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Efficacy of Metformin on Pregnancy Outcome in Healthy Overweight Pregnant Women; A Double-Blinded Parallel Randomized Clinical Trial

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Abstract

Background

Maternal obesity increases the risk of pregnancy complications such as preeclampsia, postpartum hemorrhage, weight gain and the need for cesarean section. We compared the role of metformin on pregnancy outcome in overweight mothers.

Materials and Methods: This double-blinded parallel randomized clinical trial was carried out on 360 pregnant women at 12-16 gestational weeks who referred to the gynecology clinic of Motahari hospital, Urmia, Iran, during 2019 to 2020. The intervention group received 1000 mg of metformin orally every day up to the end of pregnancy. Demographic and clinical characteristics of patients such as age, gravidity, parity, preterm infant weight, live birth, abortion, previous delivery method, maternal weight, body mass index, birth weight, delivery method, blood sugar at birth, gestational age at birth, neonatal hypoglycemia, infant mortality and anomalies were also recorded. Finally, the pregnancy outcomes (gravidity, parity, abortion and weight) were compared between the two groups.

Results: Of 180 patients, 169 patients remained in the intervention group and 171 patients remained in the control group based on the eligibility criteria. In the control group, 13 patients (7.6%), and in the intervention group, five patients (2.9%) had preeclampsia and high blood pressure during pregnancy (P= 0.053). In the control group, the mean maternal weight gain during pregnancy was 10.22 ± 3.3 kg and in the intervention group was 7.6 ± 2.3 kg (P <0.001). The two groups were homogeneous regarding gravity, parity, abortion (P>0.05).

Conclusion

The administration of 1000 mg metformin daily has been shown to be effective in preventing overweight in pregnancy, but has not affected the birth weight. Metformin did not have any side effects on pregnancy outcomes.

Key Words: Birth weight, Metformin, Pregnancy, Preeclampsia, Overweight.

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1- INTRODUCTION

Obesity and overweight are pandemic and a major health problem in pregnancy, affecting about 20-25% of pregnant women (1). Maternal obesity increases the risk of pregnancy complications such as preeclampsia, postpartum hemorrhage, weight gain and the need for cesarean section (2, 3). While obesity increases fetal outcomes such as fetal macrosomia, intrauterine death and neonatal death (4). Some studies have reported that the costs of antenatal care in overweight or obese mothers are 5-16 times higher than the normal population (5). Previous studies have shown that, dietary changes as well as lifestyle changes have not been able to reduce the complications of pregnancy associated with obesity. Recently, the role of hyperglycemia and insulin resistance have been mentioned as the factors leading to maternal weight gain during pregnancy, fetal macrosomia and gestational diabetes.

Accordingly, these findings have led to studies which predict the prophylactic role of metformin in reducing the effects of obesity and overweight in pregnancy (1). Metformin is an oral antihyperglycemic agent, and its mechanism is to reduce glucose production in the liver, decrease glucose reabsorption from the intestine, increase peripheral reabsorption, and increase insulin sensitivity. Metformin is more likely to cause euglycemic status and hypoglycemia usually does not occur as a result of its use. It is used in the treatment of gestational diabetes and in women with polycystic ovary syndrome (6-10). Metformin has no teratogenicity effects and can be prescribed during pregnancy (7, 8). It has recently been used as an adjunctive therapy in preventive strategies in obese pregnant women by reducing glucose production in the liver and improving glucose uptake into smooth muscle. Metformin improves women's metabolic status during pregnancy (10).

Metformin administration in obese mothers has reduced the incidence of preeclampsia but has no role in controlling fetal weight (11). In a study, metformin reduced endothelial dysfunction by affecting the secretion of tyrosine kinase and soluble endoglin, and by reducing vasodilation can induce angiogenesis (12). Additionally, a systematic study showed that metformin has been shown to be effective in reducing blood pressure disorders in pregnant women (11, 13). Due to the importance of pregnancy outcomes and the limited studies in this field, in this study, the prophylactic effect of 1000 mg metformin in overweight pregnant women with a body mass index of 25 to 29.9 kg/m^2 and its role in preventing maternal outcomes was examined.

2- MATERIALS AND METHODS

2-1. Study design and population

This study was a double-blinded parallel randomized clinical trial. A total of 360 pregnant women were included in the study. According to the study by Syngelaki et al. (14), and using the corresponding formula to compare the two proportions, (α =0.05, Power=0.8, Z1 - α / 2 = 1.96, Z1-β = 1.28, P1 = 0.03, p2 = 0.113), 170 was obtained for each group. Taking into account the attrition, a total of 360 pregnant women who met the eligibility criteria were included in the study.

