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Efficacy of Prophylactic Use of Metformin in Prevention of Gestational Diabetes Mellitus in Nondiabetic Obese Pregnant Women

Farzaneh Boroumand[1], Shiva Ghayur[1], Rasoul Gharaaghaji[2], Shabnam Vazifekhah[1*]

1. *Department of Obstetrics and Gynecology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran*
2. *Department of Biostatistics and Epidemiology, Urmia University of Medical Sciences, Urmia, Iran*

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Corresponding Information:
Shabnam Vazifekhah,
Department of Obstetrics and Gynecology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran

Email: vazifehkhah.s@umsu.ac.ir

ABSTRACT

Background & Objective: Maternal obesity can increases pregnancy consequences like postpartum hemorrhage, preeclampsia, need for cesarean section, neonatal death, and fetal macrosomia. In this study, the efficacy of prophylactic use of metformin to prevent gestational diabetes mellitus in nondiabetic pregnant women with obesity was examined.

Materials & Methods: This study was a clinical trial. Totally, 340 pregnant women who were in the first trimester were referred to the gynecology clinic of Motahhari hospital in Urmia after ensuring the absence of underlying diseases such as diabetes, hypertension, kidney, liver, and cardiovascular disease, without a history of allergy to metformin, in case of a singleton pregnancy, and Body Mass Index (BMI) above 30 were allocated to two equal groups. The intervention group was given 1000 mg of metformin, and the control group was given a placebo. Demographic information, including age, gravity, parity, live birth, birth, and maternal weight, previous delivery method, abortion, delivery method with its cause, polyhydramnios, NICU hospitalization, gestational age, mortality, and neonatal anomalies was also recorded. The results were analyzed using SPSS version 26.

Results: In the control group, 15 mothers (9.4%) out of 160 people, and in the intervention group, 13 mothers (8.1%) had gestational diabetes (P=0.692). In the intervention group, the mean insulin dose was 10.8 ±3 units; in the control group, the mean insulin dose was 21.2±15.7 units (P=0.048). Twenty patients (6.7%) out of 297 obese patients and 8 patients (34.8%) in the morbid obesity group had diabetes (P<0.001). In the control group, the mean weight of mothers was 8.04±2.5 kg; in the intervention group, it was 5.2±2.3 kg during pregnancy (P<0.001). Gestational diabetes, delivery method, death one week after birth, preterm birth, polyhydramnios, and intensive care unit were similar in the two groups.

Conclusion: Metformin in pregnant women with a BMI>30 deals with low maternal weight, reduced birth weight, and reduced insulin dose in diabetic mothers.

Keywords: Diabetes, Metformin, Preeclampsia, Pregnant, Prevention

Introduction

Nowadays, obesity is increasing worldwide and is a public health problem, and this general problem affects numerous women of childbearing age (1). Obesity is one of the critical factors in a pregnant woman. The most common risk factor for maternal deaths is obesity (2). Evidence approved that pregnancy consequences like preeclampsia, lasted hospital stay for mother and child, postpartum hemorrhage, neonatal mortality, and stillbirth due to obesity are increased (3). Insulin resistance and hyperglycemia are more common in women with obesity. Preventing hyperglycemia in pregnancy reduces the risk of birth defects, the incidence of gestational diabetes, preeclampsia, and preterm labor (1). Administration of medications like metformin prevents obesity and gestational diabetes mellitus (GDM). Oral hypoglycemic drugs such as metformin were previously thought to have fetal teratogenic effects, but subsequent research has shown that metformin is not teratogenic and is now used as a safe drug in pregnancy. It is more effective in controlling obesity and preventing GDM (1).

Metformin is an oral antihyperglycemic agent that reduces glucose production in the liver, reduces intestinal glucose reabsorption, and increases insulin sensitivity and peripheral reabsorption. Metformin mostly causes a glycemic state, and hypoglycemia does not usually occur due to its use. Metformin is used in the treatment of GDM as well as in women with polycystic ovary syndrome and is also effective in controlling GDM (4-6). Metformin crosses the

placenta, and studies have shown that the level of the drug in the umbilical cord reaches near maternal levels and clears from the serum with a half-life of approximately 5 hours. Regarding the possible teratogenicity of metformin, several studies have been performed in a systematic study, which showed that metformin use in the first trimester of pregnancy was associated with a 57% reduction in birth defects **(7-11)**.

