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INVESTIGATE THE OPTIMAL DOSAGE OF METFORMIN FOR PROLONGING GESTATION IN PRETERM PREECLAMPSIA AND ITS EFFECTS ON MATERNAL AND NEONATAL OUTCOMES

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Abstract

Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality, particularly when diagnosed preterm, often necessitating early delivery with substantial neonatal risks. Prolonging gestation in such cases can markedly improve neonatal survival and osutcomes. This randomized controlled trial investigated the optimal dosage of metformin for prolonging gestation and improving maternal–neonatal outcomes in women with preterm preeclampsia. Conducted at the Jinnah Postgraduate Medical Centre and Sindh Institute of Child and Maternal Health, Pakistan, between December 2023 and December 2024, 180 women diagnosed with preterm preeclampsia were randomized into three groups: low-dose (500 mg twice daily), moderate-dose (1000 mg twice daily), and high-dose (1500 mg twice daily) metformin, in addition to standard care. The primary outcome was gestational prolongation; secondary outcomes included maternal blood pressure control, maternal complications, neonatal outcomes, and tolerability. Moderate-dose metformin achieved the most significant prolongation of pregnancy (21.4 ± 5.6 days), compared with low- (14.2 ± 4.9 days, $p<0.001$) and high-dose (18.1 ± 5.2 days, $p=0.02$) groups. Maternal complications such as eclampsia and HELLP syndrome were lowest in the moderate-dose arm (10%), and neonatal outcomes, including mean birth weight, Apgar scores, and NICU admissions, were most favorable. High-dose metformin was associated with greater gastrointestinal intolerance without additional efficacy. No lactic acidosis was observed. These findings suggest that moderate-dose metformin is optimal for prolonging gestation and improving both maternal and neonatal outcomes, balancing efficacy with

tolerability. Larger multicenter trials are warranted to validate these results and establish definitive clinical guidelines.

Keywords: Metformin, preterm preeclampsia, pregnancy prolongation, maternal outcomes, neonatal outcomes

Introduction

Preeclampsia is one of the most formidable obstetric medicine challenges, and it has been associated with significant maternal and perinatal morbidity and mortality in all countries globally (Chang, Seow, and Chen, 2023; Yang, Wang, and Li, 2024; Von Dadelszen, Vidler, Tsigas, and Magee, 2021). It has been estimated to occur in 2-8 percent of known pregnancies as the burden borne by low- and middle-income nations where the limited access to specialized obstetrics care is higher. Preeclampsia is a frequent cause of maternal complications, including eclampsia, HELLP syndrome, and abruptio placenta, and is closely linked to fetal growth restriction, preterm birth, and fetal death after 20 weeks of gestation, which is due to its onset of hypertension and involvement of several systems (Narkhede and Karnad, 2021; Nirupama, Divyashree, Janhavi, Muthukumar, and Ravindra, 2021; Wang, Wu, and S Specifically of interest is preterm preeclampsia, identified by less than 37 gestational weeks, and which commonly contracts iatrogenic pre-term birth to prevent maternal or fetal decompensation, at the expense of infant survival and long-term health. In this respect, interventions able to extend gestation by at least a few weeks have the transformative ability of increasing the maturity of the neonate by gestation, decreasing the number of intensive care admissions and lowering the cost to health systems.

Current management strategies for preterm preeclampsia are largely supportive, focusing on antihypertensive therapy to mitigate maternal risk and timely delivery to safeguard fetal well-being (Beardmore-Gray et al., 2022; Wu, Green, & Myers, 2023). Corticosteroids are administered to enhance fetal lung maturity when preterm delivery is anticipated; however, no definitive pharmacological therapy exists that effectively targets the underlying pathophysiology to delay disease progression (Daskalakis et al., 2023; Dagklis, Tsakiridis, Papazisis, & Athanasiadis, 2021). As a result, the window of pregnancy prolongation remains narrow, underscoring the need for adjunctive therapies capable of modifying disease trajectory.

