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Maternal and Fetal Outcomes among Pregnant Women with Preeclampsia after Receiving either Methyldopa or Methyldopa plus Nifedipine

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Abstract

Background
Globally, hypertension during pregnancy contributes to 10% of all pregnancy-related complications and is responsible for 10-15% of maternal mortality in low-middle income countries (LMIC) (1,2). This study aimed to assess maternal and fetal outcomes among pregnant women who were on Methyldopa (MD) or Methyldopa plus Nifedipine (MD + N) for preeclampsia (PE) and severe preeclampsia (SPE).

Methods
The study used prospective descriptive observation methods. It was conducted at Muhimbili National Hospital (MNH) maternity wards, involved pregnant women with moderate to severe PE on MD or MD + N admitted for labour from July 2016 to October 2016. A case report form (CRF) was used to record maternal demographics and clinical parameters including blood pressures, haemoglobin levels, platelets counts and proteinuria. While fetal outcomes assessed were fetal body weight, Apgar score, and mortality after delivery.

Results
The average Mean Arterial Blood Pressure (MAP) for MD and MD + N patients on admission was recorded as 126.8 ± 12.5mmHg and 126.5 ± 14.73mmHg (p=0.879) and the day before delivery was 109.1 ± 9.6mmHg and 106.2 ± 11.0mmHg (p=0.061) respectively. Haemoglobin (Hb) level was 10.7±1.7mg/dl for MD group while 11.1 ± 1.4 mg/dl for MD + N group (p=0.114). Proteinuria in pregnant women on MD was 3 ± 1 while 2 ± 1 for MD+N (p=0.312). The count for stillbirth was 11.0% for MD and 16.7% for MD + N. Neonates with an Apgar score of <7 at five minutes after delivery was 11.0% for MD and 7.7% for MD + N.

Conclusion
Both methyldopa and methyldopa plus nifedipine treatment approaches are preferred to be adopted in LMIC in the management of PE and SPE and employed in all pregnant women at 28 to 34 weeks gestation age to have good and improved maternal and fetal outcomes. Close monitoring of fetal well-being is highly recommended in both groups when conservative management is preferred versus delivery when BP is not controlled. However, the use of methyldopa plus nifedipine in pregnant women with PE/SPE should be done with caution.

Keywords: *Preeclampsia (PE), Severe Preeclampsia (SPE), Maternal Outcomes, Fetal Birth Outcomes, Methyldopa, Nifedipine.*

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Introduction

Worldwide, 10% of all pregnancies result in complications related to hypertensive disorders of pregnancy (HDP). In that case, they are major causes of maternal and prenatal morbidity and mortality (5, 6). In low-to-middle income countries (LMIC), HDP contributes to 10-15% of maternal mortality (2) where as in Sub-Saharan Africa alone, PE and SPE are the major contributors to deaths and disabilities among women of reproductive age (15-49 years) (4,5). Pregnant women with PE/SPE should deliver the baby if it reaches the term (38 weeks). However, if the baby has not yet reached the term, conservative management including methyldopa or methyldopa plus nifedipine is recommended (6). Early delivery minimizes maternal risks but may result in iatrogenic prematurity and prolonged hospital stay (7). Meanwhile, using antihypertensive drugs in PE/SPE poses a challenge to assure maternal safety without compromising uteroplacental perfusion (8).

In many LMICs, methyldopa or nifedipine are used as first-line treatment for PE/SPE. Methyldopa lowers the BP mainly by reducing peripheral vascular resistance with a variable reduction in heart rate and cardiac output. It has the most dating back history of safety, hence a valid reason to be used during pregnancy (6,9). Nifedipine causes a decrease in arterial blood vascular resistance but with minimal effect on the venous system and reduces up to 20% of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) as well as MAP (10). In a study conducted 2011 in India, 105 pregnant women who were on MD alone, showed that biochemical derangements and platelet count were close to the normal values as healthy individuals after treatment (11). Additionally, the use of the MD+N did not give significant change in platelet count but there was a significant decrease in the biochemical changes post-treatment. It was also revealed that there was reduction of urine albumin levels and improved renal functional test after treatment using MD + N (10,11). Nifedipine has the ability to reduce BP quickly and clinically, it has an advantage in controlling elevation of liver enzymes by preventing rupture of hepatocytes due to high BP (12). Both treatment modalities resulted in a significant decrease in liver enzymes to their normal values and could aid to prevent Hemolysis, Elevated Liver Enzyme Levels, and Low Platelet Levels (HELLP syndrome) (11). The said treatment approaches have advantages of controlling BP, liver transaminase enzymes, hemolysis and platelet counts resulting in prevention of HELLP syndrome. Hence, the addition of nifedipine can improve maternal safety both through BP control and normal lab values.