2-2. Methods

Healthy pregnant women with a body mass index (BMI) of 25 to 29.9 kg/m^2 at 12-16 gestational weeks that referred to the gynecology clinic of Motahari hospital in Urmia, Iran, were entered into the study. The two groups were randomized using random allocation software which is available at www.randomizer.at. The patients were unaware of the allocated groups and also data analyzer received the data as group A and B without the exact

name of the groups, therefore, both parts were blind including patients and data analyzer.

2-3. Measuring

Demographic characteristics of the patients such as age, gravidity, parity, previous infant weight, live birth, abortion, previous delivery method, maternal weight, maternal height, and BMI were recorded. The data were recorded based on the required variables in the pre-designed checklist by main investigator. For all subjects at the first visit, a 75-gram oral glucose challenge test (*OGCT*) was performed to exclude patients with impaired glucose tolerance (fasting blood sugar; FBS)> 92 mg/dl and 1-*hour post* prandial (1-HPP)> 180 or 1-*hour post* prandial (2-HPP)> 153 mg/dl) (14).

2-4. Intervention

In the intervention group, 180 people received 1000 mg metformin orally per day (made by Dorsapharma, Iran), and in the control group, 180 people received placebo which was specifically designed to have no real effect (it was approved by the Urmia Pharmaceutical Company).

2-5. Ethical consideration

This study is a randomized controlled trial which is registered in the Iranian Registry of Clinical Trials (IRCT20190716044229N1, https://www.irct.ir). The study was reviewed and approved by the Ethics committee of Urmia University of Medical Sciences (IR.UMSU.REC.1398.143). We adhered to the principles of Helsinki and the informed consent of the mothers was obtained, also the placebo had no side effects and was approved by the Urmia Pharmaceutical Company. This study was extracted from residential thesis of Samira Esmaieli, at the Department of Gynecology of Urmia University of Medical Sciences.

2-6. Inclusion and exclusion criteria

Inclusion criteria were pregnant women at 12-16 gestational weeks, without underlying disease related to obesity such as diabetes, hypertension, kidney, liver and heart diseases, and with BMI of 25 to 29.9 kg/m^2. Exclusion criteria were multiple pregnancies, fetal abnormalities during screening tests, history of glucose disorder, a history of gestational diabetes or preeclampsia in the previous pregnancies, and the use of corticosteroids.

2-7. Data Analyses

For descriptive statistics, quantitative variables, central indices and dispersion (mean and standard deviation) were calculated, and for qualitative variables, frequency and percentage were calculated. T-test for mean difference between the two groups, Chi-square for qualitative variables between the two groups, ANOVA repeated measure to check trend of weight, and multivariate analysis such as regression to assess odds ratio were used to control the effects of confounders. All statistical analyses were performed using SPSS software version 21.0. P-value less than 0.05 were considered significant.

3- RESULTS

The present study was conducted on 80 hospitalized children with demographic data presented in (**Table.1**). Age, gender and among children were not significant different in the intervention and control groups (P>0.05) (**Table.1**). The mean and standard deviation of the score of behavioral responses to pain in the control and intervention group were 7.95 ± 1.084 and 2.65 ± 1.577, respectively (**Table.2**). There was a significant difference between the two groups in terms of pain (P<0.001). Also, 70% of children in the control group experienced severe pain, but most children in the intervention group (77.5%) had a little pain. There was a significant difference found by Chi-square test in terms of pain intensity in both groups (P<0.001) (**Table.3**).