In another study, it was concluded that cardiac abnormalities, rarely seen in metformin-treated diabetic mothers, were related to inadequate blood glucose control around fertilization and were not associated with metformin use. Various studies have also shown that metformin does not cause neonatal hypoglycemia and lactic acidosis and has no effect on the development of preeclampsia **(12)**. Finally, it has been concluded that metformin has no fetal teratogenic effects and can be administrated during the pregnancy period with caution because medication in the pregnancy may affect many aspects **(5, 13)**.

Recently, metformin has been used as adjunctive therapy to prevent obesity in pregnant women. Side effects of this drug are anorexia, nausea, vomiting, diarrhea, and decreased absorption of vitamin B12, which is more common in high doses and more in people with underlying kidney problems associated with drug excretion **(14)**.

In general, obesity is an almost common health problem worldwide, and maternal obesity deals with adverse maternal and fetal complications. Given that most studies in our country compare the consequences of metformin and insulin in diabetic mothers, we intend to investigate the prophylactic effect of metformin in pregnant women (BMI ≥ 30) with obesity to prevent GDM and reduce insulin use so that in the future we can take a practical step in reducing maternal complications.

Methods

Setting and Design

This clinical trial study was performed on 340 obese nondiabetic pregnant women with BMI ≥ 30 at 12 to 20 weeks of gestation referred to the obstetrics clinic of Motahhari hospital in Urmia for routine pregnancy care. Inclusion criteria included age over 16, singleton pregnancy, and a BMI≥30 kg/m^2. Exclusion criteria were fetal abnormalities, impaired glucose tolerance, multiple pregnancies, having GDM in previous pregnancies, history of underlying diseases such as hypertension, kidney failure, known liver disease, corticosteroid use, alcoholism, gastrointestinal malabsorption, and any allergies to metformin. Following a 2-hrs *Oral Glucose Tolerance Test* (OGTT) examination between weeks 12 and 16 in the laboratory of Motahhari hospital in Urmia, mothers with glucose intolerance and patients with DM were identified and excluded from the study. Age, severity, parity, weight, height, and BMI were assessed.

Intervention

In the intervention group, metformin was administered at a dose of 500 mg every 12 hours from the 12th week until the end of pregnancy. In case of side effects of metformin in patients, they were excluded from the study, and the number of people excluded from the study due to metformin intolerance was finally announced.

Following pregnancy, routinely, a 75-hour glucose screening test was checked for two hours in 24 to 28 weeks of pregnancy in the laboratory of Motahhari Hospital in Urmia, Iran. Individuals who were diagnosed with diabetes in this test (according to the fasting blood sugar/FBS equal to or greater than 92 or OGTT equal to or greater than 180 after 1 hour or OGTT equal to or greater than 153 after 2 hours) visited by a perinatologist and if necessary, they received complimentary or additional treatment. Maternal weight gain was recorded at each visit. Maternal outcomes associated with GDM include preeclampsia, polyhydramnios occurrence (Amniotic fluid index/AFI greater than or equal to 25 on the last ultrasound during the third trimester of pregnancy), and possible intrauterine fetal demise (IUFD) (no heart rate seen by a radiologist) every three times during labor. Follow-up was done by the researcher only. During delivery, infant weight, birth Apgar score, delivery method, cesarean section indications, gestational age, need for hospitalization of the infant in NICU, insulin dose if prescribed, and final maternal weight before delivery were recorded. Weight gain was calculated and compared, and the incidence of gestational diabetes was compared and analyzed in two subgroups.

Ethical Approval

The ethics committee (IR.UMSU.REC.1398.388) approved this research (Clinical trial code: IRCT20200113046112N1). Written consent was obtained from all patients.

Statistical Analysis

The data were entered into SPSS v. 21 and then analyzed. Quantitative variables were reported as central indices and qualitative variables as frequency. Student t-test and X^2 were applied to analyze the hypothesis of interest.

Results

In the metformin group, 170 people were selected for this study. Three subjects did not continue taking metformin due to nausea, vomiting, and oral intolerance to the drug and were excluded from the study. Also, 6 patients, under the influence of their respective physicians, those around them, and the health center, refused to continue taking metformin and were excluded from the study. One of the patients underwent a legal abortion and was excluded from the study due to the diagnosis of Down syndrome during amniocentesis.

