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The effect of preeclampsia on adverse perinatal outcomes in Sidama region, southern Ethiopia: a prospective open cohort study

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Abstract

Background: In Ethiopia in 2020, more than 80% of newborn deaths are caused by preventable and treatable conditions. This study aimed to measure the effect of preeclampsia on adverse perinatal outcomes and its risk factors in the Sidama region of southern Ethiopia.

Methods: A prospective open cohort study conducted from August 8, 2019, to October 1, 2020. We enrolled a total of 730 the pregnant women with preeclampsia and normotensive women at ≥20 weeks of gestation and followed until the 37th weeks. We followed them until seven days of their delivery up to the last perinatal outcome status ascertained. A log-binomial logistic regression model used to estimate the effects of preeclampsia on adverse perinatal outcomes and identify risk factors for adverse perinatal outcomes. Relative risk with a 95% confidence interval was reported. A p-value of<0.05 was considered a significant risk factor for adverse perinatal outcomes.

Results: There were 224 adverse perinatal outcomes was observed in the preeclampsia group compared to 136 deaths in the normotensive group (P<0.001). There were 23 early neonatal deaths in the preeclampsia group compared to 6 deaths in the normotensive group(P<0.001). There were 35 perinatal deaths in the preeclampsia group compared to 16 deaths in the normotensive group (P<0.05). Women with preeclampsia had a 38%(aRR=1.38, 95% CI=1.20–1.58) higher risk for adverse perinatal outcomes compared to normotensive group.

Conclusions: In this study, a higher adverse perinatal outcome occurred among women with preeclampsia. Preeclampsia had an effect on adverse perinatal outcomes, after controlling confounders. Women with severe features of preeclampsia, women who were admitted to the hospital at<34weeks, younger and older women, women with no formal education, and primary school-educated women and women with high systolic blood pressure were the risk factors for adverse perinatal outcomes.

Keywords: Adverse Perinatal Outcome, Preeclampsia, Pregnant Women, southern Ethiopia

What is already known on this topic

- Previous studies in southern Ethiopia were limited in estimating the effect of preeclampsia on adverse perinatal outcomes because of poor ascertainment of exposures and outcomes and the studies did not compare the adverse-perinatal outcomes among women with preeclampsia and normotensive.
- In 2020 in Sidama region, 22.7% of the pregnant women did not know the causes of newborn deaths, and this study didn't measure the risk of outcomes of interest.

What this study adds

- In this study, there were 224 adverse perinatal outcomes was observed in the preeclampsia group compared to 136 deaths in the normotensive group (P<0.001).
- Women in the preeclampsia group had a 38% higher risk for adverse perinatal outcomes compared to normotensive group.

How this study might affect research, practice or policy

- This study helps to provide epidemiological evidence for the effect of preeclampsia on adverse perinatal outcomes in clinical and public health practices. Considering the effect of all types of hypertensive disorders of pregnancy on the adverse perinatal outcomes shall be considered in the future studies.

Introduction

Incidence proportion of hypertensive disorders of pregnancy (HDPs) has increased from 16.30 million in 1990 to 18.08 million from 1990 to 2019 globally (1). It varied from country to country worldwide (1). In Ethiopia, in 2018, preeclampsia occurred in 2.4–67.4% of pregnancies, and severe preeclampsia occurred in 10.7–82.5% of pregnancies (2-5). A higher proportion of preeclampsia and eclampsia (10.13%) was observed in southern Ethiopia compared to Addis Ababa (5.41%) (6).

Maternal mortality related to HDPs was 27.83 thousand in 2019, which accounted for a 30.05% decrease from 1990 (1). In low-and middle-income countries (LMICs), accounting for 10%-15% of direct maternal mortalities are associated with preeclampsia and eclampsia (7). In sub-Saharan Africa in 2022, HDPs are the second leading causes of maternal deaths, followed by obstetric hemorrhage (28.8%) and HDPs (22.1%) (8). In Ethiopia in 2020, preeclampsia was the third leading cause of maternal mortality, accounting for 11% of maternal deaths (9). In southern Ethiopia in 2019, HDPs were the third leading causes of maternal deaths (16% of HDPs), followed by obstetric hemorrhage (39%), and anemia (28%) (10).