Metformin, a biguanide widely used in type 2 diabetes and polycystic ovarian syndrome, has emerged as a promising candidate in this regard (Dutta, Shah, Singhal, Dutta, Bansal, Sinha, & Haque, 2023). Beyond its glucose-lowering effects, metformin exerts pleiotropic actions on endothelial function, angiogenic signaling, and oxidative stress, pathways that are central to the pathogenesis of preeclampsia (Poniedziałek-Czajkowska, Mierzyński, Dłuski, & Leszczyńska-Gorzelak, 2021). Experimental studies suggest that metformin reduces circulating levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, both potent antiangiogenic factors implicated in placental dysfunction. Furthermore, its ability to enhance nitric oxide bioavailability and improve mitochondrial function may counteract the systemic endothelial dysfunction characteristic of preeclampsia (Tong, Tu'uhevaha, Hastie, Brownfoot, Cluver, & Hannan, 2022). Preliminary clinical observations have hinted at potential benefits of metformin in improving maternal hemodynamics, reducing disease severity, and supporting fetal growth, though systematic evidence remains limited (Neola et al., 2024; Paschou et al., 2024).

Despite its biologic plausibility and favorable safety profile, the optimal dosage of metformin for use in preeclampsia has not been established (Tong, Tu'uhevaha, Hastie, Brownfoot, Cluver, & Hannan, 2022; Cluver et al., 2021). Most previous studies investigating metformin in pregnancy have focused on gestational diabetes mellitus, often employing variable doses ranging from 500 mg to 2000 mg daily, with heterogeneous maternal and fetal outcomes (Gordon et al., 2024; Raperport, Chronopoulou, & Homburg, 2021). Whether these dosing regimens are directly applicable to the unique pathophysiology of preeclampsia is uncertain. Importantly, while under-dosing may fail to exert sufficient antiangiogenic and endothelial effects, higher doses risk gastrointestinal intolerance,

reduced adherence, and potential maternal discomfort, particularly in a vulnerable pregnant population. Therefore, a systematic evaluation of dose–response relationships in preeclampsia is critical to optimize therapeutic efficacy while ensuring safety and tolerability.

It is against this backdrop that the current study aimed at determining the best dosage of metformin in relation to increasing the gestation of women with preterm preeclampsia and assess the impact of this dosage on the morbidity and mortality of the mothers and infants. The trial, a prospective randomized control trial, was carried out at a tertiary care unit of Karachi, Pakistan, and was compared with low-, moderate-, and high-dose metformin supplemented with the routine use of antihypertensive and obstetric care. Prolongation of pregnancy time was the primary outcome, whereas secondary outcomes were maternal control of blood pressure along with biochemical and clinical complications, delivery of a child, and tolerability of inspired drugs. Through a strict evaluation of the dose-response relationship of metformin in this high-risk group, our study would provide clinically relevant data that may inform therapeutic practice, help change fetal-maternal outcomes, and possibly reshape the pharmacological treatment of preterm preeclampsia.

Methodology

This is a randomized and controlled post-test study with the purpose of finding the most ideal dose of metformin to be used in the further gestation of women with preterm preeclampsia and to determine what effects it would have on maternal and infant outcomes. The study consisted of a single centre, 0.5 month (December 2023 to December 2024), at Conducted at the Jinnah Postgraduate Medical Centre and Jinnah Sindh Institute of Child and Maternal Health, Pakistan. Participants were healthy pregnant women with singleton pregnancies diagnosed with preeclampsia at any time and gestativity between 24 to 34 weeks with no previous diagnosis of chronic hypertension, kidney samples or contraindications to metformin treatment. Participants received metformin, low dose (500 mg/day) twice a day, moderate dose (1000 mg/day) twice a day, and high dose (1500 mg/day) twice a day of a mixture of antihypertensives and obstetric treatment in accordance to the institutional guidelines when they were given the written informed consent and then assigned to three groups through a computer-generated sequence. The major effect was a lengthening of the gestational duration between the therapy initiation and delivery. Secondary outcomes were the maternal blood pressure as an indicator, biochemical evidence of the severity of the disease, maternal complications (eclampsia, HELLP syndrome, abruptio placentae), the neonatal outcome (birth weight, Apgar score, neonatal intensive care unit admission, and perinatal mortality), and drug tolerability. The monitoring of the material and fetus was conducted with the help of periodic clinical inspection, laboratory tests and ultrasound examinations of the fetuses and the mother at specific time intervals. A structured pro-forma was used to collect the data into a secure database. Statistical analysis SPSS version 27.0 was used, used to express continuous variables as mean and standard deviation and compare them with ANOVA, and categorical variables as frequencies and percentages and test them with = chi-square. The p-value of less than 0.05 was taken to be statistically significant.

