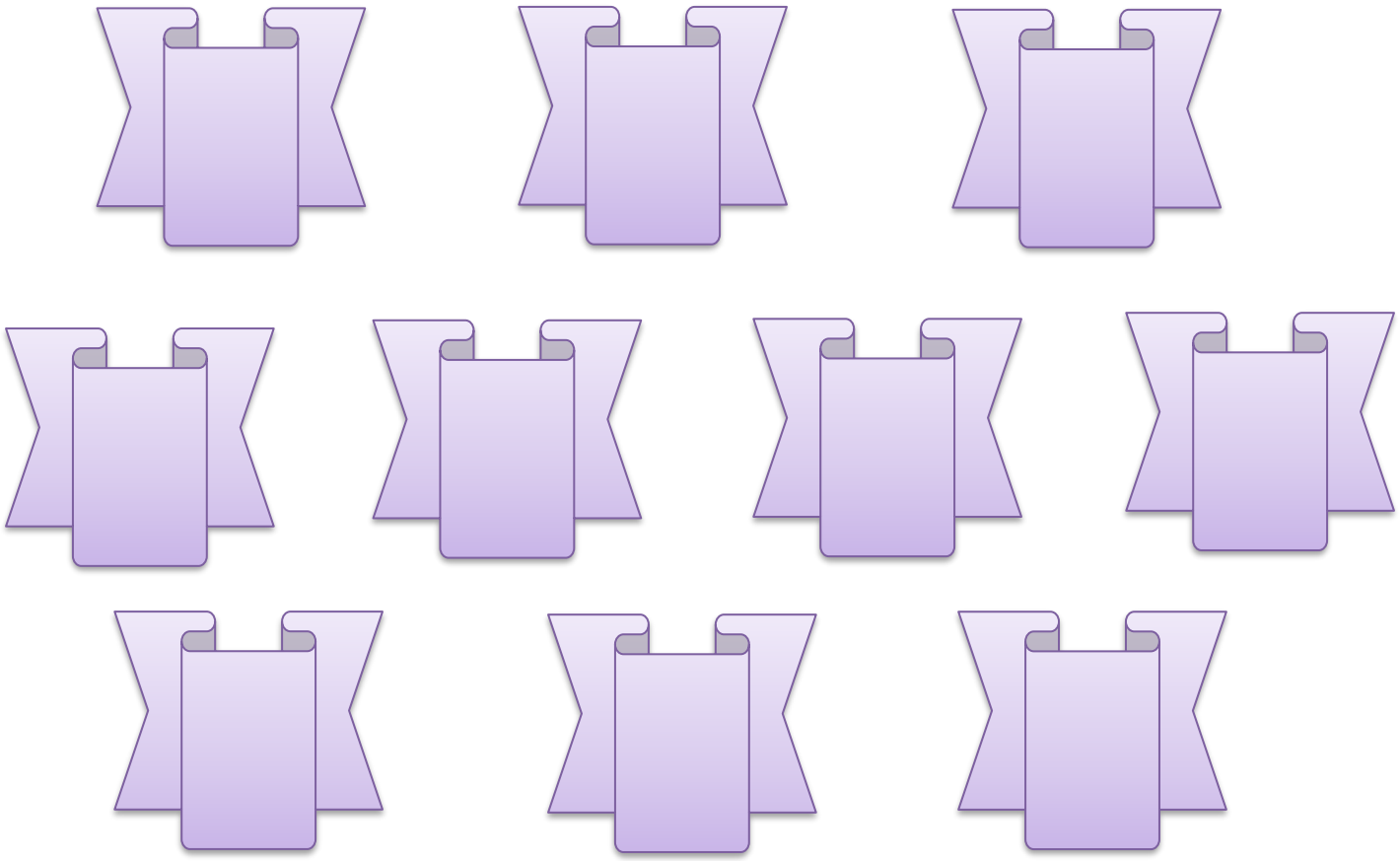
International Journal of Medical Arts

Volume 5, Issue 10, October 2023

https://ijma.journals.ekb.eg/



Print ISSN: 2636-4174

Online ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Gynecology and Obstetrics]

Original Article

Can Metformin Be Used to Prolong Gestation in Egyptian Women with Early Preterm Pre-Eclampsia? A Randomized Clinical Trial

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Article information

Received: 07-09-2023

Accepted: 03-10-2023

DOI: 10.21608/IJMA.2023.234787.1803.