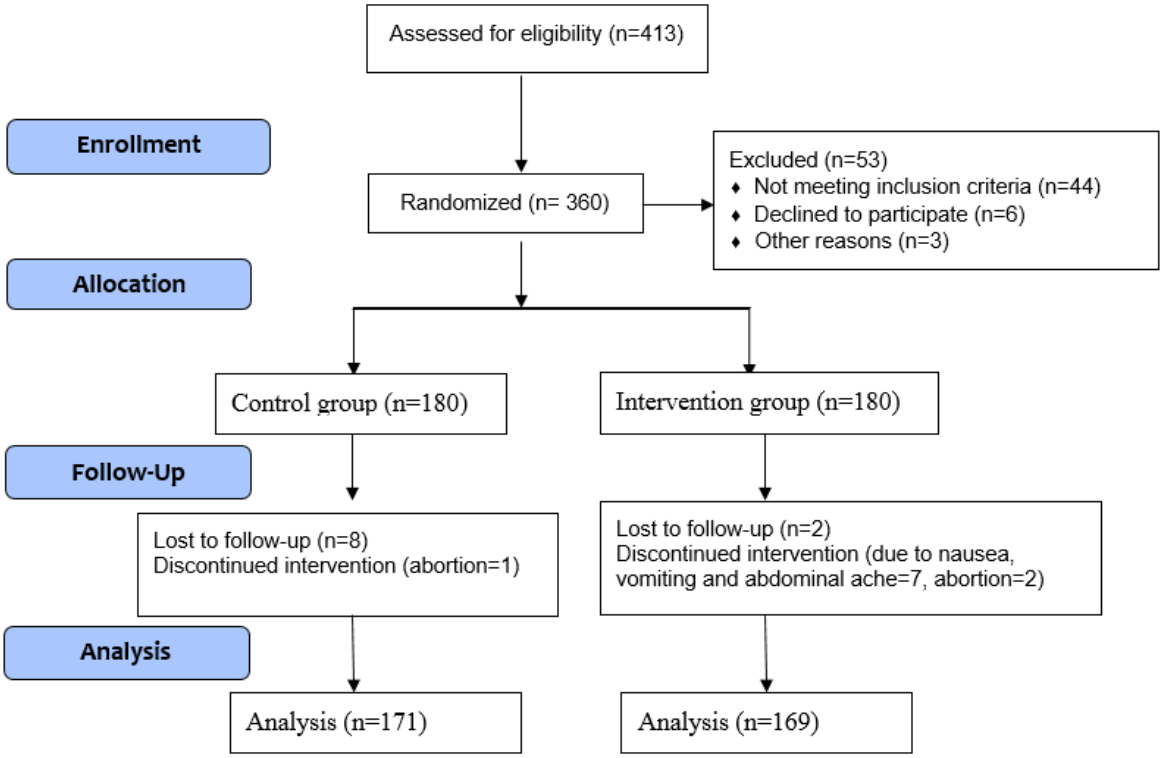

Fig.1: CONSORT (consolidated standard of reporting trial) chart for study.

Table.1 presents the comparison of the mean of demographic variables of mothers in the two groups. The mean age of mothers in the control group was 34.2±9.6 years and in the intervention group was 34.6±8.4 year. The mean parity of mothers in the control group was 1.13±0.89, and in the intervention group was 1.09±0.86. The mean birth weight of the previous delivery in the control group was 3176 ± 333.35 gr and in the intervention group was 3141 ±356.65 gr. The results showed, no statistically significant difference between two groups (P= 0.76). The mean of maternal gravidity, parity, abortion, and previous birth weight in the both groups was no statistically significant difference (P>0.05).

Table-1: Comparison of the mean of demographic variables of pregnant women in the two groups of metformin and placebo.

Variables	Group	Number	Mean	SD	P-value
Gravidity	Control	171	2.58	1.20	0.72
	Intervention	169	2.54	1.19	
Parity	Control	171	1.13	0.89	0.72
	Intervention	169	1.09	0.86	
Abortion	Control	171	0.47	0.84	0.90
	Intervention	169	0.46	0.93	
Previous birth weight (kg)	Control	171	3176.2	333.35	0.42
	Intervention	169	3141.46	356.65	
Age (year)	Control	171	34.2	9.6	0.76
	Intervention	169	34.6	8.4	

Table.2 shows that the mean birth weight of mothers in the control group was 82.88±6.28 kg and in the intervention group was 79.46±6.67 kg. To compare the means between the two groups, t-test was used which showed a statistically significant difference between two groups (P<0.001). The mean weight gain during pregnancy (weight gain) in the control group was 10.19 ± 3.06 kg and 7.69±2.36 kg in the intervention group respectively (P<0.001). The mean BMI of mothers in the control group was 28.17±1.22 kg/m^2, and 28±1.22 kg/m^2 in the intervention group (P=0.198).

Table-2: Comparison of the mean of anthropometric variables of pregnant women in the two groups of metformin and placebo.

