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Original Article

# Evaluation of Metformin Plus Insulin Versus Insulin-Only in Preventing Pre-Eclampsia in Pregnant Women with Gestational Diabetes Mellitus: A Randomized Single-Blind Clinical Trial

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**Abstract**

**Background and aims:** Gestational Diabetes Mellitus (GDM) is associated with an increased risk of pregnancy complications. The present study aimed to evaluate the effect of combined metformin and insulin therapy compared to insulin alone in preventing pre-eclampsia among pregnant women with GDM.

**Methods:** This randomized interventional clinical trial was conducted on 150 women with GDM in Isfahan from 2021 to 2023. Women in the insulin-only group received intermediate-acting insulin such as Neutral Protamine Hagedorn (NPH), at a dose of 0.2 units/kg. In the group treated with metformin plus insulin, a similar method was used, starting with an initial dose of 500 mg of metformin twice daily. The results were analyzed using SPSS software version 19.

**Results:** The number of patients with protein excretion in the insulin group was significantly higher than that in the insulin-plus-metformin group ($P=0.006$). Additionally, the insulin dose used in the insulin-plus-metformin group was significantly lower than in the insulin-only group ($P=0.013$). A significant difference was observed in the gestational age at study entry in patients with other pregnancy complications ($P=0.04$).

**Conclusion:** Adding metformin to insulin therapy in pregnant women with GDM may help reduce insulin requirements and the incidence of proteinuria in those who develop pre-eclampsia, without increasing other pregnancy complications.

**Keywords:** Metformin, Insulin, Pre-eclampsia, Pregnant females, Gestational diabetes mellitus

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## Introduction

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance with onset or first diagnosis during pregnancy. It is caused by the insufficient functioning of pancreatic beta cells to supply the required insulin. Insulin resistance during pregnancy is the primary contributing factor to this condition (1). Factors that cause GDM include maternal age, pre-pregnancy, weight and obesity, previous history of delivering a macrosomic infant, and a family history of diabetes (2).

The prevalence of GDM varies depending on the population studied and diagnostic criteria used, ranging from 1% and 14.2% in most Southeast Asian countries. The lowest rates are reported in European countries, ranging from 1.2% to 3.1% (3-6). Given that GDM has become a worldwide health problem (7), it can be associated with significant morbidity and mortality for both mothers and infants (8-11). Mothers with GDM are at an elevated risk of pregnancy-related complications, including gestational hypertension and pre-eclampsia, which often necessitate cesarean section delivery. Furthermore, mothers with a history of GDM are significantly at higher risk of developing type 2 diabetes and diabetes-related cardiovascular complications (9, 12, 13). On the other hand, babies born to mothers with GDM may have complications such as macrosomia, congenital anomalies, neonatal hypoglycemia, and an increased risk of developing diabetes and cardiovascular disorders later in life (9). Pregnancy-induced hypertension may also lead to a range of severe conditions, including seizures, hepatic and renal failure, intrauterine growth restriction (IUGR), fetal distress, preterm delivery, and perinatal mortality.

Although the exact pathophysiology of pre-eclampsia is not yet fully understood, it is believed to involve a multifactorial condition characterized by a complex interplay of genetic, environmental, and physiological factors. Extensive studies have identified glucose intolerance and insulin resistance as key contributors to pre-eclampsia. Despite numerous studies exploring the relationship between GDM and pre-eclampsia, the precise nature of their association and the underlying pathophysiological mechanisms remain ambiguous and unclear (14).

Several studies have demonstrated that elevated blood

sugar levels increase the risk of pregnancy complications, which can often be prevented through effective blood sugar control (15, 16). For a long time, insulin treatment has been the standard option for pregnant women with GDM who are unable to control their blood sugar levels through diet and exercise (17). In addition, insulin therapy, which often involves multiple injections, causes weight gain and hypoglycemia. Metformin is considered a safe medication during pregnancy and has been effectively used to control blood glucose levels in women with GDM. Metformin reduces insulin resistance and decreases glycogenesis in the liver. Additional benefits of metformin include the absence of weight gain and minimal risk of hypoglycemia (18).