In Ethiopia, in 2020, more than 80% of newborn deaths are caused by preventable and treatable conditions (11). According to the 2019 Ethiopia Mini Demographic and Health Survey report, the overall <5 child mortality rate was 55 deaths per 1,000 live births, and neonatal mortality was 30 deaths per 1,000 live births (12). In 2021, the adverse perinatal outcomes were higher among women with preeclampsia compared to normotensive women (64.1% versus 32.8%) (13).

Common risk factors for adverse perinatal outcomes were identified as uneven distribution of health resources, suboptimal quality of care, availability of anesthesia, magnesium sulphate, and intensive care unit, low child healthcare-seeking behavior, shortage of kangaroo mother care and essential health commodities, gestational age at delivery, lack of antenatal care, women who did not attend school, low birth weight, nulliparity, preterm birth, asphyxia, women who didn't decide power on health care, didn't attend postnatal care, and breastfed immediately; neonatal sepsis, neonatal tetanus, and neonatal pneumonia (11, 12, 14-16).

A significant improvement has been made by the government of Ethiopia in reducing maternal mortality (17). However, the reduction of mortality is still a challenge. Ethiopia is replacing the previous four-visit focused antenatal care (ANC) model with the new ANC eight-contact model (18). Additional contact may be required to detect the complication (18). Poor infrastructure, a scarcity of supplies and skilled labor, a weak referral system, poor quality of care, and a lack of timely obstetric care all contributed to a higher proportion of adverse perinatal mortality in Ethiopia. (19). Government of Ethiopia has taken steps to strengthen engagement with key local and international sectors and stakeholders to address determinants of health (18).

Studies in southern Ethiopia were limited in estimating the effect of preeclampsia on adverse perinatal outcomes because of poor ascertainment of exposures and outcomes, using purposive sampling techniques, and of 22.7% of the pregnant women did not know the causes of newborn deaths, poor in evidence generation for policymakers and clinical practices, did not include control groups, and didn't measure the risk of outcomes of interest (20-23). Another study in Ethiopia found that they did not include a non-exposed group that would have been important to controlling confounders like the quality of perinatal care associated morbidity and mortality (24). Thus, this study aimed to measure the effect of preeclampsia on adverse perinatal outcomes and its risk factors in the Sidama region of southern Ethiopia. The findings from this study could be used for early detection of preeclampsia during ANC visits and to improve the care and treatment for women who experience adverse perinatal outcomes associated with preeclampsia.

Methods

Study design and setting

A prospective open cohort study conducted from August 8, 2019, to October 1, 2020 in the Sidama region. In 2020, the population of the region was approximately 4 million. There were thirteen public hospitals, 138 health centers, and 540 health posts that provided maternal, newborn, and child health services. In 2020, approximately 132,031 pregnant women attended ≥4 antenatal care visits (ANC) and 127,585 women gave birth by skilled birth attendants. We enrolled participants from seven out of 13 hospitals in the region, including Adare, Hawassa, Yirgalem, Hula, Bona, Chuko, and Daye hospitals.

Patient and public involvement

The participants of this study were women with preeclampsia and normotensive women who were enrolled at ≥20 weeks of gestation until the 37th weeks. We followed them until seven days after delivery and waited for the last enrolled woman's perinatal outcome status was ascertained. During the follow up, 194 women with preeclampsia and normotensive women were admitted to the hospital at <34 weeks of gestation, and 536 women with preeclampsia and normotensive were admitted to the hospital at 34-37weeks of gestation. During the follow up, eight normotensive women developed preeclampsia. We included them into exposed groups. Pregnant women with hypertension plus proteinuria, women with mild hypertension and evidence of organ dysfunction, severe hypertensive patients without proteinuria, and evidence of organ dysfunction included in the study.