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Citation: Abdelmoaty MA, Ibrahim EM, Elboghdady AA. Can Metformin Be Used to Prolong Gestation in Egyptian Women with Early Preterm Pre-Eclampsia? A Randomized Clinical Trial. IJMA 2023 October; 5 [10]: 3742-3749. doi: 10.21608/IJMA.2023.234787.1803.

ABSTRACT

Background: Pre-eclampsia causes high maternal and newborn mortality. Hypertensive diseases during pregnancy kill Egyptian mothers and 10% of pregnant women worldwide. Preterm pre-eclampsia, a severe variant, increases mother and infant risks. Delivery is the only therapy, which might cause difficulties in premature situations. Metformin, a blood glucose medicine, may cure pre-eclampsia, according to preclinical research. However, safe and effective preterm pre-eclampsia medications are required.

Aim of the Work: The study aims to investigate whether or not metformin with extended release can lengthen pregnancy in women who have been diagnosed with premature pre-eclampsia.

Patients and Methods: A double-blind, placebo-controlled clinical trial was done involving cases diagnosed with preterm pre-eclampsia between 26+0 and 31+6 weeks of gestation. The cases were given either extended release metformin or a placebo according to a random assignment. Maternal and fetal surveillance was conducted, and various outcome measures were assessed, including gestation prolongation, fetal, composite maternal, and levels of anti-angiogenic biomarkers related to pre-eclampsia, and neonatal outcomes.

Results: The study found that there was no significant variance in the characteristics of women among the two groups. Gestation was significantly prolonged in the metformin group contrasted with the placebo group. The incidence of HELLP syndrome was significantly greater in the placebo group. Other outcomes did not show significant differences among the groups, except for a higher number of cases reaching 34 weeks' gestation in the metformin group.

Conclusion: The findings suggest that preterm preeclamptic women may benefit from using extended-release metformin to prolong gestation. However, more study is required to fully evaluate its safety and effectiveness as a treatment option.

Keywords: Metformin; Preterm; Pre-Eclampsia; Gestation.

INTRODUCTION

Pre-eclampsia is a primary cause of maternal and neonatal death. Fifteen percent of maternal deaths in Egypt can be attributed to hypertension problems during pregnancy. Hypertensive disorders affect around 10% of pregnant women, which poses a significant risk to public health [1].

Among all pregnancies, approximately 0.5% are affected by preterm pre-eclampsia, which accounts for 10% of pre-eclampsia cases [2]. Preterm pre-eclampsia is particularly severe and is related to increased rates of maternal and neonatal morbidity and death in contrast to pregnancies carried to term [3].

Presently, there are no treatments available for pre-eclampsia other than delivery [4]. In the case of preterm pre-eclampsia, early delivery is often required for maternal reasons, resulting in premature birth and placing the newborn at an increased risk of significant disability and death, especially nations with low and moderate income [5].

By delaying the course of preterm pre-eclampsia with a safe medication, newborns may be delivered at a later preterm gestation, lowering their risk of problems associated with extreme prematurity [6].

Although research has been conducted to identify safe medications for use throughout pregnancy that can reduce the course of preterm pre-eclampsia, no positive outcomes have been found. Metformin, an oral blood glucose-lowering medicine, has been successful in reducing the risk of preeclampsia in animal models [6, 7].

The purpose of this research is to determine if preterm pre-eclamptic women who take extended-release metformin may prolong gestation.