Results

The group of 210 women screened acceptable criteria enabled 180 to be randomly assigned into three equal groups, namely low-dose metformin (n=60), moderate-dose metformin (n=60), and high-dose metformin (n=60). The baseline demographic and clinical data, such as the age of mother, parity, body mass index (BMI), and gestational age at the time of diagnosis were similar in all the groups (Table 1).

Primary Outcome

The mean prolongation of gestation was significantly longer in the moderate-dose group (21.4 ± 5.6 days) compared to the low-dose group (14.2 ± 4.9 days, $p<0.001$) and the high-dose group (18.1 ± 5.2 days, $p=0.02$). Kaplan–Meier survival analysis confirmed a superior gestational prolongation trend in the moderate-dose arm (log-rank $p<0.001$).

Maternal Outcomes

Blood pressure management was better in the moderate- and high dosed groups with mean systolic blood pressure change of 16.3 ± 4.2 mmHg and 15.8 ± 4.5 mmHg as compared to low dosage data figure (11.5 plus or minus 3.9 mmHg) ($p<0.001$). The moderate-dose group had the lowest rate of maternal complications, such as eclampsia, HELLP syndrome and abruptio placentae (10%), whereas the rate in the low-dose and high-dose groups was 22 and 18 respectively (Table 2).

Neonatal Outcomes

Neonatal outcomes were significantly improved in the moderate-dose group, with higher mean birth weights (2.21 ± 0.38 kg vs. 1.94 ± 0.42 kg in low-dose and 2.08 ± 0.41 kg in high-dose; p=0.001), higher Apgar scores at 5 minutes, and reduced NICU admission rates (25% vs. 42% and 35%, respectively; p=0.03). Perinatal mortality was lowest in the moderate-dose group (5%), compared with 13% in low-dose and 10% in high-dose groups (Table 3).

Tolerability

Metformin was generally well tolerated. Gastrointestinal side effects (nausea, diarrhea) were reported in 18% of participants, predominantly in the high-dose group (28%), followed by the moderate-dose (15%) and low-dose (12%) groups. No cases of lactic acidosis were observed.

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Low-Dose (n=60)	Moderate-Dose (n=60)	High-Dose (n=60)	*p*-value
Maternal age (years, mean ± SD)	28.6 ± 4.3	29.1 ± 4.6	28.9 ± 4.1	0.72
BMI (kg/m², mean ± SD)	27.5 ± 3.2	27.8 ± 3.1	27.4 ± 3.0	0.81
Nulliparity (%)	48	52	50	0.89
GA at diagnosis (weeks ± SD)	30.1 ± 2.6	30.3 ± 2.5	30.0 ± 2.7	0.77