Operational definitions

Birth asphyxia was defined as a baby with trouble in breathing (gasping or breathing very irregularly or no breathing). Small for gestational age of pregnancy was defined as a birth weight of newborn below the tenth percentile of weight distribution at the specified gestational age of a pregnancy. Stillbirth was defined as a baby born with no signs of life at or after 28 weeks gestation. Preterm delivery was defined as the delivery of the baby before 37 weeks gestation. Low birth weight was defined as a baby with a birth weight less than 2.5kg. Low Apgar score was defined as a newborn baby with an Apgar score of less than seven at 1 and 5 minutes.

Perinatal death was defined as a stillbirth or an early neonatal death. Early neonatal death was defined as the death of a live newborn in the first seven days of life. Intrauterine growth restriction of newborns was defined as birth weight and/or birth length below the 10^{th} percentile for their gestational age and whose abdominal circumference was below the 2.5^{th} percentile with pathologic restriction of fetal growth.

Sample size and sampling

The sample size was calculated using EPI INFO version 7. We considered the following assumptions for sample size calculations such as early neonatal death (15), the ratio of exposed to unexposed group (1 to 1), the proportion of early neonatal death among women with preeclampsia was 5%, and the proportion of early neonatal death among normotensive women was 1%. The

sample size was estimated to be 733 (366 women with preeclampsia and 367 with normotensive), accounting for a design effect of two and 10% loss to follow-up. We also assumed a two-sided confidence level of 95%, with a power of 80%.

Two-stage cluster sampling techniques were used to recruit study participants. In the first stage, seven of the thirteen hospitals were selected using the simple random sampling technique. In the second stage, perinatal condition was selected from women with preeclampsia and normotensive women using simple random sampling technique.

Exposure ascertainments

The main exposure variable for this study was preeclampsia (preeclampsia with or without severity features). Preeclampsia with severe features was defined as one or more of the following conditions: blood pressure (BP) of ≥160mmHg systolic or ≥110mmHg diastolic, ≥3+protein on two urine samples taken four hours or more apart or 5gm of protein in a 24hr urine sample (25). Preeclampsia without severe features was defined as raised BP>140/90 mmHg plus 24-hour urine protein >300mg/24 hour or urine dipstick >+1 after 20 weeks of gestation in previously normotensive women (25). Normotensive women were defined as pregnant women having a (BP)<140/90mmHg with ≥20 weeks of gestations or who did not develop preeclampsia and proteinuria (25). Gestational age calculated based on the woman's recall of her last menstrual period. However, an ultrasound scan was used for those women who could not remember their last menstrual period.

Outcome variable

Adverse-perinatal outcomes were defined as newborn with the occurrence of at least one of the following outcomes: birth asphyxia, low birth weight, small for gestational age, preterm delivery, admission to neonatal intensive care unit, and perinatal death.

Data collection

We validated the tool before data collection (26). We followed the recommended tool validation steps and procedures. Two bilingual (in Sidamic and English) forward translators who were capable of translating the original (English) version into the Sidamic version were selected. Translations into the Sidamic language more accurately reflected the tones of the language. The

translations were compared and discrepancies were noted during the translation process. The poorer wording choices were identified and resolved in a discussion between the translators.

The back translations were performed by two translators in the source language (English). This was a validity checking process to ensure that the translated version reflected the same item content as the original versions. Face and content validation of the tool was done by the panel of experts (midwife experts, epidemiologists, and gynecologists). The panel of experts independently assessed the tool for readability, understanding, clarity, and ease of use. The internal consistency for each dimension was checked using Cronbach's alpha (Cronbach's alpha=0.98) (26).

All participants responded to all items in the local Sidamic version and marked them correctly. No missing items were found. Data collectors reported no difficulties in asking the questions, and no participants reported having any problems understanding the items. The tool was tested for the second time two weeks later after the first measurement. The two-week test-retest reliability result was shown to have an excellent correlation between reliable strategy to assess these point scores (ICC for agreement 0.78; $p< 0.001$) (26).

Trained midwives conducted face-to-face interviews at antenatal care clinics using a locally translated and validated tool. A checklist was used to collect information from the maternal and neonatal records of women with preeclampsia and normotensive women in each hospital. The socio-demographic variables such as maternal age, religion, residence, parity, marital status, education, and maternal and husband's occupation collected.