PATIENTS AND METHODS

We conducted a double-blind, placebo-controlled clinical trial to evaluate the effectiveness of metformin in prolonging gestation in Egyptian women diagnosed with early preterm pre-eclampsia between the ages of 26+0 to 31+6 weeks. The study was conducted at the Al-Hussein University Hospital, a tertiary health care facility in Egypt, from December 2020 to February 2023, and included a total of 299 subjects who were followed at the hospital's maternity units.

The study enrolled women diagnosed with early preterm pre-eclampsia between 26 + 0 to 31 + 6 weeks of pregnancy. Each participant was randomly assigned to receive either 3 grams of extended-release metformin [1 gram three times a day] or an identical placebo. To be included in the study, women had to be candidates for expectant care, with no clinical reason for rapid delivery based on medical evaluations by attending physicians.

Women who met the criteria for an otherwise healthy pregnancy and the ability to provide informed consent were considered eligible for participation. Exclusion criteria included diabetes or gestational diabetes, contraindications to metformin [such as hyper-sensitivity to metformin, baseline creatinine > 1.40 mg/dL or 124 μmol/L, or metabolic acidosis], use of metformin-interacting medications [such as furosemide, glyburide, or cationic medicines], and multiple pregnancies.

Those with significant proteinuria [>300 mg of protein assessed on a 24-hour urine sample] were included in the analysis of pre-eclampsia, which was classified consistent with the International Society for the Study of Hypertension in Pregnancy Classification [8].

Women who met our criterion of pre-eclampsia, which included those with new-onset hypertension afterward 20 weeks' gestation or those on therapy for chronic hypertension who had a loss of blood pressure control, were eligible to participate. In an expectant management plan, the mother and baby would both be admitted to the hospital and closely monitored.

The mothers had four-hour blood pressure readings, twice-day clinical assessments, daily urine, and twice-weekly biochemical testing. Blood samples were analyzed for hemoglobin, urea, creatinine, and platelet count.

Further testing, such as the measurement of liver enzymes and lactate dehydrogenase levels, was performed if biochemical abnormalities were found. Fetal ultrasonography and Doppler velocimetry were performed shortly after admission, with further assessments occurring once a week or more frequently if necessary [due to factors such the existence of missing end diastolic flow in the umbilical artery].

The patient underwent a cardiotocogram. Participants were given two doses of betamethasone 24 hours apart upon admission and a second course of dosage one week later if delivery had not yet occurred. This was all done in an effort to promote fetal lung maturity. The decision to induce labor and deliver the baby before 34 weeks was made by the woman's healthcare providers and to avoid bias, the authors were not involved in such cases.

Randomization and trial group assignment

Using a web-based, 1:1 random sequence generator, the ladies were given either extended-release metformin or a placebo. We used block sizes of four to six and stratified the randomization along with gestation at enrollment [stratum 1: 26+0 to 28+6 weeks; stratum 2: 29+0 to 31+6 weeks] since gestation may influence the duration of pregnancy extension.

Each pill contained 500 milligrams of metformin hydrochloride, while the inactive placebo pills had no active ingredient. All the pills were identical in shape, weight, color, and size. The women were initially given a single trial pill three times a day. If this dose was well tolerated, they were then given two tablets three times daily. In case of adverse effects, the dose could be reduced to one pill twice a day, with a possible increase to 3,000 milligrams per day if symptoms subside.

The remaining pills were recorded when the treatment packets were retrieved after delivery. The health research ethics committee and the data monitoring and safety committee were informed of any serious adverse events, and the situation was addressed in accordance with standard clinical procedures.

Women's plasma was taken at random and then every two weeks until they gave delivery. The samples were prepared and frozen at −80 °C.

Outcome measures

The length of time that passed between the first dosage of the trial medicine and the expected time of delivery was considered the primary outcome. We planned ahead to do an analysis for women who got treatment [those who took any of the trial medications] and another analysis for those who took all of the treatments [from the time of randomization to the time of birth].