However, there is lack of criteria to guide obstetrician in deciding between methyldopa and nifedipine on which should be used first (13). In that regard, the decision relies in hands of the obstetrician. Consequently, this study aimed to assess maternal and fetal outcomes among pregnant women who were on methyldopa and methyldopa plus nifedipine as a conservative management plan for PE/SPE at a large tertiary training hospital in an LMIC. Both maternal and fetal birth outcomes between pregnant women on MD alone and that on MD+N were assessed.

Material and Methods

Study design and participants

A prospective descriptive observation design was conducted at Muhimbili National Hospital (MNH) maternity block, Dar es Salaam, Tanzania. The study involved pregnant women admitted between July 2016 to October 2016, where all pregnant women diagnosed with PE/SPE at gestation age of 28 to 34 weeks and initiated on MD or MD + N treatment were eligible. The pregnant women admitted were closely followed from the day they began using either MD or MD + N until the time of delivery.

Sampling technique

A consecutive recruitment sampling technique was used, whereby all eligible pregnant women with preeclampsia and severe preeclampsia under the conservative treatment of methyldopa or methyldopa plus nifedipine, they were recruited after signing consent form.

Data collection and management

Maternal socio-demographic characteristics were extracted from the antenatal clinic card which included; age, maternal body weight, marital status, occupation, and gravidity. The diagnosis of whether the pregnant women had PE or SPE was obtained from the medical charts. Preeclampsia defined as an elevation of blood pressure above 140/90 mmHg with proteinuria during admission. Severe preeclampsia is diagnosed by an increase in blood pressure to 160/110 mmHg, proteinuria, with either signs and symptoms of headaches, blurred vision, nausea, upper abdominal pain, oliguria or with biochemical derangements (elevated liver enzymes, creatinine, uric acid. The pregnancy induced hypertension to be PE or SPE it should be first diagnosed after 20^{th} weeks gestation. While conservative treatment at MNH is done between the 28^{th} to 34^{th} week of gestation. After 34^{th} week of gestation delivery is planned and the choice of either spontaneous vaginal delivery or caesarian section depends on maternal clinical condition. Also, prescribed medicines and

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mode of delivery either spontaneous vaginal delivery, SVD or caesarian section, SC were noted from the medical chart. The BP was taken daily, morning and evening, and was used as a primary indicator to assess treatment outcomes. A minimum decrease of SBP by 10mmHg, and DBP by 5mmHg indicated good response for both MD and MD + N. Close follow-up to pregnant women were made until delivery under the conservative treatment.

Maternal treatment outcomes included; blood pressure and liver transaminase enzymes (ALT and AST), haemoglobin level, platelet count and uric acid taken from weekly blood samples. Proteinuria results were taken and categorized clinically as +1, +2 and +3, with respect to protein concentration in urine. Birth outcomes consisted of neonatal body weight, Apgar score 5minutes after delivery and infant mortality.

Table 1: Social demographic and obstetrics characteristics of pregnant women and delivered babies (N=169)

Medical Condition Parameters N (%)		MD N-91	MD+N N-78	P-Value (2-sided)
Age Groups (years)	15-25	29 (49.2)	30 (50.8)	0.616
	26-35	51 (57.3)	38 (42.7)	
	36-45	11 (52.4)	10 (47.6)	
Age (years)		29.0 ± 5.9	27.7 ± 5.5	0.141
Body Mass Index	Below Normal (<18.5kg/m2)	0 (0.0)	2 (100)	0.180
	Normal (18.5-25kg/m2)	15 (45.5)	18 (54.5)	
	Overweight (25-30kg/m2)	27 (50.9)	26 (49.1)	
	Obese (>30kg/m2)	49 (60.5)	32 (39.5)	
Body Mass Index (Kg/m2)		30.9 ± 5.3	30.6 ± 7.2	0.009
Recovery Duration (days)		5.8 ± 3.2	5.7 ± 4.0	0.887
Gestation Age (weeks)		32.8 ± 1.5	32 ± 1.6	0.308
Gravidity		2	2	0.634
Parity		1	1	0.857
Gestation Age (Weeks)	28-30	10 (45.5)	12 (54.5)	0.397
	31-34	81 (55.1)	66 (44.9)	
Medical Conditions	PE	52 (44.8)	64 (55.2)	0.001
	SPE	39 (73.6)	14 (26.4)	
Delivery Mode	SVD	36 (48.6)	38 (51.4)	0.232
	CS	55 (57.9)	40 (42.1)	

