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The Effect of Metformin in Preventing of Superimposed Preeclampsia: a Randomized Clinical Trial

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ABSTRACT

Background & Objective: Preeclampsia is associated with the release of soluble endoglin (sENG) into the maternal circulation. It inhibits sENG secretion, inhibiting the complex I of the mitochondrial electron transport chain. Therefore, using metformin may be helpful in the prevention of preeclampsia. The aim of this study was to evaluate the effect of metformin in preventing superimposed preeclampsia.

Materials & Methods: This single-blind randomized clinical trial was conducted on 60 pregnant women 25-40 years old with chronic hypertension before the 20th week of pregnancy. The patients were randomized and divided into two groups (n=30). The first group received 1000 mg metformin (tablet metformin 500 mg bid), and the second group received a placebo (2 tablets daily). Then the incidence of preeclampsia and intrauterine retardation growth of the fetus were compared in the two groups.

Results: The metformin consumption significantly reduced the incidence of preeclampsia (P=0.04) and intrauterine growth restriction (P=0.035) compared to the control group.

Conclusion: Metformin effectively reduced the incidence of superimposed preeclampsia and related factors in a pregnant patient with chronic hypertension.

Keywords: Chronic Hypertension, Metformin, Pregnancy, Superimposed Preeclampsia

Introduction

Preeclampsia is a multisystem progressive disorder and affects 5–8% of pregnancies. It as the main pregnancy complication was responsible for the deaths of 400 perinatal and over 100 maternal a day **(1-4)**.

The WHO announced that 76,000 maternal deaths occur by preeclampsia annually, accounting for 16% of global maternal mortality **(5)**.

It is a complication characterized by new-onset hypertension, typically after 20 weeks of gestation, with evidence of end-organ damage, including renal injury, neurological injury, liver injury, and hemolytic effects **(3)**.

The exact mechanism of preeclampsia is not known. It is more a syndrome with various subtypes than a single disease. The pathogenesis of this disease was multifactorial due to an interaction of environmental and genetic factors and abnormal placentation **(5-7)**. The environmental etiology of preeclampsia is different based on variables, including socioeconomic status, weight, and geographical area. The genetic etiology of preeclampsia is evident in patients with a family history of the disease **(1)**.

The main step in the pathophysiology of this disease may be hypoxia and placental ischemia, leading to the release of soluble endoglin (sENG) and FMS-like tyrosine kinase 1 (sFlt-1) into the maternal circulation **(1)**.

There are no therapies to prevent disease progression and expectant management, and it seems that delivery is the only treatment option **(1)**. A medication that decreases placental sFlt-1 and sENG secretion may be efficient in treating or preventing preeclampsia. Metformin is known as dimethyl-biguanide hydrochloride. It is an anti-diabetic agent and shows this effect by inhibiting gluconeogenesis **(5)**. There is evidence that metformin inhibits sFlt-1 and sENG secretion by inhibiting the complex I of the mitochondrial electron transport chain **(1)**. Moreover, metformin may prevent preeclampsia by improving insulin sensitivity and cardiovascular function and preventing gestational weight gain **(8)**. This also reduces vascular cell adhesion molecule 1 (VCAM-1);

however, metformin's most common side effects are transient gastrointestinal symptoms, including vomiting, nausea, diarrhea, and a metallic taste after ingestion **(9)**.

Given that 5-10% of pregnant women suffer from hypertension disorder and preeclampsia during pregnancy **(10-16)** and the use of metformin may be helpful in the prevention of preeclampsia, and there is no comprehensive study regarding the effect of metformin in preventing preeclampsia in our country, this study aimed to assess the evaluating the effect of metformin in preventing preeclampsia.

Methods

Sample Selection

This single-blind randomized clinical trial was conducted on 60 pregnant women with chronic hypertension treated with methyldopa tablet before the 20th week of pregnancy in the prenatal clinic of Akbarabadi Hospital, Faculty of Medicine, Iran University, from June 2020 to September 2021.

Inclusion and Exclusion Criteria

Age between 20-45, being diagnosed with chronic hypertension, without preeclampsia signs, singleton pregnancy, and gestational age before 20 weeks were inclusion criteria. Multiple pregnancies, chronic renal impairment, intrauterine growth restriction, diabetic patients, and non-cooperation of patients to take medication were exclusion criteria from the study.

Smoking or a history of preeclampsia in last pregnancies were not exclusion criteria, but their frequency was matched in two groups.

Material and Methods

A total of 60 pregnant patients with chronic hypertension treated with methyldopa were divided into two groups (n=30). Two groups were matched in demographic data, including age, gravida, parity, previous preeclampsia, body mass index, and smoking. The first group received 500 mg metformin (Aria co.) twice daily, and the second group received a placebo (capsules containing starch) (Barij Essence, Kashan, Iran) twice daily. The patients were followed up every 1-2 weeks after study admission until delivery. Blood pressure was checked during each visit by electronic monitoring, and if BP >= 140/90, or if the patient complained of headache, heartburn, diplopia, nausea, vomiting, or if a patient was a candidate for termination of pregnancy, we checked blood pressure, platelet, urinary protein, liver enzymes, in all patients.