Compound maternal, fetal, or neonatal outcomes were considered secondary endpoints in studies of pre-eclampsia. The maternal composite outcome included eclampsia, maternal death, pulmonary edema [oxygen saturation 90 percent with clinical symptoms requiring treatment], severe renal impairment [serum creatinine 125 mol/L or 1.41 mg/dL], cerebral vascular event, placental abruption, and liver haematoma or rupture.

An estimated fetal weight at birth that was lower than the third centile on either the GROW [gestation related optimal weight] chart or the World Health Organization charts, or both, was considered to be indicative of fetal growth restriction. [9,10] Intrauterine fetal death was also included in the fetal composite outcome.

The neonatal composite outcome was any of the following within 28 days of birth: neonatal death within 6 weeks of due date; cranial ultrasonographic evidence of intraventricular hemorrhage of grade III or IV; radiographic evidence of necrotizing enterocolitis; or bronchopulmonary dysplasia requiring supplemental oxygen at day 28 of life. Clinical outcomes of individuals were included in the investigation.

Ethical Approval

The university's Ethics Board gave its stamp of approval to the study, and participants voluntarily gave their informed, written agreement to be a part of the research. This work has been conducted out in compliance with The Code of Ethics of the World Medical Association, often known as the Declaration of Helsinki, which governs how research involving humans should be carried out.

Statistical Analysis

For the data analysis, IBM-SPSS version 24 was utilized [May 2016]. In order to evaluate whether or not there was statistical significance, the Kristall-Wallis test and Wilcoxon's test were applied, in addition to Spearman's correlation and logistic regression analysis. Each variable was analyzed [whether parametrically or not] according to the sort of data that it contained. If the P-values were lower than 0.05, which represents five percent, we regarded the results as statistically significant.

RESULTS

Table [1] shows no significant variance amongst both groups concerning Characteristics of women included in both groups.

Table [2] shows that gestation was significantly prolonged in metformin group. HELLP syndrome was significantly increased in placebo group. There was no significant variance among the two groups concerning other outcomes.

Table [3] shows that there was significant increase in cases reached 34 weeks' gestation in metformin group compared with placebo. There was no significant variance among other groups concerning rest of parameters.

Table [4] shows that the incidence of headaches was slightly greater in the metformin group [12.75%] contrasted with the placebo group [7.33%], but the variance was not statistically significant. The metformin group experienced a greater incidence of nausea [20.81%] compared to the placebo group [11.33%], and this difference was statistically significant. Diarrhea was stated more often in the metformin group [32.21%] contrasted with the placebo group [6%], and the difference was highly significant. A significantly higher proportion of participants in the placebo group [68%] took the full treatment dose compared to the metformin group [44.97%]. Moreover, a larger number of participants in the metformin group [40.94%] decreased their treatment dose but did not stop compared to the placebo group [14%].

It can be observed in Figure [1] that at the beginning of the study [day 0], both groups had a similar number of contributors, with 149 in the metformin group & 150 in the placebo group. As the research progresses, the number of participants decreases in both groups, but the rate of reduction varies with more decrease [less prolongation of delivery] in placebo group.

Table [1]: Characteristics of women with preterm pre-eclampsia at enrollment randomized to extended release metformin or placebo