N, number; MD, methyldopa; MD+N, methyldopa plus nifedipine; PE, preeclampsia; SPE, severe preeclampsia; SVD, spontaneous delivery; CS, caesarian section

Ethical clearance was sought from MUHAS Research and Publication Committee, and it was permitted by the Executive Director and the Head of Department of Obstetrics and

Gynecology MNH. Mean arterial blood pressure was used to compare the BP between the two treatment groups. Also, maternal lab results were assessed and compared between MD and MD + N treatment. Neonatal birth outcomes were also thoroughly evaluated and compared based on either the mother was on MD or MD + N treatment.

Statistical analysis

BP and MAP were recorded in Microsoft Excel and analyzed by the IBM SPSS STATISTICS version 20. Proportions were used to summarize categorical variables and a Chi-square test was used to test for statistical difference between variables. The mean and standard deviation summarized continuous variables. All data were tested for validity by MED CALC.

Results

A total of 334 pregnant women with PE and SPE were admitted during the study period. Whereby, 169 (PE, 53 and SPE, 116) pregnant women were eligible for conservative treatment and followed up till delivery.

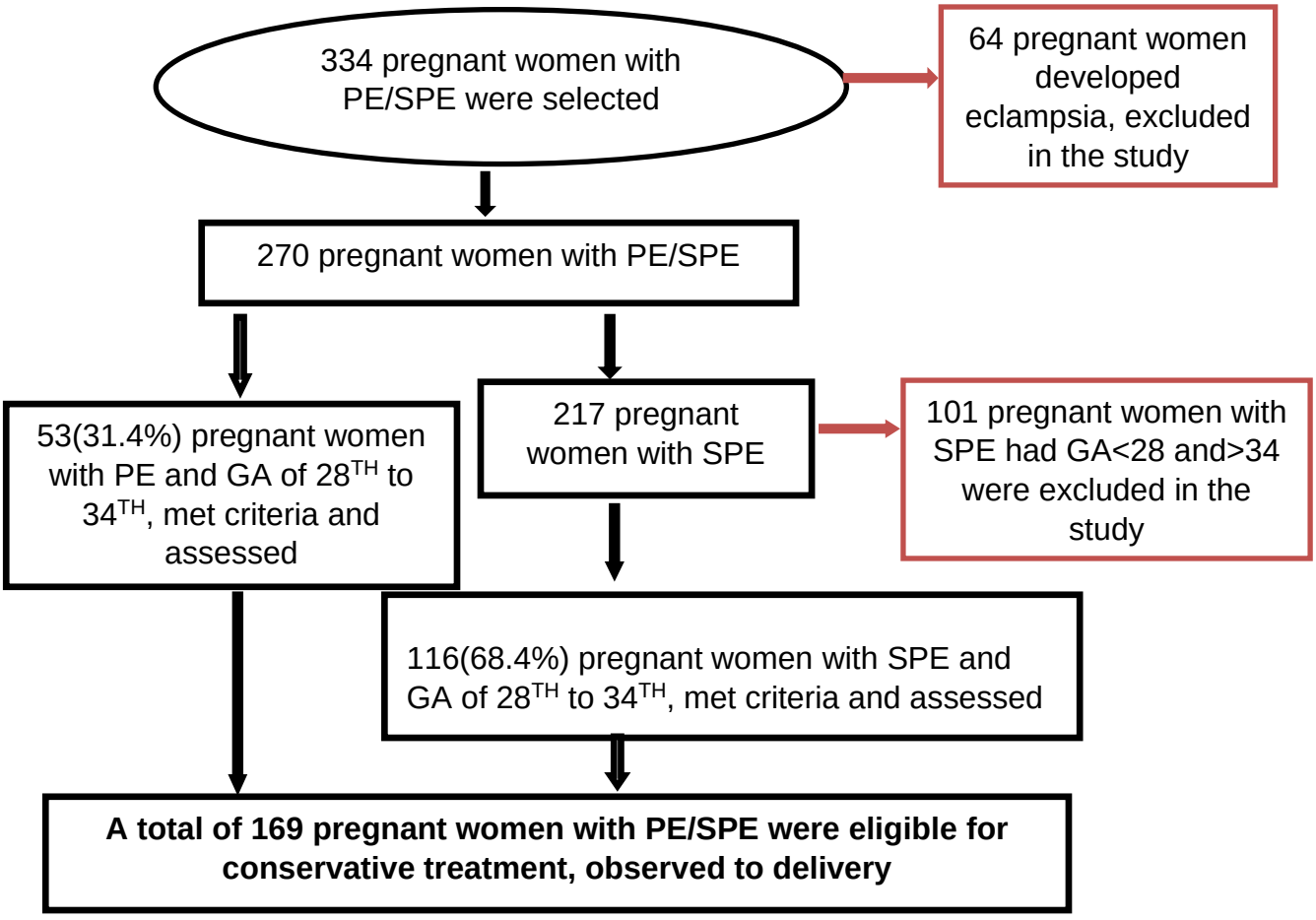

Figure 1. Systematic flow chart of pregnant women involved in the study

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The proportion of pregnant women with PE on MD differ widely with women with SPE on the treatment, which occupied 44.8% and 73.6% separately. Mean days taken during conservative treatment was 5.8 ± 3.2 days and 5.7 ± 4.0 for MD and MD + N (p=0.887) respectively. The mean gestational age for MD was 32.8 ± 1.6 weeks and MD + N was 32.0 ± 1.6 weeks (p=0.308). The treatment groups had an almost similar MAP (mmHg) on admission was 126.8 ± 12.5 for MD and 126.5 ± 14.7 for MD + N (p=0.879) (Table 2).