Variables	Group	Number	Number	Mean	SD	P- value
Weight of mother before intervention (kg)	Control	171	171	72.69	5.40	0.145
	Intervention	169	169	71.77	6.11	
Weight of mother at delivery time (kg)	Control	171	171	82.88	6.28	0.001
	Intervention	169	169	79.46	6.67	
Weight gain during pregnancy (kg)	Control	171	171	10.19	3.06	0.001
	Intervention	169	169	7.69	2.36	
BMI (kg/m^2)	Control	171	171	28.17	1.22	0.198
	Intervention	169	169	28.00	1.22	

Intervention: metformin group, Control: placebo group.

Table.3 shows the comparison of mothers' weight gain during pregnancy in the two groups of metformin and placebo. According to the findings, 124 mothers (72.5%) in the control group and 160 mothers (94.7%) in the intervention group during pregnancy had normal weight gain. Chi-Square test was used to compare the two groups. The results showed that there was a statistically significant difference between the two groups (P<0.001), and the administration of metformin decreases the development of abnormal weight gain (odds ratio = 0.148). If the odds ratio is less than 1, it means that the intervention has preventive effect and 0.148 is smaller than 1.

Table-3: Comparison of mothers' weight gain in the two groups of metformin and placebo.

Variables			Abnormal weight gain		Total
			No	Yes	
Group	Control	Number	124	47	171
		%	72.5	27.5	100
	Intervention	N	160	9	169
		%	94.7	5.3	100
Chi-Square =30.34, P=0.001, Odds ratio=0.148, Confidence interval 95%=0.070-0.314.					

Intervention: metformin group, Control: placebo group.

Table.4 shows the comparison of the mean variables of neonates in the two groups of metformin and placebo. According to the findings, the mean weight at 34-32 gestational weeks, 37 gestational weeks, mean birth weight and gestational age in the two groups showed no statistically significant differences (P> 0.05). The mean neonatal blood glucose in the control group was 78.02±5.70 g/dl and in the intervention group was 79.52±6.93 g/dl. To compare the mean between the two groups, t-test was

used which showed a statistically significant difference between the two groups (P=0.030). Regarding gestational diabetes, preeclampsia, type of delivery, macrosomia, preterm birth (birth less than 36 week of pregnancy), hospitalization in NICU, the results showed, no statistically significant difference between the two groups (P> 0.05). The trend of weight changes is presented in **Figure.2**.

Table-4: Comparison of the mean variables of neonates in the two groups of metformin and placebo.

Variables	Group	Number	Mean	SD	P- value
Weight at 32-34 weeks (kg)	Control	171	2075.09	260.53	0.27
	Intervention	169	2108.70	292.01	
Weight at 37 weeks (kg)	Control	171	2905.59	338.56	0.46
	Intervention	169	2876.80	351.41	
Weight at birth (kg)	Control	171	3328.07	462	0.61
	Intervention	169	3302.93	457.89	
Neonatal blood glucose (g/dl)	Control	171	78.02	5.70	0.03
	Intervention	169	79.52	6.93	
Gestational age (week)	Control	171	38.54	1.27	0.34
	Intervention	169	38.40	1.47	

Intervention: metformin group, Control: placebo group.