		Metformin group [n=149]	Placebo group [n=150]	P. Value
Gestation at randomization [weeks + days], Mean [SD]		29+2 [28+3-30+5]	29+4 [28+2-31+2]	0.99
Gestation <29 weeks [+ 0 days] at randomization		60 [40.27%]	60 [40%]	0.96
Maternal age [years], Mean [SD]		29.33 [5.49]	28.33 [9.41]	0.26
Body mass index, Mean [SD]		30 [7.84]	29 [7.84]	0.27
Aspirin use during pregnancy		16 [10.74%]	6 [4%]	0.02
Calcium supplement use during pregnancy		19 [12.75%]	13 [8.67%]	0.25
Chronic hypertension		40 [26.85%]	36 [24%]	0.57
Parity	Nulliparous	45 [30.2%]	51 [34%]	0.48
	Multiparous	104 [69.8%]	99 [66%]	0.41
Hypertension in previous pregnancy		79 [53.02%]	79 [52.67%]	0.95
New paternity in current pregnancy		30 [20.13%]	27 [18%]	0.64
Highest blood pressure before randomization [mm Hg], Mean [SD]	Systolic	164.5 [17.86]	171.03 [16.26]	0.001
	Diastolic	98.7 [13.09]	100.37 [14.33]	0.29
Hemoglobin [g/L], Mean [SD]		114.61 [14.52]	114.38 [12.81]	0.88
Platelet count [×109 /L], Mean [SD]		237.51 [81.51]	227.3 [76.02]	0.26
Urea [mmol/L], Mean [SD]		3.54 [1.33]	3.84 [1.73]	0.09
Creatinine [g/L], Mean [SD]		57.79 [13.34]	57.94 [13.63]	0.92
Proteinuria [g/24 h], Mean [SD]		1.57 [1.94]	1.5 [1.74]	0.74
Proteinuria ≥3 g/24 h		39 [26.17%]	33 [22%]	0.40
Fetal weight centile on GROW chart, Mean [SD]		16.7 [28.45]	16.7 [24.3]	0.51
Fetal weight on GROW chart	< 3rd centile	46 [30.87%]	41 [27.33%]	0.42
	3rd to < 10th centile	24 [16.11%]	30 [20%]	0.38
	≥ 10th centile	79 [53.02%]	79 [52.67%]	0.95
Fetal weight on WHO charts	< 3rd centile	45 [30.2%]	44 [29.33%]	0.77
	3rd to < 10th centile	24 [16.11%]	32 [21.33%]	0.31
	≥ 10th centile	80 [53.69%]	74 [49.33%]	0.52
Absent end diastolic blood flow on umbilical artery Doppler velocimetry		0 [0%]	1 [0.67%]	0.31

Table [2]: Preterm pre-eclampsia outcomes with extended-release metformin vs placebo