Intrauterine growth complications were assessed in these patients using Doppler ultrasound every 4-6 weeks in pregnancy.

Ethical Consideration

After obtaining written consent from patients, the current study was approved by the Ethical Committee of Iran University of Medical Sciences (IR. IUMS. FMD.REC.1398.472).

Statistical Analysis

Data were entered into SPSS version 19. The comparison of variables between the case and control groups was assessed by the Independent T-test, Fisher exact test, and Chi-Square test. The comparison of variables before and after intervention in the case and control group was evaluated using the paired sample T-test. P-value<0.05 was assumed significant.

Results

Figure 1 shows the consort flowchart of patients with chronic hypertension.

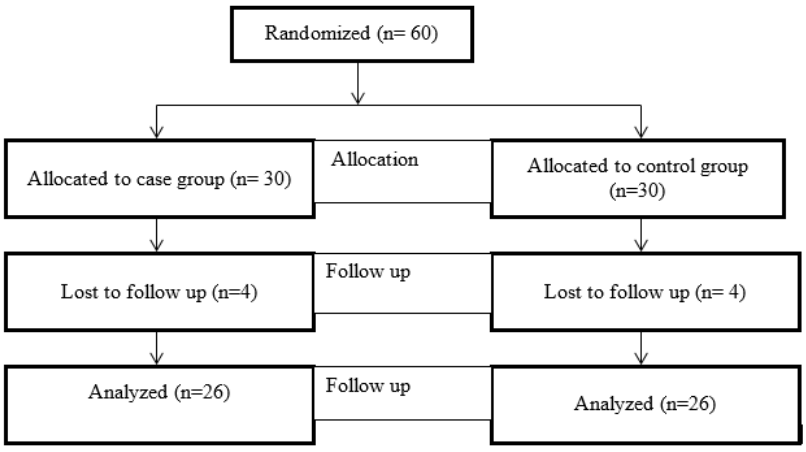

Figure 1. The consort flowchart of patients with chronic hypertension

The comparison of the case and control groups in terms of variables, including age, parity, gravida, previous preeclampsia, and smoking, is shown in Table 1.

Table 1. The demographic variables of the case and control groups

Group	Case	Control	P-value
Age (year)	33.8±4.49	33.38±7.32	0.37
BMI (kg/m^2)	28.68 ±4.9	30.59 ± 7.98	0.30
Gravida Number (percent)			
1	4 (15.4)	4 (15.4)	
2	4 (15.4)	8 (30.9)	
3	10 (38.5)	7 (26.9)	0.59
4	6 (23.1)	4 (15.4)	
5	2 (7.6)	1 (3.8)	
8	0 (0)	2 (7.8)	
Total	26 (100)	26 (100)	
Parity Number (%)			
0	4 (15.4)	4 (15.4)	
1	12 (46.2)	11 (42.3)	
2	8 (30.8)	7 (26.9)	0.83
3	2 (7.7)	2 (7.7)	
4	0 (0)	2 (7.6)	
Total	26 (100)	26 (100)	
Previous Preeclampsia			
Yes	15 (57.7)	8 (30.8)	0.051
No	11 (42.3)	18 (69.2)	
Total	26 (100)	26 (100)	
Smoking			
Yes	1 (3.8)	0 (0)	0.31
No	25 (96.2)	26 (100)	
	26 (100)	26 (100)	

As shown in Table 1, no significant difference was observed between the two groups regarding age, BMI, parity, gravida, preeclampsia, diabetes, and smoking (P>0.05).

The comparison of the case and control groups before and after metformin administration regarding variables, including platelet and urinary protein, is shown in Table 2.

Table 2. The case and control groups were compared in terms of variables, including age, parity, gravida, preeclampsia, diabetes, and smoking

0	Before administration of metformin		P-value	After administration of metformin		P-value
	Case	Control		Case	Control	
Platelet (×1000/mm3)	246.2±41	239.8±52.8	0.6	227.7±58.6	192.3±50.35	0.023
***AST (unit/liter)**	18.38±5.04	17.95±3.26	0.72	22.53±9.26	31.15±14.25	0.013
****ALT (unit/liter)**	20.34±7.5	19.92±4.31	0.8	20.26±7.24	25.84±10.74	0.033
Urinary protein>300mg/24h	0 (0)					
	26(100)	0 (0)				
Yes	26 (100)	26(100)		2 (7.7)	8 (30.8)	
No		26 (100)		24 (92.3)	18 (69.2)	
Total			1-	26 (100)	26 (100)	0.034

*: Aspartate aminotransferase
**: Alanin aminotransferase

As shown in Table 2, there was no significant difference between the control and case groups in terms of PLT, AST, ALT, and urinary protein before metformin administration (P>0.05).

There was a significant difference between the case and control groups in terms of PLT, AST, ALT, and urinary protein, after administration of metformin (P<0.05).

The comparison of variables before and after treatment in the case and control groups is shown in Table 3.