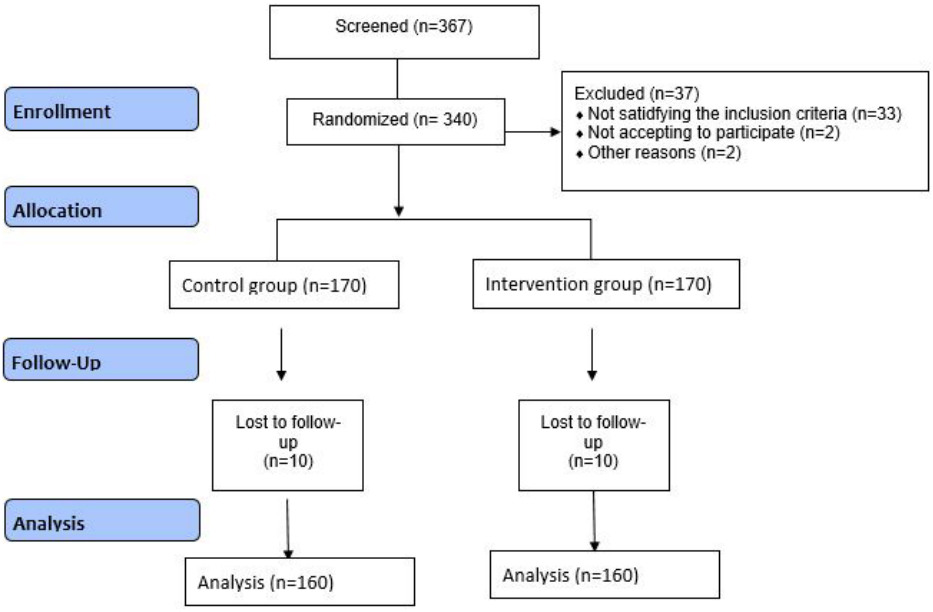

Figure 1. Flow chart for the trial

In the control group of 170 patients, 2 patients had spontaneous abortions at 16 and 19 weeks, so they were excluded. Eight subjects were not satisfied to continue their cooperation due to the advice of those around them and the relevant physician (Figure 1). The mean age of the mother in both groups was not statistically different (*P*=0.860). Also, gravidity (*P*=0.191), parity (*P*=0.063), abortion rate (*P*=0.902), stillbirth (*P*=0.109), BMI (*P*=0.879) and previous IUFD (*P*=0.109) were not statistically different (Table 1).

Table 1. Baseline data of the participants

Group	Previous IUFD	BMI	Abortion	Parity	Gravidity	Age
Intervention	1.2 ± 0.48	34.9 ± 3	1.1 ± 0.8	1.8 ± 1.19	3.1 ± 1.4	32.6 ± 6.2
Control	0.9 ± 0.26	34.9 ± 2.9	1.1 ± 0.3	2 ± 0.9	3.31 ± 1.2	32.4 ± 8.6
P value	0.109	0.879	0.902	0.063	0.191	0.860

In the control group, 15 patients (9.4%) out of 160 patients, and in the intervention group, about 13 patients (8.1%) had gestational diabetes which was not significant in the Chi-square test (*P*=0.692). About 7 patients (46.7%) out of 15 mothers with gestational diabetes in the control group and about 5 patients (38.4%) out of 13 mothers with diabetes in the intervention group needed insulin (*P*=0.718). In the intervention group, 5 patients who had to use insulin had a mean insulin dose of 10.8 units; in the control group, 7 patients had to use insulin, and the mean insulin dose was 21.2 units. In the control group, 86 mothers out of 160 mothers (53.75%) had undergone a cesarean section (CS), and in the intervention group, 83 mothers out of 160 mothers (51.87%) underwent CS (*P*=0.431) (Table 2).

Table 2. Reasons for cesarean section by group

Reasons for cesarean section	History of APR	Preeclampsia	Fetal distress	Breech position	Macrosomic	Non-descent	Meconium	History of cesarean section
Control	2	1	1	1	2	0	2	77
Intervention	2	1	2	1	1	2	4	70

Two infants in the control group died in the first week after birth, one at 26 weeks due to RDS and the other at 30 weeks due to IVH, both due to spontaneous preterm labor, while the intervention group did not have neonatal death (*P*=0.156). In the control group, 10 out of 147 obese patients (8.6%) and 5 out of 13 patients (4.38%) with morbid obesity had gestational diabetes. In the intervention group, 10 out of 150 obese patients (6.6%) and 3 out of 10 patients (30%) with morbid obesity had gestational diabetes. In total, out of 320 patients studied, 23 patients experienced morbid obesity. Among these, 20 patients (6.7%) out of 297

obese patients had gestational diabetes, and 8 patients (34.8%) with morbid obesity had diabetes (*P*<0.001). Sixteen neonates (10%) in the control group and 15 neonates (9.4%) in the intervention group were born before 37 weeks (*P*=0.85). About 3 neonates (1.9%) in the intervention group and about 5 neonates (3.1%) in the control group had polyhydramnios, which was not significant (*P*=0.723). The mean weight of neonates born in the control group was 3795.62±404.7 gr and 3450.6± 334.9 gr in the intervention group. This difference was significant in the independent t-test (*P*=0.001). Fourteen neonates in the control group (8.8%) and 13 neonates (8.1%) in the intervention group were hospitalized in ICU after birth (*P*=0.84). The mean gestational age did not have a significant difference (*P*=0.680) (Table 3).