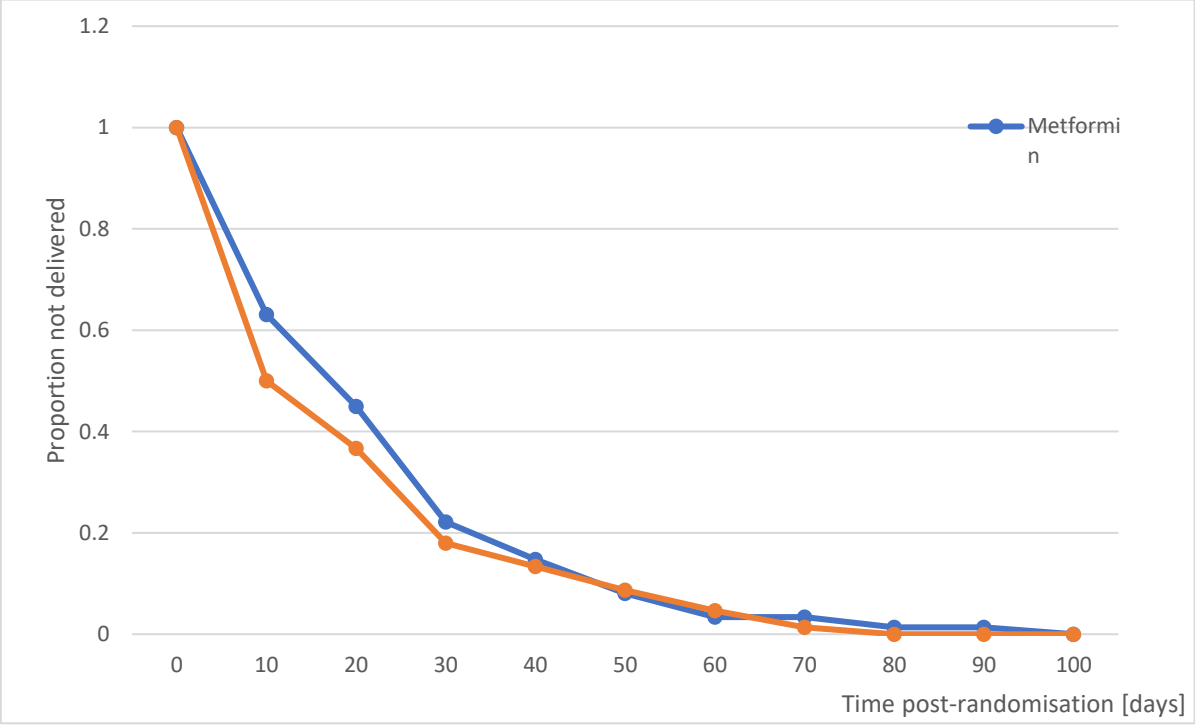
		Metformin group [n=149]	Placebo group [n=150]	P. Value
Primary outcome				
Prolongation of gestation [days], Mean [SD]		17.5 [8.82]	12.63 [10.55]	0.00002*
Secondary and composite, outcomes				
Exploratory outcomes [Maternal]				
Pulmonary edema		6 [4.03%]	3 [2%]	0.31
Acute renal failure [serum creatinine ≥125 µmol/L]		1 [0.67%]	2 [1.33%]	0.56
Placental abruption		0 [0%]	2 [1.33%]	0.16
Admission ICU		12 [8.05%]	12 [8%]	0.99
Posterior reversible encephalopathy syndrome		0 [0%]	2 [1.33%]	0.16
Left ventricular failure		0 [0%]	2 [1.33%]	0.16
HELLP syndrome		4 [2.68%]	12 [8%]	0.04*
Platelet count <100×109 /L		12 [8.05%]	11 [7.33%]	0.81
Platelet count <50×109 /L		0 [0%]	2 [1.33%]	0.16
Major postpartum hemorrhage		3 [2.01%]	0 [0%]	0.08
Thromboembolic disease		1 [0.67%]	2 [1.33%]	0.56
Moderate to severe ascites		18 [12.08%]	15 [10%]	0.56
Highest blood pressure during expectant management [mm Hg], Mean [SD]	**Systolic**	157.09 [12.12]	159.51 [13.97]	0.11061
	Diastolic	93.77 [9.54]	93.58 [9.48]	0.86298
Highest blood pressure after delivery [mm Hg], Mean [SD]	**Systolic**	152.4 [13.86]	154.99 [14.82]	0.11963
	Diastolic	91.08 [10.28]	92.37 [11.14]	0.29888
Neonatal exploratory outcomes				
Birth weight [g], Mean [SD]		1641.06 [624.77]	1534.16 [671.62]	0.15518
Gestation at delivery [weeks], Mean [SD]		32.01 [2.72]	31.49 [2.68]	0.09696
GROW centile at birth	**<3rd centile**	82 [55.03%]	84 [56%]	0.86647
	3rd to <10th centile	27 [18.12%]	26 [17.33%]	0.8585
	≥10th centile	40 [26.85%]	40 [26.67%]	0.97212
WHO centile at birth	**<3rd centile**	73 [48.99%]	88 [58.67%]	0.09342
	3rd to <10th centile	31 [20.81%]	26 [17.33%]	0.44474
	≥10th centile	45 [30.2%]	36 [24%]	0.22767
Neonatal death		12 [8.05%]	9 [6%]	0.48716
Grade III or IV Intraventricular hemorrhage		3 [2.01%]	6 [4%]	0.31479
Necrotising enterocolitis		12 [8.05%]	15 [10%]	0.55713
Broncho-pulmonary dysplasia		0 [0%]	0 [0%]	
Apgar score <7 at 5 minutes		6 [4.03%]	11 [7.33%]	0.21702
Surfactant use		19 [12.75%]	26 [17.33%]	0.26793
NICU admission		18 [12.08%]	24 [16%]	0.32944
Intubation and mechanical ventilation		12 [8.05%]	14 [9.33%]	0.69459
Continuous positive airway pressure support		92 [61.74%]	101 [67.33%]	0.31249
Grade III or IV hyaline membrane disease		22 [14.77%]	21 [14%]	0.85048
Retinopathy of prematurity		1 [0.67%]	3 [2%]	0.3173
Neonatal sepsis		25 [16.78%]	33 [22%]	0.25359