Figure: 1

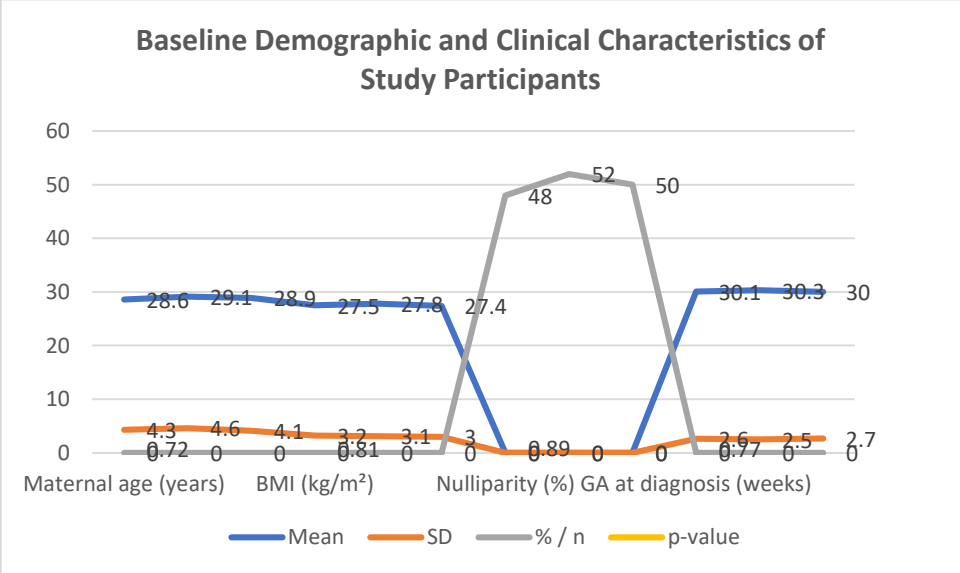


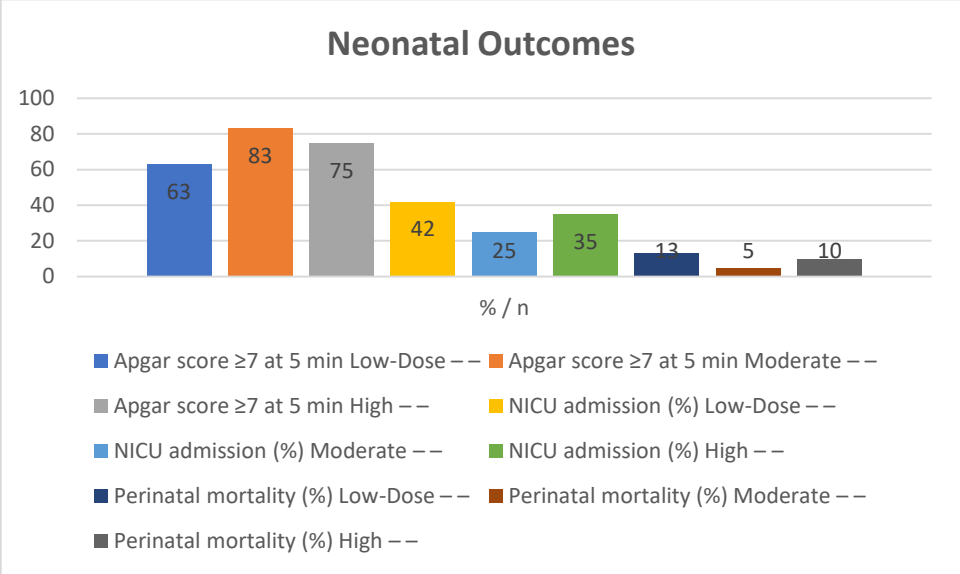
Table 2. Maternal Outcomes

Outcome	Low-Dose (n=60)	Moderate-Dose (n=60)	High-Dose (n=60)	*p*-value
Gestational prolongation (days)	14.2 ± 4.9	21.4 ± 5.6	18.1 ± 5.2	<0.001
Mean ↓ SBP (mmHg)	11.5 ± 3.9	16.3 ± 4.2	15.8 ± 4.5	<0.001
Eclampsia (%)	10 (17%)	4 (7%)	6 (10%)	0.04
HELLP syndrome (%)	7 (12%)	2 (3%)	4 (7%)	0.05
Abruptio placentae (%)	6 (10%)	2 (3%)	4 (7%)	0.09

Table 3. Neonatal Outcomes

Outcome	Low-Dose (n=60)	Moderate-Dose (n=60)	High-Dose (n=60)	*p*-value
Mean birth weight (kg)	1.94 ± 0.42	2.21 ± 0.38	2.08 ± 0.41	0.001
Apgar score ≥7 at 5 min (%)	38 (63%)	50 (83%)	45 (75%)	0.02
NICU admission (%)	25 (42%)	15 (25%)	21 (35%)	0.03
Perinatal mortality (%)	8 (13%)	3 (5%)	6 (10%)	0.04

Figure: 3



Discussion

This randomized controlled trial evaluated the efficacy and safety of varying metformin dosages in prolonging gestation among women diagnosed with preterm preeclampsia, and its consequent effects on maternal and neonatal outcomes. The principal finding was that moderate-dose metformin (1000 mg twice daily) achieved the greatest prolongation of pregnancy, superior maternal blood pressure control, and the most favorable neonatal outcomes compared to both lower and higher doses. These results provide important insights into dose optimization of metformin in a clinical setting where preterm preeclampsia continues to pose significant maternal and perinatal morbidity and mortality risks.