The difference of mean MAPs on admission and after delivery between the pregnant women on methyldopa and methyldopa plus nifedipine was not statically significant.

Table 2: Comparison of an average MAP between methyldopa and methyldopa plus nifedipine on admission and after delivery

Treatment categories	Blood pressure mean ± SD (range) (mmHg)					
	SBP on Admission	SBP after Delivery	DSP on Admission	DBP after Delivery	MAP on Admission	MAP after Delivery
MD	173.0± 18.4 (80.0)	143.9 ± 11.8 (64.0)	103.7 ± 14.4 (80.0)	92.0 ± 11.9 (75.0)	126.8 ± 12.5 (73.4)	109.1 ± 9.6 (57.7)
MD + N	173.6 ± 19.7 (101.0)	139.7 ± 14.2 (68.0)	102.9 ± 17.5 (131.0)	89.4 ± 13.8 (63.0)	126.5 ± 14.7 (94.0)	106.2 ± 11.0 (55.7)
P-value	0.837	0.041	0.750	0.190	0.879	0.061

MAP, mean arterial blood pressure; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure

Maternal outcomes analysed involved haemoglobin levels (mg/dl), platelet counts(k/ul), proteinuria, serum creatine (mg/dl), uric acid levels (mmol/L), ALT (U/L) and AST(U/L) (Table 3). Generally, all biochemical derangements between MD and MD + N treatment categories looked different. The dissimilarities were pronounced for serum creatinine (75.3 ± 34.0, MD and 103.7 ± 103.8, MD + N, (p=0.051) and liver transaminase enzymes (ALT 45.4 ± 58.1, MD and 60.4 ± 96.8, MD + N, p=0.286; AST, 44.0 ± 71.9 MD and 78.0 ± 132.4, MD + N, p=0.073). Neonatal treatment outcome consisted of proportion of babies with <1kg birth weight to be 3.3% for MD and 2.6% for MD + N treatment group, while >3kg birth weight to be 20.9% for MD and 14.1% for MD + N (Table 4). The proportion of neonates delivered alive were 89.0% from MD group and 83.7% from MD + N group. All neonatal outcomes diverged between the two treatment categories for management of PE/SPE.