Table [3]: Indications for delivery in preterm pre-eclampsia patients on extended-release metformin or placebo

	Metformin group [n=149]	Placebo group [n=150]	P
Reached 34 weeks' gestation	60 [40.27%]	42 [28%]	**0.025***
Declined further expectant management	2 [1.34%]	2 [1.33%]	0.99
Spontaneous preterm birth	7 [4.7%]	2 [1.33%]	0.09
HELLP syndrome	2 [1.34%]	2 [1.33%]	0.99
Platelet count <100, no HELLP	0 [0%]	2 [1.33%]	0.32
Imminent eclampsia	3 [2.01%]	3 [2%]	0.99
Loss of blood pressure control	5 [3.36%]	5 [3.33%]	0.99
Maternal ascites	13 [8.72%]	15 [10%]	0.81
Pulmonary edema	2 [1.34%]	2 [1.33%]	0.99
Renal deterioration	5 [3.36%]	7 [4.67%]	0.71
Fetal indication	49 [32.89%]	66 [44%]	0.14
Fetal distress	49 [32.89%]	63 [42%]	0.22
Abnormal Doppler velocimetry result	0 [0%]	2 [1.33%]	0.32
Poor fetal growth	0 [0%]	2 [1.33%]	0.32

Table [4]: Adverse events and medication discontinuation in preterm pre-eclampsia women taking extended-release metformin or placebo

Side Effects [Days]	Metformin group [n=149]	Placebo group [n=150]	P. Value
Headache	19 [12.75%]	11 [7.33%]	0.12
1	3 [2.01%]	6 [4%]	0.31
2	4 [2.68%]	1 [0.67%]	0.17
3	9 [6.04%]	2 [1.33%]	0.03*
≥4	3 [2.01%]	2 [1.33%]	0.65
Vomiting	7 [4.7%]	5 [3.33%]	0.55
1	3 [2.01%]	3 [2%]	0.99
2	1 [0.67%]	0 [0%]	0.31
3	0 [0%]	0 [0%]	-
≥4	3 [2.01%]	2 [1.33%]	0.65
Nausea	31 [20.81%]	17 [11.33%]	0.026*
1	7 [4.7%]	9 [6%]	0.62
2	4 [2.68%]	3 [2%]	0.69
3	10 [6.71%]	2 [1.33%]	0.018*
≥4	10 [6.71%]	3 [2%]	0.045*
Diarrhea	48 [32.21%]	9 [6%]	<0.0001*
1	3 [2.01%]	3 [2%]	0.99
2	12 [8.05%]	3 [2%]	0.016*
3	15 [10.07%]	2 [1.33%]	0.001*
≥4	18 [12.08%]	1 [0.67%]	0.00005*
Adherence to Trial Drug			
Took full treatment dose	67 [44.97%]	102 [68%]	0.00006*
Decreased treatment dose but did not stop	61 [40.94%]	21 [14%]	<0.0001*
Stopped treatment	19 [12.75%]	26 [17.33%]	0.26793
Incomplete information on dosing	1 [0.67%]	2 [1.33%]	0.56566