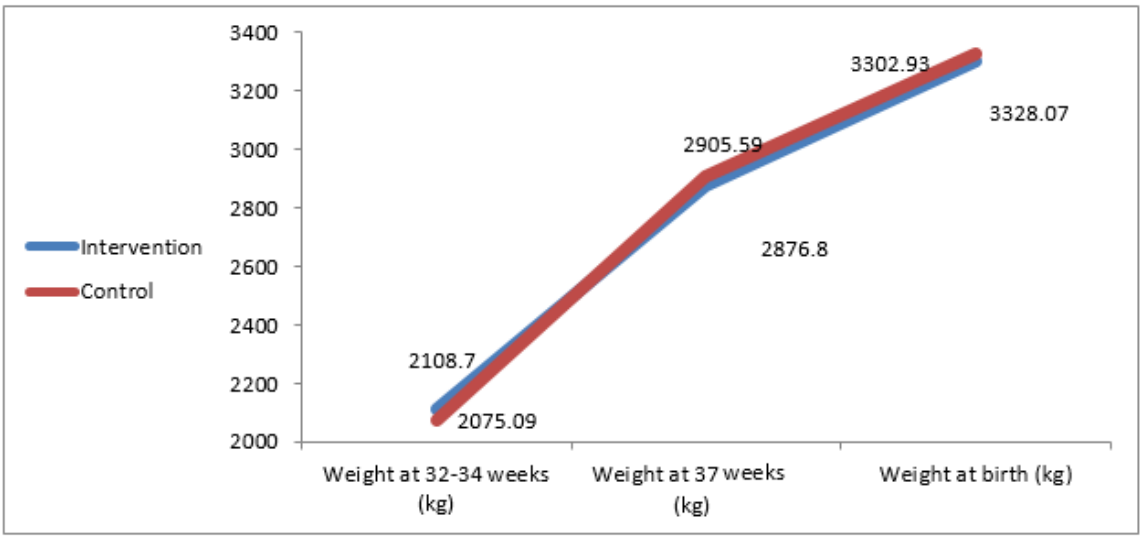

Fig.2: Trend of weight changes in three points in the two groups of metformin and placebo.

4- DISCUSSION

In the present study, we compared the role of 1000 mg metformin orally on pregnancy outcome in overweight mothers with BMI of 25 to 29.9 kg/m2. In summary our study revealed that metformin can prevent abnormal weight gain during pregnancy but has no effect on other outcomes. The administration of metformin, in addition to dietary and lifestyle recommendations, did not affect infants weighing more than 4,000 grams at birth compared to placebo group. Maternal weight gain during pregnancy in the metformin group was significantly lower. Maternal weight gain was lower than the guideline in the metformin group compared to the control group. Metformin is increasingly used during pregnancy to

treat gestational diabetes, and there is evidence to support its safety. Rowan et al showed no difference in the birth weight of women with gestational diabetes treated with insulin or metformin (14). Neonates exposed to metformin in uterus have higher BMI than insulin group, which has been explained by increased central fat deposition and metric dose (17). The findings of our study showed that the administration of metformin had no effect on the outcome of pregnancy, gestational diabetes, preeclampsia, and intrauterine fetal death and fetal macrosomia. The finding was consistent with the results of other studies (15, 18, 19). Singelaky et al. reported a significant reduction in the risk of preeclampsia using metformin (15). The results presented for preeclampsia as secondary results in a small number of samples do not appear to be reliable. In a meta-analysis, metformin has an indefinite effect on pregnancy hypertension (18, 15).

In our study, metformin has been shown to be effective in reducing weight gain during pregnancy in overweight women. In a recent meta-analysis similar to our study, the administration of metformin had no effect on fetal macrosomia, preterm birth before 32, 34 and 36 gestational weeks, infant weight at 34-34 gestational weeks, 37 gestational weeks, and birth weight (17). The results were similar to those of Singelaki et al. (3000 mg metformin), and El-Fattah (1000 mg metformin) (15, 19).

In the study of Dodd et al., the partial effect of metformin in reducing the weight gain of overweight (not obese) and macrosomic mothers has been described and due to its description in the secondary results, its approval depends on the results of other studies (20). In a study by Chiswick et al., metformin (500 to 2500 mg) was not effective in reducing maternal weight gain during pregnancy and neonatal weight (19). However, these studies were used to select patients based on body mass index and metformin doses were different. Further studies with large samples will need to confirm these results. In our study, metformin had no effect on cesarean section and vaginal delivery, which was similar to previous studies. In a recent meta-analysis, the probability of occurrence of at least one of the side effects of metformin was described as about 1.6 times and the most common complication was diarrhea (20). It seems that the reason for the lower rate of side effects in our study is the lower dose of metformin. Hypoglycemia was not evident in any of the neonates after birth in our study that was consistent with the results of studies by Singelaki et al., Chiwick et al., and meta-analysis performed by Dodd et al. (15, 18, 21).

4-1. Study Limitations

Problems such as patients' unwillingness to continue taking the drug, intolerance to gastrointestinal side effects of the drug could be solved with appropriate scientific explanations about the positive effects of metformin on gestational weight control, prevention of gestational diabetes and preeclampsia, hence we provided a suitable solution and increased the motivation of the subjects to continue the treatment.

5- CONCLUSION

The administration of 1000 mg metformin daily has been shown to be effective in preventing overweight in mothers during pregnancy and balancing the weight gain during pregnancy, but has not affected the birth weight and macrosomia. The administration of metformin has no effect on abortion.

6- AUTHORS' CONTRIBUTION

SE and SV designed the study. SE performed the experiments. SV collected data from patients and helped in performance of experiments. SE and JR

prepared the primary draft after analysis. All authors read and signed the final paper.

7- ACKNOWLEDGMENTS

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8- CONFLICT OF INTEREST: None.

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