Furthermore, two studies have indicated that using metformin during the first trimester of pregnancy does not increase the risk of fetal malformations compared to insulin therapy (19, 20). Elevated levels of certain markers, including tyrosine kinase-1 and antiangiogenic peptide-1, can impair endothelial function in pregnant women and are associated with an increased risk of pre-eclampsia. Notably, metformin may help manage pre-eclampsia by inhibiting and reducing the secretion of these antiangiogenic substances from human tissues. However, the number of studies in this field remains limited (21, 22).

Given these findings, the use of metformin among pregnant women with GDM is increasing. It is hypothesized that metformin can prevent the occurrence of pre-eclampsia. Therefore, the present study aimed to evaluate the combined use of metformin and insulin compared to insulin alone in preventing pre-eclampsia in pregnant women with GDM.

## Materials and Methods

### *Study Setting and Population*

This study was conducted as a randomized interventional clinical trial (RCT) on 150 women with GDM, referred to Al-Zahra, Shahid Beheshti, and Amin medical centers in Isfahan, Iran, from 2021 to 2023.

### *Sampling Method and Sample Size*

A total of 150 eligible participants were enrolled using convenience sampling among pregnant women diagnosed with GDM (see Figure 1). Considering a type I error of 0.05 and a type II error of 0.2 and assuming expected proportions of $p_1 = 67.5\%$ and $p_2 = 87.5\%$, the required sample size was estimated using the following formula. After accounting for a 10% dropout rate, the final sample size was calculated to be 75 participants per group.

$$n = \frac{(z_{1-\frac{\alpha}{2}}\sqrt{2P(1-P)} + z_{1-\beta}\sqrt{p_1q_1 + p_2q_2})^2}{(p_2 - p_1)^2}$$