We collected clinical and laboratory variables prospectively in each hospital through medical records and using a check list: blood pressure, urine protein, gestational age, acute kidney injury, platelet count, creatinine, serum glutamic oxaloacetic transaminase, number of maternal intensive care unit admissions (ICUs), convulsion, parity, gravidity, sonographic scan). Pregnant women were selected by health care providers: general medical practitioners, emergency surgical officers, or obstetricians/gynecologists during antenatal care follow-up. Three maternity and reproductive health professionals supervised the data collection procedures.

Outcome ascertainment

Adverse perinatal outcomes were ascertained by obstetricians/gynecologists and trained midwives. Client medical registration was also used to retrieve adverse perinatal outcome status. The

perinatal condition was determined at the follow-up appointment for those who were discharged, and a phone call was used for those who did not show up for this follow-up.

Missing data

Pregnant women's loss means dropout from the follow-up for those women who had complications during the follow up period. Those with adverse perinatal outcomes had their status determined at a later time and were contacted by phone. The loss to follow up was computed to minimize its effects on the conclusion, including as missing completely at random, missing at random, and missing not at random.

Statistical analysis

Data were cleaned, coded and analyzed using STATA 14. Identifying outliers and missing values was performed. Data consistency was checked using the original questionnaire for the responses using participants' code numbers. Frequencies and percentages were computed for categorical variables. Mean and standard deviations were computed for continuous variables. An incidence proportion of adverse perinatal outcomes was conducted in relation to women who had preeclampsia and normotensive women. Cross tabulation was also performed to test the relation of variables with the outcome variable. A chi-squared test was used to compare categorical variables between women with preeclampsia and normotensive women. Gestational age was calculated either from last normal menstrual period or from ultrasound report.

Principal component analysis was computed and used for wealth index computation and was ranked in three groups as low, middle, and high. Different items for urban and rural areas were computed separately. The suitability of data was computed by Bartlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) measure of sample adequacy. The KMO > 0.6 was used to confirm the sample adequacy for factor analysis (8).

A multivariable log-binomial logistic regression model was performed to identify the risk factors for adverse perinatal outcomes. Variables with a p-value<0.25 were included in the multivariable log-binomial logistic regression model (9). Multivariable log-binomial logistic regression analysis was performed by estimating the risk ratios with a 95% confidence interval. Attributable fractions (AF) were calculated from the adjusted risk ratio to evaluate to what extent the occurrence of

adverse perinatal outcomes could have been reduced if a particular risk factor was prevented. A p-value of<0.05 was considered a significant risk factor for adverse perinatal outcomes.

We checked the multicollinearity among predictors using variance inflation factor at a cutoff point of ten. The goodness of the fit was tested using the Hosmer-Lemeshow test. The one that was greater than the significance level (p-value >0.05) was accepted.

Ethical considerations

This study was reviewed and ethically approved by the Institutional Review Board of the University of Gondar R.No: (O/V/P/RCS/044/2019 in March 2019). All participants signed an informed consent document before study participation began. Pregnant women having abnormal clinical and laboratory results were referred for treatment. Women with severe hypertension were provided with antihypertensive drugs; those with convulsions were given magnesium sulphate.

Results

Socio-demographic and economic characteristics of study participants

Of the 733 women with preeclampsia and normotensive women, we enrolled 730 women with preeclampsia and normotensive women. Three (0.41%) of the participants were lost to follow-up and two of them were from the normotensive group. During the follow up, eight normotensive women developed preeclampsia. We included them into exposed groups (Figure 1).

The mean gestational age at the diagnosis of women with preeclampsia was 32.85 (SD± 3.25) weeks and that of normotensive women was 33.90 (SD± 2.75) weeks. The mean duration of follow-up of women with preeclampsia was 6.51 (SD± 3.15) weeks and that of normotensive women was 5.68 (SD± 2.97) weeks (Figure 1).