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Table 3: Assessing maternal biochemical derangement between methyldopa and methyldopa plus nifedipine

Labs parameters	Treatment categories	N	Mean ± SD	P-Value
Haemoglobin level (mg/dl)	MD	72	10.7 ± 1.7	0.114
	MD + N	66	11.1 ± 1.4	
Platelets count (k/ul)	MD	65	187.8 ± 87.0	0.856
	MD + N	62	184.6 ± 108.2	
Proteinuria	MD	79	3 ± 1	0.312
	MD + N	72	2 ± 1	
Serum Creatinine (mg/dl)	MD	60	75.3 ± 34.0	0.051
	MD + N	64	103.7 ± 106.8	
Uric acid (mmol/L)	MD	61	0.4 ± 0.1	0.591
	MD + N	61	0.4 ± 0.2	
ALT (U/L)	MD	65	45.4 ± 58.7	0.286
	MD + N	65	60.4 ± 96.8	
AST (U/L)	MD	64	44.0 ± 71.9	0.073
	MD + N	64	78.0 ± 132.4	

N - number; ALT - alanine aminotransferase; AST - aspartate aminotransferase

Table 4: Neonates treatment outcomes delivered by pregnant women on methyldopa and methyldopa plus nifedipine

Neonate Birth Weight (kg) vs. medications		Treatment categories		Common P- value
		MD	MD + N	
Birth Weight (kg)	<1	3(3.3%)	2(2.6%)	0.627
	1.0-2.0	34(37.4%)	35(44.9%)	
	2.0-3.0	35(38.5%)	30(38.5%)	
	>3	19(20.9%)	11(14.1%)	
Birth outcome	Live	81(89.0%)	65(83.3%)	0.198
	Dead	10(11.0%)	13(16.7%)	
Apgar score	<7	9 (11%)	5(7.7%)	
	>7	73(89%)	60(92.3%)	
Mean Apgar score		8.3 ± 3.0	7.8 ± 3.7	0.283

Apgar Score stands for Appearance, Pulse, Grimace, Activity, and Respiration. it is used to assess babies immediately after delivery and performed at 1 minute and again at 5 minutes after birth.

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Discussion

Maternal Outcomes

Findings from two groups had shown similar mean MAPs on admission, after undergoing the conservative treatment and endpoints were similar. It implies there is additional advantage of adding nifedipine on methyldopa for management of PE/SPE. When comparing one by one individuals on methyldopa plus nifedipine, they had higher BP compared to methyldopa monotherapy at the time of admission. This cohort had more women with SPE, 116(68.4%) with pathologically higher blood pressure. It provides a very strong indication that methyldopa plus nifedipine played a significant role in lowering the MAP of the SPE group. The finding is similar to Juno and colleagues reported in 2013, where Nifedipine add-on had a pronounceable benefit in the maternal control of the MAP in the SPE (14). An intervention study to compare the effectiveness of Methyldopa in mild PE versus MD + N in SPE reported that MD is effective in controlling mild PE while an MD + N was effective in moderate to SPE (11). Contrary, Abalos E, 2007 and NICE, 2011 reported that MD was superior when compared to other antihypertensive medications such as nifedipine in management of PE and SPE. Also, the two studies revealed the effectiveness of methyldopa when is used as solo therapy and a choice for managing PE/SPE (15,16).

Full blood count results including platelets, haemoglobin, and liver enzymes, were normal and similar between methyldopa and methyldopa plus nifedipine treatment groups. These results are similar to the analysis from India in 2011, in which all pregnant women treated with MD alone reported similar blood counts to healthy control women (11). Additionally, pregnant women on MD alone had no decrease in proteinuria compared to those on MD + N. The reasons may be due to improvements in renal function, vasodilatation effects and quick onset of nifedipine when added to methyldopa. The variation seen on results such as full blood counts parameters are in same line with the understanding of the disease in that many pregnant women in our study who on methyldopa alone were preeclamptic with moderate renal, liver and blood counts deterioration. Also, nifedipine with its good impact of quick BP reduction has role to improve renal and hepatic functions and reduces the disturbances on blood counts. Pregnant women on MD + N showed the failure of drugs to control uric acid and serum creatinine, although there was decrease in proteinuria. These findings are contrary from the study by Jayasutha, 2011 that stated an improvement in all parameters to their normal values with the patients on methyldopa alone as well as a well-controlled BP. In addition, the study further showed no significant changes in renal functions

and with a significant decrease in liver enzymes (11). But for pregnant women with PE/SPE, the use of methyldopa plus nifedipine has added benefits due to its potency on the decrease of blood pressure especially for those who failed on methyldopa alone.