### *Inclusion and Exclusion Criteria*

Inclusion criteria included a diagnosis of GDM based on

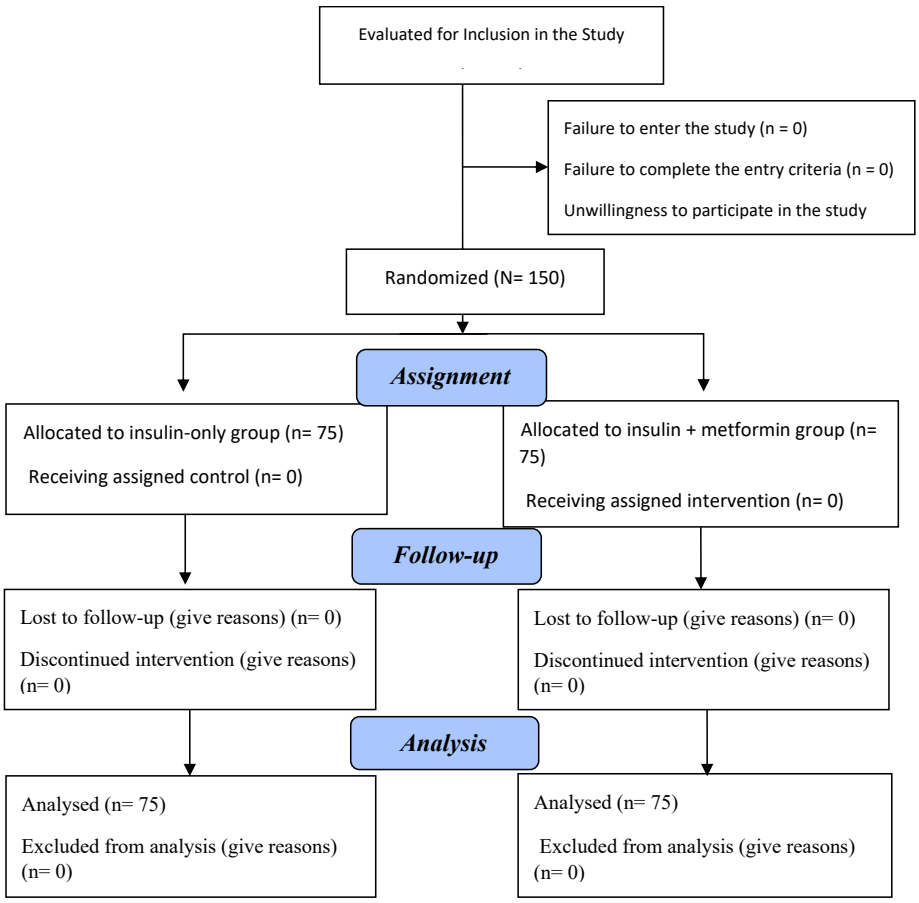


**Figure 1.** Consort Diagram of the Implementation Process of the Trial

glucose challenge test (GCT), impaired glucose tolerance test (GTT), or impaired fasting blood sugar (FBS), age between 18 to 40 years, singleton pregnancy, gestational age between 20 to 34 weeks, and FBS greater than 95 mg/dL or blood glucose levels more than 120 mg/dL (two hours after a meal). Exclusion criteria include having hypertension before pregnancy, history of systemic disease (e.g., cardiovascular, kidney, liver, and autoimmune), history of drug and substance abuse, overt diabetes (except for prior GDM), major neonatal malformations, and obesity with body mass index (BMI) higher than 30.

### *Randomization Method*

Participants were randomly assigned in a 1:1 ratio to either the insulin-only treatment group or the combined insulin-plus-metformin group. The block randomization method was employed to ensure equal group sizes.

### *Blinding Method*

This study was conducted as a single-blind trial. While participants and clinical care providers were aware of the assigned interventions due to the nature of the treatments, the outcome assessors responsible for evaluating pre-eclampsia and other maternal-fetal outcomes were blinded to group allocation to minimize assessment bias.

### *Study Interventions*

The diagnosis of GDM in women was based on the GCT using 50 g of oral glucose. If the blood glucose level exceeded 140 mg/dL after one hour, the participants underwent further evaluation using a GTT with 100 g of oral glucose, and blood glucose levels were assessed three hours later. A diagnosis of GDM was confirmed if two or more of the following GTT values were abnormal:

- Fasting > 95 mg/dL
- 1-hour > 180 mg/dL
- 2-hour > 155 mg/dL
- 3-hour > 140 mg/dL

