose of 1500 mg. If the targets were not achieved with metformin alone,

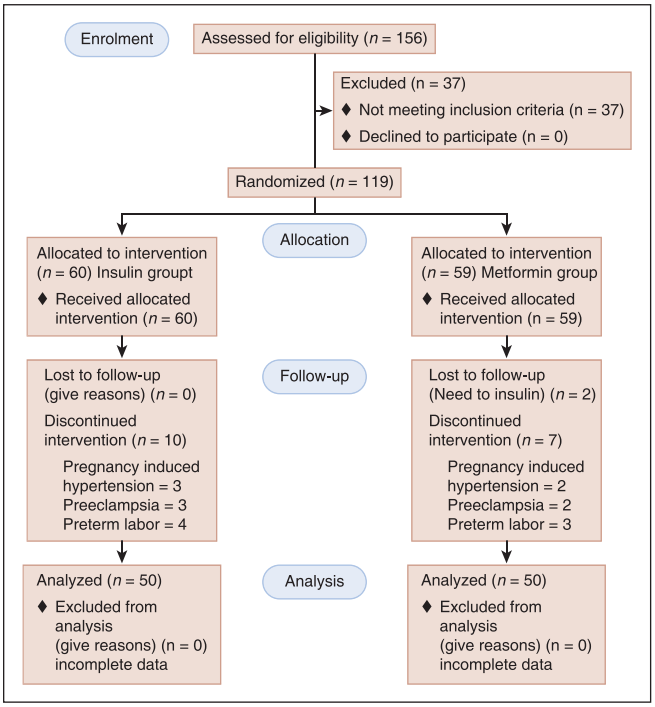

Figure 1: CONSORT statement

insulin was added. Metformin was stopped if maternal contraindications (such as liver or renal impairment or sepsis), PIH, or preeclampsia were developed. Insulin was administered with an initial dose of 0.2 IU/kg/day and titrated to meet glycemic targets according to usual practice. Plasma glucose target levels were defined as fasting blood sugar (FBS) <95 mg/dl and BS 2 h <120 mg/dl[15] After achieving target levels of BS, the patients were discharged with written prescription of drug and follow-up schedule for every 2 weeks. FBS and BS 2 h were recorded every 2 weeks up to labor time. If any disturbance in glucose level was observed, new dose adjustments were accomplished.

Randomization was generated by a third party physician using tables of random numbers. Care providers and physician assessing outcomes were blinded for each other works and results.

In each visit (every 2 weeks), the following pregnancy outcomes were recorded: Pregnancy-induced hypertension (PIH; blood pressure elevation detected for the first time during pregnancy without proteinuria), and preeclampsia (increased blood pressure >140/90 mmHg accompanied by proteinuria >0.3 g/24 h). Furthermore after delivery, the following neonatal outcomes were recorded: Birth weight (grams and standard deviation [SD] for gestational weeks), macrosomia (birth weight >4500 g and/or >2 SD), the incidence of SGA (birth weight <2 SD), preterm labor (birth <37 weeks of gestation), Apgar score at the age of 5 min, umbilical artery pH <7.05, hypoglycemia (serum glucose <2.6 mmol/l, or 46.8 mg/dl, measured during the first 2 h postpartum), hyperbilirubinemia (need for phototherapy), need for intensive care treatment, RDS (need for at least 4 h of respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive-pressure ventilation during the first 24 h after delivery) and shoulder dystocia.[15,20,32]

Statistical analysis

The data were analyzed by Chi-square, independent *t*-test and Fisher exact test. All analyzes were performed using Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA) and $P < 0.05$ was considered to be statistically significant for all analyses.

RESULTS

The demographic and clinical features of the sample are reported in Table 1. Pregnancy complications or preterm labor were not different significantly between two groups. There were no statistically significant differences on demographic data and clinical features between intervention groups. Two groups were similar in mean FBS ($P = 0.7$) and postprandial measurements ($P = 0.8$) throughout GDM treatment. Rate of cesarean section in insulin and metformin groups was 35 (70%) and 37 (74%) respectively, and Chi-square analysis revealed no significant differences ($P = 0.66$) in this. There were two subjects with hypoglycemia in insulin group (37 and 42 mg/dl) who were treated; and no one in metformin group developed hypoglycemia. The difference was not statistically significant. However, the average of neonatal BS during 1 and 2 h postpartum was significantly lower in the insulin group ($P = 0.033$ and 0.002, respectively) [Table 1, Figures 2 and 3]. The Apgar score of 5th min after birth, in insulin and metformin group was distributed as scores of seven, eight, and nine [Table 1]. Fisher exact test did not show any significant difference in 5th min Apgar score between groups ($P = 0.59$). None of subjects had Apgar score of <7.

