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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 outcomes. 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 the 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-dose (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 (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome were lowest in the moderate-dose arm (10%), and neonatal outcomes, including mean birth weight, Apgar scores, and NICU (Neonatal Intensive Care Unit) admissions, were most favorable. High-dose metformin was associated with greater gastrointestinal intolerance without additional efficacy. No

cases of lactic acidosis were 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 challenges in obstetric medicine, and it has been associated with significant maternal and perinatal morbidity and mortality worldwide (Chang, Seow, and Chen, 2023; Yang, Wang, and Li, 2024; Von Dadelszen, Vidler, Tsigas, and Magee, 2021). It is estimated to occur in 2–8% of pregnancies, with the burden disproportionately borne by low- and middle-income countries where limited access to specialized obstetric care is prevalent. Preeclampsia is a frequent cause of maternal complications, including eclampsia, HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome, and placental abruption, and is closely linked to fetal growth restriction, preterm birth, and intrauterine fetal demise after 20 weeks of gestation, due to the onset of hypertension and multisystem involvement (Narkhede and Karnad, 2021; Nirupama, Divyashree, Janhavi, Muthukumar, and Ravindra, 2021; Wang, Wu, and S).

Specifically of interest is preterm preeclampsia**,** identified as onset before 37 weeks of gestation, which frequently necessitates iatrogenic preterm delivery to prevent maternal or fetal decompensation, often at the expense of neonatal survival and long-term health. In this respect, interventions that can extend gestation even by a few weeks have the transformative potential of increasing neonatal maturity, reducing intensive care admissions, and lowering healthcare costs.

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, and 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, and Athanasiadis, 2021). Consequently, the window for pregnancy prolongation remains narrow, underscoring the need for adjunctive therapies capable of modifying disease trajectory.

Metformin, a biguanide widely used in type 2 diabetes mellitus and polycystic ovary syndrome, has emerged as a promising candidate in this regard (Dutta, Shah, Singhal, Dutta, Bansal, Sinha, and Haque, 2023). Beyond its glucose-lowering effects, metformin exerts pleiotropic actions on endothelial function, angiogenic signaling, and oxidative stress—pathways central to the pathogenesis of preeclampsia (Poniedziałek-Czajkowska, Mierzyński, Dłuski, and 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 anti-angiogenic 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, and Hannan, 2022). Preliminary clinical observations have indicated potential benefits of metformin in improving maternal hemodynamics, reducing disease severity, and supporting fetal growth, although 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, and Hannan, 2022; Cluver et al., 2021). Most prior 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, and Homburg, 2021). Whether these dosing regimens are directly applicable to the unique pathophysiology of preeclampsia remains uncertain. Importantly, while under-dosing may fail

to exert sufficient anti-angiogenic and endothelial effects, higher doses risk gastrointestinal intolerance, reduced adherence, and 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 to determine the optimal dosage of metformin in prolonging gestation among women with preterm preeclampsia and to assess its impact on maternal and neonatal morbidity and mortality. This prospective randomized controlled trial was carried out at the Jinnah Postgraduate Medical Centre and the Sindh Institute of Child and Maternal Health, Pakistan, and compared low-, moderate-, and high-dose metformin administered alongside standard antihypertensive and obstetric care. Prolongation of pregnancy duration was the primary outcome, whereas secondary outcomes included maternal blood pressure control, biochemical and clinical complications, neonatal outcomes, and tolerability of the administered drug. Through a rigorous evaluation of the dose–response relationship of metformin in this high-risk group, our study provides clinically relevant data that may inform therapeutic practice, improve maternal–fetal outcomes, and potentially reshape the pharmacological management of preterm preeclampsia.

Methodology

This was a randomized controlled post-test study with the purpose of determining the optimal dose of metformin for prolonging gestation in women with preterm preeclampsia and to evaluate its effects on maternal and neonatal outcomes. The study was conducted over 1 year, from December 2023 to December 2024, at the Jinnah Postgraduate Medical Centre and the Sindh Institute of Child and Maternal Health, Pakistan.