All participants were prescribed a therapeutic diet and regular physical activity (150 minutes over 3 days with one rest day in between), which was checked by phone calls. Patients who met the entry criteria were included in the study and randomly divided into two groups: diabetes treatment with insulin (group 1) and simultaneous treatment with insulin-plus-metformin (group 2), with a ratio of 1:1. Patients were taught by a trained nurse how to measure capillary blood sugar using a glucometer. With the assistance of a nurse, blood sugar levels were measured our times daily (fasting and 2 hours after breakfast, lunch, and dinner). The goal of treatment was to maintain FBS at or below 95 mg/dL or to keep the blood sugar level below 120 mg/dL (two hours after meals), according to the guidelines provided by the American Diabetes Association (ADA).

Women treated with insulin were initiated on intermediate-acting insulin, such as Neutral Protamine Hagedorn (NPH), at a dose of 0.2 units per kilogram of body weight. In the group treated with both metformin and insulin, metformin was initiated at a dose of 500 mg twice daily, in addition to insulin administered as described above. Before initiating metformin, liver enzymes and creatinine levels were assessed, and metformin was not prescribed in cases of abnormal findings. Moreover, insulin doses were adjusted based on the patients' glycemic response to metformin. All women underwent transabdominal ultrasound as a part of routine prenatal care to assess fetal growth and health. Blood pressure was monitored every two weeks, and participants were examined for symptoms of pre-eclampsia. Additionally, urinalysis was performed every two weeks. A diagnosis of pre-eclampsia was confirmed when systolic blood pressure exceeded 130 mmHg and diastolic blood pressure exceeded 90 mmHg on more than two occasions, after which treatment was initiated.

### *Statistical Analysis*

Data were analyzed using SPSS software version 19. The two groups were compared using independent t-test, ANOVA, and regression analysis. The chi-square test was used to compare the relative frequency of pre-eclampsia between the two groups.