Metformin	149	94	67	33	22	12	5	5	2	2	0
Placebo	150	75	55	27	20	13	7	2	0	0	0

Figure [1]: Prolongation of gestation [in days] between the two groups

DISCUSSION

Our results in this investigation, which included women who were diagnosed with preterm pre-eclampsia at 32 weeks [+0 days] gestation, were similar with those found in a prior study that was conducted by **Cluver *et al.*** [6]. We found that individuals who were given extended-release metformin reported a little extension of gestation by 7.6 days compared to those who were given a placebo. This finding is consistent with the findings that they obtained. According to the criteria of the Pre-eclampsia Intervention Trial [11], this variance did not approach statistical significance. However, it is crucial to emphasize that this finding should be taken into consideration. The occurrence of a larger degree of variance in the length of pregnancy among the participants is one possible reason for the lack of statistical significance shown in this study. Nevertheless, there are a number of factors that lend credence to the possibility of metformin's efficacy. These include biological plausibility, as indicated by previous research [6, 12], predefined per protocol analyses that showed a longer gestational prolongation in Participants who maintained metformin administration at any dosage or the full dose, and favorable neonatal outcomes. The neonates that were given metformin had a greater birth weight by 110 grams and spent less time in the tertiary care newborn nursery at Tygerberg Hospital, with a decrease of 12 days in the total length of their stay in the neonatal nursery.

In spite of the fact that metformin treatment led to an extension of the gestation period, it is important to point out that the medication did not result in a decline in the circulating levels of anti-angiogenic factors. This is especially true for soluble fms-like tyrosine kinase-1, which is believed to be a major factor contributing to the pathogenesis of pre-eclampsia [13]. This data implies that metformin may exercise its positive effects on preterm pre-eclampsia via alternate mechanisms that do not entail lowering the production of anti-angiogenic factors. These mechanisms would allow metformin to achieve its favorable effects on preterm pre-eclampsia patients. It is consistent with the findings of preclinical research that indicate the pleiotropic qualities of metformin. These properties guard against the vascular abnormalities that affect both the placenta and the mother in pre-eclampsia [14, 15]. The capacity of metformin to extend gestation is consistent with these findings. Consequently, although lowering the levels of soluble fms-like tyrosine kinase-1 continues to be an important therapy method in pre-eclampsia, the findings of previous research show that doing so may not be necessary to achieve symptom alleviation.

Metformin's shown efficacy in the management of gestational diabetes contributes to the medication's desirability as a potential treatment for preterm pre-eclampsia. In addition, there is no need to worry about the effects of giving it to a pregnant woman for a limited time. Metformin's accessibility at an affordable price is a significant factor in the drug's potential for broad use, in particular in low- to middle-income nations, which are home to the greatest rates of premature preeclampsia. Notably, epidemiological research [16, 17] has demonstrated that metformin taken during pregnancy does not have any deleterious impacts on growth and developmental outcomes in childhood. This is a significant finding. However, for future research, the need of collecting follow-up data over a longer period of time should be taken into consideration.

In spite of this, it is essential to realize that metformin has the potential to induce adverse effects on the gastrointestinal tract, especially at greater doses than those examined in this research. When evaluating its potential usage as a therapeutic alternative, this restriction is something that has to be taken into consideration.

We acknowledge that our study has certain limitations that should be considered: [1] Sample Size: One of the limitations of our study is the relatively small sample size, with approximately 150 patients in each arm of the study. While we aimed to include as many participants as feasible within the scope of our research, a larger sample size would have allowed for more robust statistical analyses and potentially increased the generalizability of our findings, [2] Our study primarily focused on clinical aspects when comparing metformin to placebo in patients with preterm preeclampsia. We did not perform a direct comparison of biochemical markers such as soluble fms-like tyrosine kinase 1 [sFlt-1] or placental growth factor [PlGF] levels in both treatment groups before and after intervention. Incorporating such biochemical analyses could have provided valuable insights into the underlying mechanisms of metformin's effects and added depth to our

findings. We acknowledge that future studies may benefit from including these assessments to further elucidate the therapeutic mechanisms involved.

Conclusion: The findings from this clinical trial offer a tentative basis for optimism regarding the potential advantages of extended-release metformin in postponing the occurrence of preterm pre-eclampsia among pregnant women, albeit with a need for caution.

Financial and non-financial relations and activities of interest: None

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Print ISSN: 2636-4174
Online ISSN: 2682-3780