The average (±SD) of neonatal birth weight in insulin and metformin groups were 3342 (±506) mg and 3176 (±438) mg,

Table 1: Demographics and clinical characteristics of subjects ($n = 100$)

Characteristics	Insulin ($n = 50$)	Metformin ($n = 50$)	*P* value
Age (year)	23.4±2.5	24.6±6.3	0.68*
Body mass index (kg/m^2)	25.1±3.4	26.4±2.8	0.61*
Gestational age (week)	26.7±3.5	27.6±3.3	0.71*
Blood pressure at enrollment, (mm Hg)			
Systolic	120.7±17.8	117.3±20.1	0.37*
Diastolic	75.3±13.3	71.6±17.3	0.23*
Family history of DM	5 (10)	3 (6)	0.24†
Cesarean section	35 (70)	37 (74)	0.66†
Neonatal blood sugar (mg/dl)			
1 h postpartum	59.5±14.9	64.9±9.5	0.033*
2 h postpartum	59.8±13.3	67.2±9.4	0.002*
5th min Apgar score			
7/10	1 (2)	3 (6)	0.59†
8/10	16 (32)	13 (26)	
9/10	33 (66)	34 (68)	

Data are mean±SD or number (%); *P* values calculated by*Independent *T*-test and †Chi-square; SD = Standard deviation; DM = Diabetes mellitus

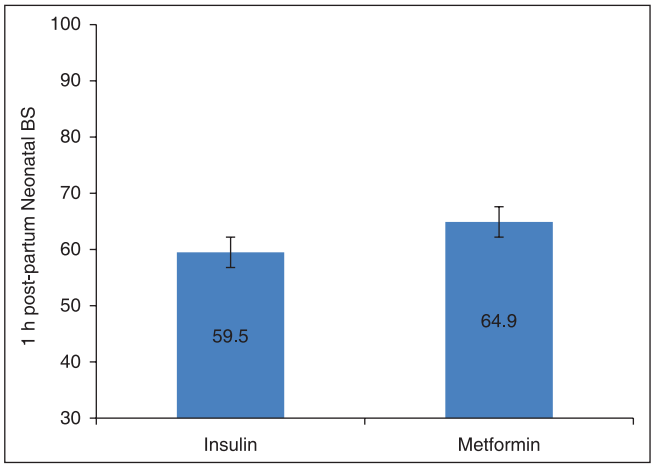

Figure 2: The average of neonatal blood sugar after 1 h postpartum in both groups

respectively which did not differ statistically significant ($P = 0.08$) [Figure 4]. Thirteen subjects in insulin and seven subjects in metformin group had weight more than 3500 mg, and Fisher's exact test revealed no significant difference for this ($P = 0.33$), but there was no macrosomia in either group. One subject in each group was observed with SGA [Figure 4].

The average (±SD) of umbilical artery pH was 7.22 (±0.15) in insulin group and 7.24 (±0.13) in metformin group. It was not different significantly. There were no subjects with umbilical artery pH <7.05 in either group. Considering the shoulder dystocia, hyperbilirubinemia, prenatal mortality, need for intensive care treatment and RDS, no significant statistical differences were seen between groups [Table 2].

Bloating and abdominal discomfort was experienced in 17 subjects (29%) of metformin group.

DISCUSSION

This study compared metformin and insulin in neonates of women with GDM for outcomes in early neonatal period.

Table 2: Comparison of neonatal outcomes between groups

Neonatal outcome	Insulin *n* = 50	Metformin *n* = 50	*P* value
Umbilical artery pH <7.05	0 (0)	0 (0)	NS
Hyperbilirubinemia (need for phototherapy)	1 (2)	0 (0)	NS
RDS	3 (6)	1 (2)	NS
Need for intensive care treatment	2 (4)	0 (0)	NS
Shoulder dystocia	1 (2)	0 (0)	NS
Hypoglycemia	2 (4)	0 (0)	NS
5th min Apgar score <7	0 (0)	0 (0)	NS
Macrosomia	0 (0)	0 (0)	NS
Small for gestational age	1 (2)	1 (2)	NS
Prenatal mortality	0 (0)	0 (0)	NS

Data are number (%); *P* values calculated by Chi-square test; NS = Nonsignificant; RDS = Respiratory distress syndrome

Two subjects of 59 (3.3%) in metformin group did not achieve the target of glycemic control and needed additional insulin treatment. This rate of treatment failure was 46% in Rowan *et al*. study,[20] 18% in Tertti *et al*. study,[15] and 21% in Gandhi *et al*. study.[29] This can be important because in spite of these studies which used metformin up to 2500 mg for glycemic control, we used only 1500 mg as maximum dose. This results was similar to Moore *et al*. study which the majority (27 subjects of 32) were easily controlled on the initial dosage (500 mg twice a day) of metformin.[24] This proportion is likely to vary, depending on patient characteristics and target levels of glucose. However, this result can show that metformin can be used for glycemic control in GDM effectively.