## Results

According to the current findings, no significant differences were found between the two groups regarding pregnancy complications associated with the absence of a prior history of GDM. However, a statistically significant difference was observed in the frequency of patients with protein excretion among the groups ($P=0.006$) regarding pre-eclampsia. Specifically, the number of patients with protein excretion in the insulin-only group was significantly higher than those in the insulin-plus-metformin group. Nonetheless, this difference was not significant among patients without other pregnancy complications. Furthermore, there were no significant differences between the insulin-only and insulin-plus-metformin groups concerning the severity of pre-eclampsia, method of pregnancy termination, abnormal liver enzyme laboratory findings, polyhydramnios, BMI, history of pregnancy-related complications or IUGR, maternal age at delivery, or instances of macrosomia in patients with pregnancy complications and pre-eclampsia (Table 1).

*Note.* All data in the table are expressed as numbers (percentages). GMD: Gestational diabetes mellitus; NVD: Normal vaginal delivery; MBI: Body mass index: IUGR: Intrauterine growth restriction.

The results of this study demonstrated that insulin dose was significantly lower in the combination therapy group among individuals with pre-eclampsia ($P=0.013$). Furthermore, a significant difference in gestational age at study entry was observed in the group with other complications ($P=0.04$), as depicted in Table 2. However, no significant difference was found in gestational age

**Table 1.** Pregnancy Complications in Insulin-only vs. Insulin-Plus-Metformin Groups Based on Various Factors

| Parameters | | Groups | Having Pre-eclampsia | Other Complications | Without Other Pregnancy Complications |
|---|---|---|---|---|---|
| Previous History of GDM | Yes | Insulin-only | --- | --- | 1 (50) |
| | | Insulin-plus-metformin | --- | --- | 1 (50) |
| | No | Insulin-only | 20 (60.6) | 22 (64.7) | 32 (39.5) |
| | | Insulin-plus-metformin | 13 (39.4) | 12 (35.3) | 49 (60.5) |
| *P*-value | | | --- | --- | 0.99 |
| Protein Excretion | Yes | Insulin-only | 11 (91.7) | 2 (28.6) | 3 (75) |
| | | Insulin-plus-metformin | 1 (8.3) | 5 (71.4) | 1 (25) |
| | No | Insulin-only | 9 (42.9) | 20 (74.1) | 30 (38) |
| | | Insulin-plus-metformin | 12 (57.1) | 7 (25.9) | 49 (62) |
| *P*-value | | | 0.006 | 0.07 | 0.29 |
| Severity of Pre-eclampsia | Not severe | Insulin-only | 9 (50) | --- | --- |
| | | Insulin-plus-metformin | 9 (50) | --- | --- |
| | Intense | Insulin-only | 11 (73.3) | --- | --- |
| | | Insulin-plus-metformin | 4 (26.7) | --- | --- |
| *P*-value | | | 0.17 | --- | --- |
| Termination Method | NVD | Insulin-only | 13 (51.9) | 2 (40.0) | 33 (39.8) |
| | | Insulin-plus-metformin | 9 (40.9) | 3 (60.0) | 50 (60.2) |
| | Cesarean section | Insulin-only | 7 (63.6) | 20 (69.0) | --- |
| | | Insulin-plus-metformin | 4 (36.4) | 9 (31.0) | --- |
| *P*-value | | | 0.81 | 0.32 | --- |
| Laboratory Disturbance in Abnormal Liver Enzymes | Yes | Insulin-only | 1 (33.3) | --- | --- |
| | | Insulin-plus-metformin | 2 (66.7) | --- | --- |
| | No | Insulin-only | 19 (63.3) | 22 (64.7) | 33 (39.8) |
| | | Insulin-plus-metformin | 11 (36.7) | 12 (35.3) | 50 (60.2) |
| *P*-value | | | 0.54 | --- | --- |
| Polyhydramnios | Yes | Insulin-only | --- | 2 (100.0) | --- |
| | | Insulin-plus-metformin | --- | 0 (0.0) | --- |
| | No | Insulin-only | 20 (60.6) | 20 (62.5) | 33 (39.8) |
| | | Insulin-plus-metformin | 13 (39.4) | 12 (37.5) | 50 (60.2) |
| *P*-value | | | --- | 0.53 | --- |
| BMI | Yes | Insulin-only | 12 (63.2) | 12 (80.0) | 16 (42.1) |
| | | Insulin-plus-metformin | 7 (36.8) | 3 (20.0) | 22 (57.9) |
| | No | Insulin-only | 8 (57.1) | 10 (52.6) | 17 (37.8) |
| | | Insulin-plus-metformin | 6 (42.9) | 9 (47.4) | 28 (62.2) |
| *P*-value | | | 0.73 | 0.09 | 0.69 |
| History of Previous Pregnancy Complications | Yes | Insulin-only | 2 (100.0) | --- | 4 (57.1) |
| | | Insulin-plus-metformin | 0 (0.0) | --- | 3 (42.9) |
| | No | Insulin-only | 18 (58.1) | 22 (64.7) | 29 (38.2) |
| | | Insulin-plus-metformin | 13 (41.9) | 12 (35.3) | 47 (61.8) |
| *P*-value | | | 0.24 | --- | 0.32 |
| History of IUGR in previous pregnancies | Yes | Insulin-only | 1 (100.0) | --- | 3 (75.0) |
| | | Insulin-plus-metformin | 0 (0.0) | --- | 1 (25.0) |
| | No | Insulin-only | 19 (59.4) | 22 (64.7) | 30 (38.0) |
| | | Insulin-plus-metformin | 13 (40.6) | 12 (35.3) | 49 (62.0) |
| *P*-value | | | 0.41 | --- | 0.14 |
| Pregnancy Termination Age (weeks) | Yes | Insulin-only | 4 (66.7) | 2 (28.6) | 5 (45.5) |
| | | Insulin-plus-metformin | 2 (33.3) | 5 (71.4) | 6 (54.5) |
| | No | Insulin-only | 15 (60.0) | 20 (74.1) | 24 (35.8) |
| | | Insulin-plus-metformin | 10 (40.0) | 7 (25.9) | 43 (64.2) |
| *P*-value | | | 0.99 | 0.07 | 0.54 |