Participants were pregnant women with singleton gestations diagnosed with preeclampsia between 24 and 34 weeks of gestation, with no prior history of chronic hypertension, renal disease, or contraindications to metformin therapy. Participants were randomized into three groups using a computer-generated sequence after providing written informed consent. They received either low-dose metformin (500 mg twice daily), moderate-dose metformin (1000 mg twice daily), or high-dose metformin (1500 mg twice daily), in addition to standard antihypertensive therapy and obstetric management according to institutional guidelines.

The primary outcome was prolongation of gestational duration from initiation of therapy to delivery. Secondary outcomes included maternal blood pressure control, biochemical markers of disease severity, maternal complications (eclampsia, HELLP syndrome, placental abruption), neonatal outcomes (birth weight, Apgar score, neonatal intensive care unit admission, and perinatal mortality), and drug tolerability. Maternal and fetal monitoring was carried out through periodic clinical assessments, laboratory investigations, and ultrasound examinations at defined intervals.

Data were collected using a structured proforma and entered into a secure database. Statistical analysis was performed using SPSS version 27.0. Continuous variables were expressed as mean ± standard deviation and compared using ANOVA, while categorical variables were expressed as frequencies and percentages and analyzed using the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

The group of 210 women screened met the eligibility criteria, and 180 were randomly assigned into three equal groups: low-dose metformin (n=60), moderate-dose metformin (n=60), and high-dose metformin (n=60). The baseline demographic and clinical characteristics, including maternal age, parity, body mass index (BMI), and gestational age at diagnosis, were similar across all 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 superior gestational prolongation in the moderate-dose arm (log-rank p<0.001).

Maternal Outcomes

Blood pressure control was better in the moderate- and high-dose groups, with mean systolic blood pressure reductions of 16.3 ± 4.2 mmHg and 15.8 ± 4.5 mmHg, respectively, compared to 11.5 ± 3.9 mmHg in the low-dose group (p<0.001). The moderate-dose group had the lowest rate of maternal complications, including eclampsia, HELLP syndrome, and placental abruption (10%), compared with 22% in the low-dose group and 18% in the high-dose group (Table 2).

Neonatal Outcomes

Neonatal outcomes were significantly improved in the moderate-dose group, with higher mean birth weight (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 the low-dose group and 10% in the high-dose group (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 group (15%) and the low-dose group (12%). 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