Pregnancy complications were not different significantly between two groups, and this is consistent with most of recent studies in this topic.[13,15,25,28,29] In this study, the difference in the rate of cesarean delivery was not statistically significant between the insulin and metformin groups, and it was similar to Balani *et al*. study.[13] However, Goh *et al*. revealed that cesarean delivery was more in insulin group.[23]

Although in this study, the average of BS during 1 and 2 h postpartum was significantly lower in the insulin group, but the incidence of hypoglycemia was not statistically different between two groups. Neonatal hypoglycemia in studies of Rowan *et al*.,[20] Goh *et al*.,[23] and Tertti *et al*.[15] was less in the metformin group significantly, but consistent to this study the difference between groups was not significant in Moore *et al*. study.[24]

Preterm labor revealed no difference between the two groups statistically; similar results were reported by Balani *et al*.[13] and Moore *et al*.,[24] but Goh *et al*.[23] showed that women treated with insulin had higher rates of preterm births, and Rowan *et al*.[20] showed that this rate was more in metformin group.

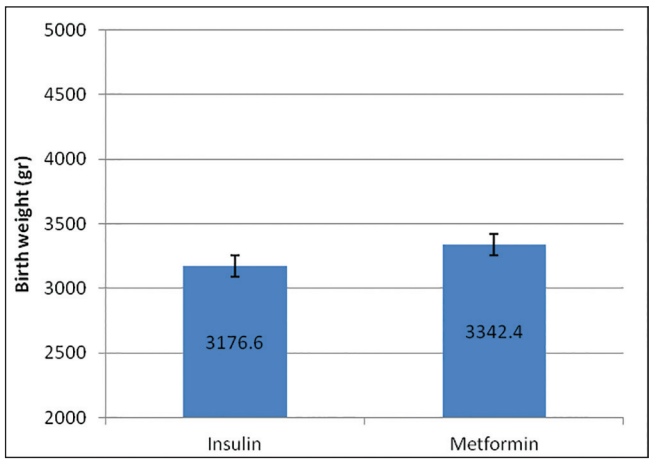

Figure 3: The average of neonatal blood sugar after 2 h postpartum in both groups

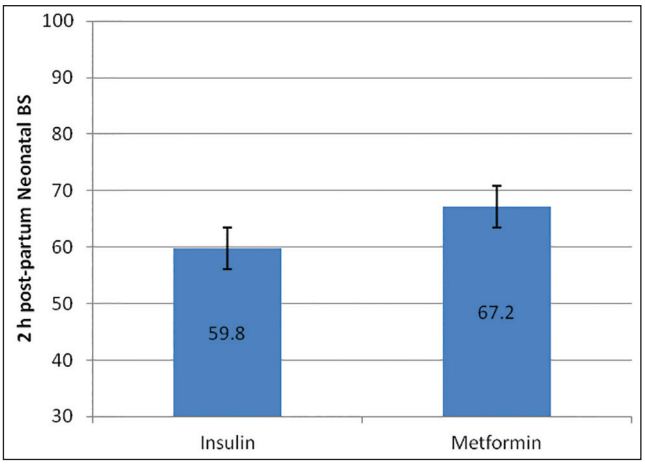

Figure 4: The average of neonatal birth weight in both groups

In this study, hyperbilirubinemia was not different significantly between groups, as well as Tertti *et al*.[15] and Moore *et al*.[24] studies. Furthermore, RDS and need for intensive care treatment were similar in both groups. But Mesdaghinia *et al*. showed that hyperbilirubinemia, RDS and need for intensive care treatment were more in the insulin group. This may be because of higher rates of preterm labor in insulin group in their study.[32]

There was no macrosomia in either group in present study, and the rate of SGA was not different between groups, which was consistent with Rai *et al*. study.[25] But Niromanesh *et al*.[28] and Gandhi *et al*.[29] concluded that the neonates of metformin group had less rate of birth weight >90th centile than insulin group.

Other neonatal outcomes, such as umbilical artery pH <7.05, shoulder dystocia, prenatal mortality, and 5th min Apgar score <7, did not differ significantly between groups. These outcomes were also similar in both groups in most of previous studies.[15,24,28,29,32]

Bloating and abdominal discomfort was experienced in metformin group, but not as severe as leading to non-compliance. This could be because of low doses of metformin we used (one or two) in most of the patients.

CONCLUSION

Based on these preliminary data, metformin appears to be an effective and safe alternative to insulin in the treatment of GDM.

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AUTHORS' CONTRIBUTION

SR carried out the design and coordinated the study, participated in most of the experiments and prepared the manuscript. SE provided assistance in the design of the study, coordinated and carried out all the experiments and participated in manuscript preparation. ZA provided assistance in the design of the study and provided assistance for all experiments. All authors have read and approved the content of the manuscript.

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