**Table 1.** Continued.

| Parameters | | Groups | Having Pre-eclampsia | Other Complications | Without Other Pregnancy Complications |
|---|---|---|---|---|---|
| Macrosomia | Yes | Insulin-only | --- | 1 (50.0) | --- |
| | | Insulin-plus-metformin | --- | 1 (50.0) | --- |
| | No | Insulin-only | 20 (60.6) | 21 (65.6) | 33 (39.8) |
| | | Insulin-plus-metformin | 13 (39.4) | 11 (34.4) | 50 (60.2) |
| *P*-value | | | --- | 0.99 | --- |

**Table 2.** Comparison of Clinical Parameters by Pregnancy Complications in Insulin-Only vs. Insulin-Plus-Metformin Groups (Mean ± SD)

| Parameter | Current Pregnancy Complications | Groups | Number | Mean ± SD | *P*-value |
|---|---|---|---|---|---|
| Insulin Dose | Having pre-eclampsia | Insulin-only | 20 | 23.95 ± 18.59 | 0.013 |
| | | Insulin-plus-metformin | 13 | 12.07 ± 5.66 | |
| | Other complications | Insulin-only | 22 | 13.41 ± 6.71 | 0.16 |
| | | Insulin-plus-metformin | 12 | 25.33 ± 27.52 | |
| | Without any other pregnancy complications | Insulin-only | 33 | 17.21 ± 11.39 | 0.22 |
| | | Insulin-plus-metformin | 50 | 13.90 ± 12.23 | |
| HbA1c Level | Having pre-eclampsia | Insulin-only | 20 | 5.51 ± 0.52 | 0.25 |
| | | Insulin-plus-metformin | 13 | 5.73 ± 0.50 | |
| | Other complications | Insulin-only | 22 | 5.44 ± 0.49 | 0.79 |
| | | Insulin-plus-metformin | 12 | 5.49 ± 0.57 | |
| | Without any other pregnancy complications | Insulin-only | 33 | 5.50 ± 0.44 | 0.37 |
| | | Insulin-plus-metformin | 50 | 5.41 ± 0.49 | |
| Gravida | Having pre-eclampsia | Insulin-only | 20 | 3.05 ± 1.14 | 0.11 |
| | | Insulin-plus-metformin | 13 | 2.38 ± 0.96 | |
| | Other complications | Insulin-only | 22 | 2.27 ± 1.24 | 0.68 |
| | | Insulin-plus-metformin | 12 | 2.08 ± 1.24 | |
| | Without any other pregnancy complications | Insulin-only | 33 | 2.18 ± 1.13 | 0.75 |
| | | Insulin-plus-metformin | 50 | 2.28 ± 1.19 | |
| Weight Gain During Pregnancy | Having pre-eclampsia | Insulin-only | 20 | 12.15 ± 2.08 | 0.32 |
| | | Insulin-plus-metformin | 13 | 12.92 ± 1.80 | |
| | Other complications | Insulin-only | 22 | 12.54 ± 1.96 | 0.24 |
| | | Insulin-plus-metformin | 12 | 13.08 ± 2.77 | |
| | Without any other pregnancy complications | Insulin-only | 33 | 12.45 ± 1.93 | 0.60 |
| | | Insulin-plus-Metformin | 50 | 12.26 ± 1.79 | |
| Weight Gain After Entering the Study | Having pre-eclampsia | Insulin-only | 20 | 8.15 ± 1.22 | 0.33 |
| | | Insulin-plus-metformin | 13 | 7.76 ± 1.16 | |
| | Other complications | Insulin-only | 22 | 7.54 ± 2.21 | 0.07 |
| | | Insulin-plus-metformin | 12 | 12.16 ± 12.41 | |
| | Without any other pregnancy complications | Insulin-only | 33 | 7.77 ± 1.62 | 0.61 |
| | | Insulin-plus-metformin | 50 | 8.00 ± 1.38 | |
| Gestational Age at Diagnosis | Having pre-eclampsia | Insulin-only | 20 | 27.85 ± 1.89 | 0.62 |
| | | Insulin-plus-metformin | 13 | 27.61 ± 1.44 | |
| | Other complications | Insulin-only | 22 | 27.54 ± 2.24 | 0.48 |
| | | Insulin-plus-metformin | 12 | 26.83 ± 1.52 | |
| | Without any other pregnancy complications | Insulin-only | 33 | 27.93 ± 2.41 | 0.46 |
| | | Insulin-plus-metformin | 50 | 27.52 ± 1.88 | |
| Gestational Age at the Time of Study Entry | Having pre-eclampsia | Insulin-only | 20 | 29.05 ± 2.68 | 0.87 |
| | | Insulin-plus-metformin | 13 | 28.76 ± 1.30 | |
| | Other complications | Insulin-only | 22 | 29.18 ± 1.99 | 0.04 |
| | | Insulin-plus-metformin | 12 | 27.75 ± 2.59 | |
| | Without any other pregnancy complications | Insulin-only | 33 | 28.96 ± 2.59 | 0.66 |
| | | Insulin-plus-metformin | 50 | 28.76 ± 2.21 | |

*Note.* SD: Standard deviation; HbA1c, Hemoglobin A1C.

among patients with pregnancy complications specifically due to pre-eclampsia. Additionally, no statistically significant differences were found between the two groups regarding HbA1c levels, number of pregnancies, weight gain during pregnancy and after entering the study, or gestational age at the time of diagnosis among patients with various complications in the current pregnancy (Table 2).

## Discussion

Pre-eclampsia is one of the leading causes of maternal and neonatal morbidity and mortality. Early pre-eclampsia is one of the most severe forms of the condition, affecting nearly 0.5% of all pregnancies, which corresponds to approximately 10% of all pre-eclampsia cases (23, 24). This early pre-eclampsia is significantly associated with maternal and neonatal complications and mortality compared to late-onset pre-eclampsia. Currently, delivery remains the only definitive cure for pre-eclampsia (25). The present study evaluated the effectiveness of metformin as an adjuvant drug along with insulin in preventing pre-eclampsia among pregnant women with GDM.