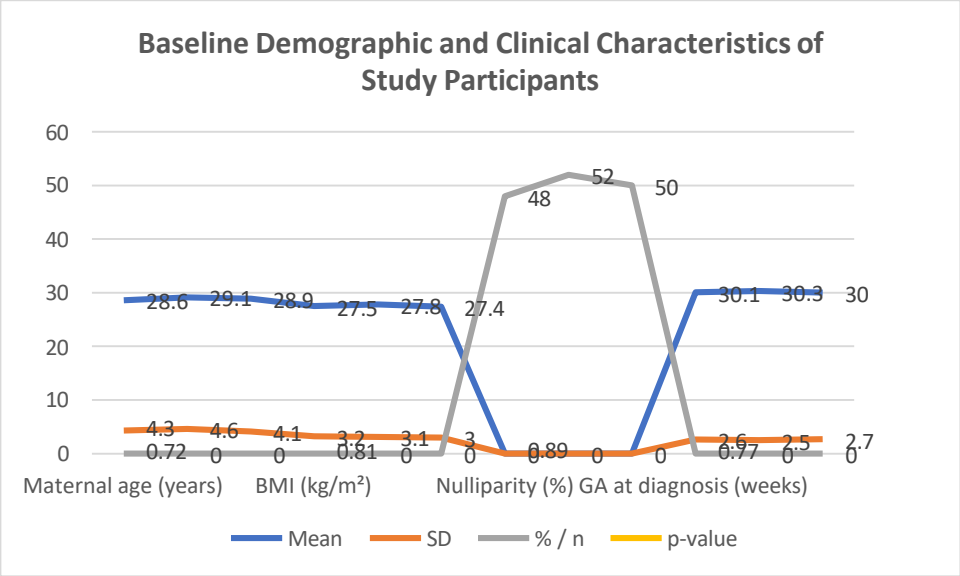


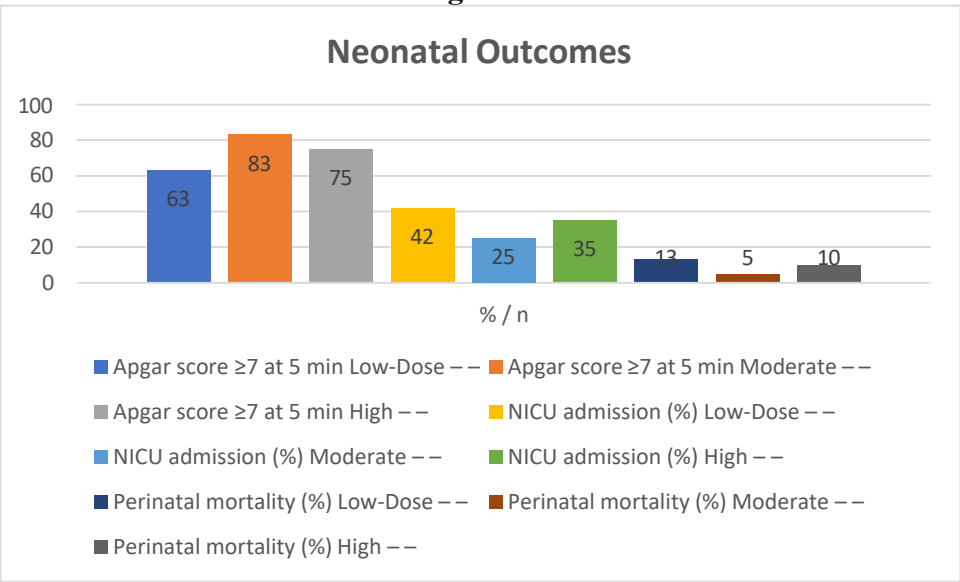
Table 2. Maternal Outcomes

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 anti-angiogenic 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 a 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 at the Jinnah Postgraduate Medical Centre and the Sindh Institute of Child and Maternal Health, Pakistan, also ensured standardized management of preeclampsia across all participants. However, certain limitations merit consideration. The study was potentially limiting generalizability to broader populations with diverse genetic and sociodemographic characteristics. The 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 highly relevant in the context of preeclampsia.

Conclusively, our experiment demonstrates that moderate-dose metformin is the most effective option to prolong gestation and achieve improved maternal and neonatal outcomes in preterm preeclampsia, compared to both lower and higher doses. The implications of these results are that metformin may serve as an adjunct to conventional antihypertensive therapy in this high-risk group. The validity of these findings should be confirmed through future large-scale multicenter research and longitudinal follow-up of mother–child dyads to further clarify the role of metformin in the pathophysiology of preeclampsia and elucidate the mechanistic basis of its effects.

Conclusion

This randomized controlled trial shows that moderate doses of metformin (1000 mg twice daily) provide the best balance between efficacy and tolerability in the management of preterm preeclampsia. Moderate-dose therapy was also associated with improved neonatal outcomes, including increased birth weights, higher Apgar scores, reduced NICU admissions, decreased perinatal mortality, prolonged gestation, better maternal blood pressure control, and a lower incidence of severe complications such as eclampsia and HELLP syndrome, with minimal recurrence of eclampsia and reduced risk of sudden infant death syndrome (SIDS). Notably, although high-dose metformin demonstrated some advantages, its increased gastrointestinal intolerance reduced clinical applicability, underscoring the limited relevance of dose maximization. Importantly, no cases of lactic acidosis were observed, supporting the safety profile of metformin in carefully selected patients. These outcomes highlight the potential of metformin as a safe and effective adjunctive therapy in preterm preeclampsia, with implications for improved perinatal outcomes and reduced maternal morbidity in resource-limited settings.

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