Fetal Outcomes

The study revealed, the addition of nifedipine on methyldopa to pregnant women led to decreased fetal birth weight and an increase in fetal deaths in comparison to the use of methyldopa alone. Pharmacologically, the addition of nifedipine compromises the uteroplacental and fetal hemodynamics due to its effect of dilating blood vessels (17). It has also revealed number of neonates with an Apgar score <7 at five minutes after their delivery, in one-by-one comparison was higher in MD + N group. Moreover, there were fewer improvements on fetal outcomes when nifedipine was added on methyldopa, rather, there were a slight increase in neonatal death and babies who were underweight compared to when methyldopa was used alone. However, the differences found were not statistically significant. The use of methyldopa prevents subsequent progression of SPE in pregnancy and that it does not seem to have adverse effects on uteroplacental/fetal hemodynamics and fetal well-being (9,17). The results showed birth weight and other neonatal complications were similar in children exposed to methyldopa as in the placebo group (9). The two studies narrate the advantages of methyldopa monotherapy in management of PE/SPE which improves fetal outcome. It was described, overzealous BP control done by nifedipine add-on may lead to placental hypo-perfusion and this in turn may compromise the fetus oxygen and nutrients supply, thereby resulting in intrauterine growth reduction (18).

The study has some limitations. The design did not allow any intervention for allocating and providing medications and ordering lab investigations from pregnant women and neonates, all findings were taken and supervised by nurses under obstetrician guide. There were no regular weekly laboratory investigations request. Also, many pregnant women came to the hospital at a late stage, affected the response to medication. Likewise, it did not provide enough time for medications to work and produce required therapeutic effects.

Still, at MNH, methyldopa (500mg to be taken three times a day) is adopted as the frontline treatment in PE/SPE and is initiated in all pregnant women with PE or SPE until the BP is controlled. Where there is poor control of BP with methyldopa alone, a slow release of nifedipine is added starting with 10 mg dosage and the dose varies depending on an individual's response. Despite these limitations, this study aimed at assessing the birth

outcomes in pregnant women with PE and SPE receiving methyldopa and methyldopa plus nifedipine as adopted at MNH might give a better estimation of means and proportions of aforementioned parameters and the findings may be valid and generalized for the target population.

Conclusion

The use of methylidopa or methyldopa plus nifedipine in conservative treatment of PE and SPE are prefered and be adopted in LMICs. Close montoring of maternal and fetal outcomes are recommended while the addition of nifedipine to methyldopa in women with PE/SPE should be done with caution. The interventional prospective analytical study is proposed to be done with use of electronic fetal monitoring to delivery.

Ethics

Ethical clearance was sought from the MUHAS Research and Publication Committee, and it was permitted by the Executive Director and the Head of Department of Obstetrics and Gynecology MNH.

Consent for Publication

All participants have consented for publication of the result of this study (Maternal and fetal outcomes among pregnant women with preeclampsia after receiving either methyldopa or methyldopa plus nifedipine).

Competing Interests

The authors declare that they have no competing interests.

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Authors' contribution

KBZ developed the concept note and design, acquisition of data, analysis, and interpretation of data as well as initial development of the manuscript. PJW made substantial contributions to design, acquisition of data, analysis, and interpretation of data. OMM has made substantial contributions to the interpretation of data and initial draft the manuscript and led the final write up of the manuscript. All the authors have been involved in drafting the manuscript and revising it critically for important intellectual content, and; have given final approval of the version to be published.

Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
CRF	Case Report Form
CS	Caesarian Section
DBP	Diastolic Blood Pressure
GA	Gestation Age
Hb	Haemoglobin
HDP	Hypertensive Disorders Of Pregnancy
HELLP syndrome	Haemolysis, Elevated Liver Enzyme Levels, and Low Platelet Levels
LMIC	Low-Middle Income Countries
MAP	Mean Arterial Blood Pressure
MD + N	Methyldopa Plus Nifedipine
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
NICE	National Institute for Health and Care Excellent
PE	Preeclampsia
SBP	Systolic Blood Pressure
SPE	Severe Preeclampsia
SVD	Spontaneous Vaginal Delivery

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