Our study's findings demonstrated a statistically significant difference in the frequency of protein excretion between the two groups categorized by pre-eclampsia status ($P=0.006$). Specifically, a higher number of patients in the insulin-only group exhibited protein excretion compared to those in the insulin-plus-metformin group. Additionally, the amount of insulin dosage differed significantly between the groups based on pre-eclampsia status ($P=0.013$), with the insulin-plus-metformin group requiring significantly lower insulin doses compared to the insulin-only group. A significant difference was also observed in gestational age at the time of study entry among patients with other pregnancy complications ($P=0.04$).

Cluver et al conducted a study to evaluate whether extended-release metformin could prolong gestation in women undergoing expectant management for preterm pre-eclampsia. The findings demonstrated that metformin successfully prolonged pregnancy duration in women with early-onset pre-eclampsia; however, further trials are necessary to confirm these findings (26). Their study supports the notion that treatment for early pre-eclampsia is possible. Nonetheless, their study's results are inconsistent with our findings, primarily due to the absence of insulin use. Additionally, their study included a placebo-controlled group, whereas our study did not utilize a control group- an aspect that should be considered in future research.

An *in vivo* study by Brownfoot et al reported that metformin can prevent pre-eclampsia by reducing levels of fms-like tyrosine kinase-1 receptor, which is directly related to the severity and timing of pre-eclampsia onset (21). It has also been hypothesized that metformin reduces the risk of pre-eclampsia by improving cardiovascular function and limiting weight gain during pregnancy (27, 28).

In their RCT, Niromanesh et al investigated women with GDM who had singleton pregnancies and gestational ages between 20 and 34 weeks. Participants were randomly assigned to receive either metformin (n = 80) or insulin (n = 80). The results indicated that metformin was an effective and safe alternative to insulin for women with GDM. Furthermore, this study found no significant risk of adverse maternal or neonatal outcomes associated with metformin use (29). However, the findings of this study are not aligned with the results of our study due to the lack of evaluation of pre-eclampsia in patients as an outcome in their research.

A systematic review and meta-analysis investigated the effect of metformin on the prevention of hypertensive disorders of pregnancy in women with GDM or obesity (30). The study concluded that metformin use is associated with a reduced incidence of hypertensive disorders of pregnancy compared to other treatments or placebo. Given the clinical importance of this finding and the magnitude of the observed effect, the authors recommended that further prospective trials are urgently needed (30).

### *Randomization*

Participants were randomly allocated in a 1:1 ratio to either the insulin-only treatment group or the combined insulin-plus-metformin treatment group. Randomization was performed using a computer-generated block randomization schedule to ensure equal group sizes.

### *Blinding*

This study employed a single-blind trial. While participants and clinical care providers were aware of the interventions due to their nature, outcome assessors responsible for evaluating pre-eclampsia and other maternal-fetal outcomes were blinded to group allocation to minimize assessment bias.

## Limitations of the Study

The study was conducted in a single geographic region across three medical centers in Isfahan, which may further restrict external validity. As the study employed a single-blinded design, with only outcome assessors blinded, the potential for performance bias cannot be fully excluded, particularly regarding participant behavior and treatment adherence.

## Conclusion

The findings suggest that the combination therapy with metformin and insulin was associated with reduced proteinuria and lower insulin requirements among women who developed pre-eclampsia compared to insulin-only therapy. Other pregnancy outcomes remained similar between the two groups. These results indicate a potential benefit of adding metformin to insulin therapy in reducing specific markers associated with pre-eclampsia in GDM pregnancies without increasing adverse pregnancy outcomes.

The results of the present study provide a comprehensive perspective on optimal strategies for blood sugar control in pregnancy, particularly to prevent complications related to pregnancy and blood pressure. With further research in this area, it may be possible to significantly minimize the incidence of pre-eclampsia in women with GDM, thereby improving both maternal and fetal outcomes.

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## Authors' Contribution

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## Competing Interests

The authors declare no conflict of interests.

## Ethical Approval

Informed consent was obtained from all individual participants included in the study. Moreover, this research was approved by the Ethics Committee of Isfahan University of Medical Sciences (Ethical Code: IR.MUI.MED.REC.1400.639) and was registered in the National Registry of Clinical Trials (Trial Code: IRCT20220107053652N1). The study proposal for this research was designed according to the ethical principles of Helsinki.

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