Table 3. Comparison of weight, insulin dose, and gestational age by group

Variable		Min	Max	Mean ± SD	P-value*
Mother weight gain, kg	Control	2.5	18.5	8.04 ± 2.5	<0.001
	Intervention	2.5	17	5.2 ± 2.3	
Weight at birth, gr	Control	1100	4800	3795.62 ±404.7	0.001
	Intervention	1700	4500	3450.6±334.9	
Insulin dose, IU	Control	6	55	21.1±15.7	0.048
	Intervention	6	14	10.8 ± 3	
Gestational age, year	Control	37.3	40.2	38.6 ± 1.3	0.680
	Intervention	37.3	40.2	39 1.4	

*P-value of independent t-test

Discussion

In the present study, weight gain of mothers with a BMI above 30 during pregnancy was less in the metformin receivers, and their infants had lower birth weight, which could be justified by Pederson's 1952 theory of maternal and fetal hyperglycemia, resulting in hyperinsulinemia and neonatal weight gain **(15)**. Preliminary findings from the Rowan *et al.* study showed no difference in birth weight for women with gestational diabetes receiving metformin/insulin **(16)**. Metformin administration is related to a meaningful reduction in weight gain during pregnancy in mothers with obesity, but this had little effect on fetal weight loss **(2)**. However, follow-up of 2-year-old children showed that infants whose mothers take metformin had higher subcutaneous fat than insulin exposures, which was explained by reduced central fat deposition and better insulin sensitivity **(8)**. In the present study, metformin showed no effect on gestational age, preterm birth, neonatal Apgar score, polyhydramnios in the last 3 semister of pregnancy, and diabetes in obese mothers. Mothers with morbid obesity (BMI greater than 35) had a relatively higher incidence of gestational diabetes than obese mothers (BMI between 30 and 35). These results were consistent as reported in other research **(3, 6, 17)**. Metformin has been illustrated to reduce insulin dose prescribed to diabetics while in a study by Bettencourt-Silva *et al.*, metformin administration in women with obesity did not show effect on glycemic status and insulin administration **(18)**. The results were similar to studies by Singylaki (3000 mg metformin) *et al.* and El Fattah *et al.* (1000 mg metformin) **(9, 19)**. Dodd *et al.* revealed that metformin is able to reduce the weight gain of overweight (not obese) **(20)**. But Chiswick *et al.* showed no effect of metformin to lower pregnant weighting with a BMI>30 kg/kg^2 during pregnancy. Also, in this study, the hospitalization of intensive care units in infants of mothers taking metformin use was less described while in our study, intensive care unit admission had no meaningful difference across groups **(3)**. Another study with a smaller statistical population did not find metformin use effective in reducing the birth weight of mothers with a history of non-obese polycystic ovaries **(21)**. Efficacy of prophylactic use of metformin is a challenging subject and more studies were done in this regard that can be noticed in making decision **(22-24)**.

Further studies with large samples are needed to approve more precise results. In our study, 2 infants died in the control group in the first week after birth, which is about 1% in a study by Chiswick *et al*. **(3)** It is better to check glucose levels in pregnant women who report GDM regularly; if so, metformin is a choice agent **(25, 26)**.

Conclusion

Prophylactic use of metformin has been shown to reduce maternal weighting in the pregnancy period and birth weight without any effect on DM and the need for insulin in pregnant women. Metformin can reduce the dose of insulin used in people with gestational diabetes. Finally, studies with larger sample sizes and higher doses of metformin should be performed to obtain more comprehensive results.

Acknowledgments

None.

Study Limitations

Loss of follow-up was one of the limitations. It was not possible to use a placebo in the control group due to the problems of placebo preparation. On the other hand, the placebo had practically no effect on gestational diabetes.

Authors' contribution

SG, FB, and SV designed the study. SG, FB, and SV performed the experiments. FB and SV collected data from patients and helped perform experiments. RG and SG prepared the preliminary draft after analysis. All authors read and signed the final paper.

Conflict of Interest

The authors declared no conflicts of interest.

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