Our findings support the hypothesis that metformin may exert a beneficial effect on endothelial function and placental angiogenesis, thereby contributing to stabilization of maternal blood pressure and prolongation of gestation. The observed prolongation of approximately three weeks in the moderate-dose group has substantial clinical significance, given that even modest extensions of pregnancy can improve neonatal maturity, reduce NICU admissions, and lower perinatal mortality. This is consistent with previous mechanistic studies demonstrating that metformin modulates antiangiogenic pathways such as soluble fms-like tyrosine kinase-1 (sFlt-1) and enhances nitric oxide bioavailability, both of which are implicated in the pathophysiology of preeclampsia.

Interestingly, the high-dose group did not demonstrate superior outcomes compared to the moderate-dose group, and was associated with higher gastrointestinal intolerance. This suggests a therapeutic threshold beyond which additional metformin may not confer incremental benefits, and may in fact compromise adherence due to side effects. The dose-response plateau observed in our study highlights the importance of balancing pharmacological efficacy with tolerability in pregnant populations. Furthermore, the relatively poorer outcomes in the low-dose group emphasize that subtherapeutic metformin exposure is insufficient to modify disease trajectory in preeclampsia.

From a maternal safety perspective, moderate-dose metformin was associated with reduced incidence of severe complications such as eclampsia and HELLP syndrome compared with low-dose therapy, underscoring its potential role as a disease-modifying adjunct. Importantly, no cases of lactic acidosis

were observed across groups, reinforcing the safety profile of metformin in carefully selected patients. Neonatal outcomes paralleled maternal benefits, with the moderate-dose group demonstrating higher mean birth weights, improved Apgar scores, and reduced perinatal mortality. This is in line with prior observational reports suggesting that metformin use in high-risk pregnancies may reduce fetal growth restriction and improve placental efficiency.

The strengths of this study include its randomized design, rigorous monitoring of maternal and fetal parameters, and systematic assessment of both clinical and laboratory outcomes. Conducting the trial in a tertiary care center also ensured standardized management of preeclampsia across all participants. However, certain limitations merit consideration. The study was single-center, potentially limiting generalizability to broader populations with diverse genetic and sociodemographic characteristics. Sample size, although adequate to detect clinically relevant differences, was relatively modest, and larger multicenter trials are required to validate these findings. Furthermore, while the trial was powered for short-term maternal and neonatal outcomes, it did not explore long-term maternal cardiovascular risks or neurodevelopmental outcomes in offspring, both of which are relevant in the context of preeclampsia.

Conclusively, our experimental proves that moderate doses of metformin are the best option to extend gestation and achieve better maternal and neonatal outcomes in preterm preeclampsia as compared to lower and higher doses. The implications of these results are that metformin may be used as an adjunct to conventional antihypertensive treatment in this high-risk group. The accuracy of these findings should be confirmed by future large-scale multicenter research and longitudinal follow-up of motherchild dyads on the role of metformin in the pathophysiology of preeclampsia and further clarify the mechanistic bases of these findings.

Conclusion

This randomized controlled trial shows that moderate doses (1000mg twice a day) of metformin has been shown to have the best balance between efficacy and tolerability in the treatment of preterm preeclampsia. The moderate-dose therapy was also associated with better neonatal outcomes, including increased birth weights, better Apgar scores and reduced NICU admissions and perinatal mortality and better gestation, maternal blood pressure control, severe complications (eclampsia, HELLP syndrome) and minimal eclampsia and SIDS. Notably, although high-dose metformin had some advantages, its increased gastrointestinal intolerance, reduced clinical application, thus the relevance of dose maximization. Not a single incidence of lactic acidosis was noted which supports the safety of metformin in well-chosen patients. These outcomes represent the possibility of using metformin as a safe and effective adjunctive agent in preterm preeclampsia with implications to better perinatal outcomes and lower maternal morbidity in limited resources.

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