Table 3. The comparison of variables before and after treatment in the case and control group

Variables	Group	Before treatment	After treatment	P-value
ALT	Case	20.34±7.5	20.26±7.24	0.96
	Control	19.92±4.31	25.84±10.74	0.016
AST	Case	18.38±5.04	22.53±9.26	0.057
	Control	17.96±3.2	31.15±14.25	P<0.001
PLT	Case	264.23±41.36	227.76±58.06	0.14
	Control	239.8±52.82	192.3±50.35	0.001

As shown in Table 3, there was no significant difference before and after treatment in the case group in terms of ALT, AST, PLT (P>0.05). However, a significant difference was seen in the mean of variables before and after treatment in the control group (P<0.05).

Table 4 is shown the frequency of incidence of IUGR, HELLP syndrome, superimposed preeclampsia, and HELLP syndrome.

Table 4. The characteristic frequency of patients

Characteristics	Case group	Control group	P-value
Intrauterine growth retardation (IUGR)	2	8	0.035
The incidence of HELLP syndrome	0	1	0.09
Preeclampsia severity			
Non-severe	0	2	0.08
Severe	1	8	0.04

Severe preeclampsia and IUGR were significantly lower in the metformin group than in the placebo group.

Discussion

The current study's findings showed that there was a significant difference between the case and control groups in terms of superimposed preeclampsia. In this regard, the frequency of patients with preeclampsia in the case group was significantly lower than in the control group.

Also, the mean PLT and AST level of patients in the control group increased more than before the intervention. Still, there was no significant difference in the intervention group regarding the mean PLT and AST level. ALT levels also increased significantly in the control group, but these changes were not significant in the case group.

Løvvik *et al.* assessed the effect of metformin on treating pregnant women with polycystic ovary syndrome (PCOS) and observed that there was no significant difference between the intervention and placebo groups in terms of preeclampsia pregnancy complications such as GDM **(17)**.

The finding of this study regarding the effect of metformin administration on diabetic pregnancy was consistent with our study; however, the current study revealed that metformin administration reduced the incidence of preeclampsia which was inconsistent with Løvvik *et al.* study. The reason for this discrepancy between the two studies may be due to differences in sampling, the effect of confounders, inclusion and exclusion criteria, and the sample size.

Alqudah *et al.* evaluated the risk of preeclampsia in women taking metformin and observed no significant difference between the case and control groups regarding preeclampsia; however, a significant

difference was seen between metformin and insulin groups in terms of preeclampsia. In this regard, metformin reduced the incidence of preeclampsia by 68% compared to insulin **(18)**. Although in the current study, we did not compare metformin with another medication, it was found that metformin administration reduced the incidence of preeclampsia. Still, this effect in Alqudah *et al.* study was seen only compared to insulin. Therefore, a comprehensive study regarding the effect of metformin on preeclampsia in different groups of pregnant women should be done to evaluate the exact effect of metformin on gestational preeclampsia and observe that metformin reduced the incidence of hypertensive disorders in pregnancy than insulin and placebo. The finding of this study was consistent with the findings of our study, indicating lower blood pressure and preeclampsia after metformin administration **(18)**.

Romero *et al.* evaluated the effect of metformin in preventing preeclampsia and observed that metformin had the same role as aspirin in reducing the risk of cardiovascular disease in reducing preeclampsia **(19)**. The finding of this study was consistent with our study. However, pathophysiological evaluation to reduce the incidence of preeclampsia following metformin administration requires a more detailed examination.

Nascimento *et al.* evaluated the administration of metformin in patients with preeclampsia and observed that metformin reduced the risk of preeclampsia to some extent. Still, it had a greater preventive effect on pregnancy-induced hypertension **(20)**.

Brownfoot *et al.* reported that metformin caused vasodilation and angiogenesis, which was mediated by tyrosine kinase and endoglin, leading to the prevention and treatment of preeclampsia. Therefore, based on the findings of this study and our study, it can be concluded that metformin through tyrosine kinase and endoglin can prevent preeclampsia. However, a more detailed study should be conducted in this area **(21)**.

Jamal *et al.* assessed the effect of metformin on pregnancy outcomes and uteroplacental circulation in pregnant women with PCOS **(1)**. In this regard, the mean decrease in pulsatility index of uterine arteries from the 12th to the 20th week of pregnancy was 0.38 in the metformin group and 0.16 in the placebo group. The incidence of preeclampsia, gestational diabetes, and preterm labor was higher in the placebo group than in the metformin group, but this difference was not statistically significant. The findings on reducing the incidence of preeclampsia were similar to the current study. But in the study, despite the reduction in the incidence of preeclampsia, no statistically significant difference was observed in this regard, which was inconsistent with the current study. It seems that this difference may be due to differences in the sample size.

Conclusion

The current study's findings showed that metformin consumption significantly reduced the incidence of preeclampsia compared with the control group.

Acknowledgments

None.

Ethical Committee

(IR. IUMS. FMD.REC.1398.472).

Clinical trial code: IRCT20210316050725N1

Conflict of Interest

The authors declared no conflict of interest.

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