Mean age of the preeclamptic women was 25.42 (SD±4.76) years old, and 24.6 (SD±4.48) years old for the normotensive group. More than half of the women with preeclampsia (56.7%, 206/363, P < 0.001) were 16–24 years old, compared to normotensive group (35.9%, 132/367, P< 0.001). A higher proportion of women with preeclampsia was observed (81%, 294/363), P<0.001) among women who resided in rural areas compared to urban residents (19%, 69/363), P<0.001) (Table 1).

Table 1: Socio-demographic and economic characteristics of women with preeclampsia and normotensive women in Sidama region, southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Women with preeclampsia (n=363)	Normotensive women (n=367)	Total (n=730)	P-value
Age group (in year)	mean 25.42(±4.76)	mean 24.6 (±4.48)		
16-24	206(56.7)	132(35.9)	338(46.3)	
25-34	147(40.5)	213(58)	360(49.3)	P<0.001
≥35	10(2.8)	22(6)	32(6)	
Maternal education				
No formal education	33(9.1)	16(4.3)	49(6.7)	
Primary education	164(45.2)	145(39.5)	309(42.3)	P<0.05
Secondary education	98(27)	110(30)	208(28.5)	
College/University	68(18.7)	96(26.2)	164(22.5)	
Husband education				
No formal education	15(4.1)	7(1.9)	22(3)	
Primary education	122(33.6)	87(23.7)	209(28.5)	P<0.05
Secondary education	99(27.3)	117(31.9)	216(29.6)	
College/University	127(35)	156(42.5)	283(38.8)	
Maternal occupation				
House wife	191(52.6)	163(44.4)	354(48.5)	
Merchant	70(19.3)	76(20.7)	146(20)	
Employed	64(17.6)	88(24)	152(20.8)	P>0.05
Student	23(6.3)	21(5.7)	44(6)	
Farmer	10(2.8)	10(2.7)	20(2.7)	
Daily laborer	5(1.4)	9(2.5)	14(1.9)	
Husband occupation				
Employed	116(32)	149(40.6)	265(36.3)	
Merchant	126(34.7)	136(37.1)	262(35.9)	
Farmer	75(20.7)	45(12.3)	120(16.4)	P<0.05
Daily laborer	31(8.5)	23(6.3)	54(7.4)	
Student	7(1.9)	10(2.7)	17(2.3)	
Unemployed	8(2.2)	4(1.1)	12(1.6)	
Place of residence				
Rural	294(81)	331(90.4)	104(14.3)	P<0.001
Urban	69(19)	35(9.6)	625(85.7)	
Wealth Index				
Low	157(43.3)	95(26)	252(34.6)	
Middle	105(28.9)	139(28)	244(33.5)	P<0.001
Rich	101(27.8)	132(36.1)	233(32)	

‡‡Others= widowed or single

Obstetric characteristics of women with preeclampsia and normotensive

Compared to the normotensive group (35.7%, 131/367, P < 0.001), a higher proportion of women with preeclampsia (40.8%, 148/363, P<0.001) was observed in the Yirgalem hospital. A higher proportion of very preterm births was reported in the preeclampsia group (6.6%, 24/363, P<0.001) compared to normotensive group (0.3%, 1/367, P< 0.05). A higher proportion of women with preeclampsia (28.4%, 103/363), P<0.05) was reported among women who were admitted at < 34 weeks compared to normotensive group (24.5%, 91/367, P<0.05) (Table 2).

Table 2: Obstetrics factors for women with preeclampsia and normotensive women in Sidama region, southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Women with preeclampsia (n=363)	Normotensive women(n=367)	Total (n=730)	P-value
Fetal sex				
Male	202(55.6)	195(53.1)	397(54.4)	P>0.05
Female	161(44.4)	172(46.9)	333(45.6)	
Number of neonates delivered				
Singleton	337(92.8)	350(95.4)	687(95.4)	
Twin	26(7.2)	17(4.6)	43(5.9)	P>0.05
Gravida				
1	46(12.7)	77(21)	123(16.8)	
2-3	253(69.7)	208(56.7)	461(63.2)	P>0.05
≥4	64(17.6)	82(22.3)	146(20)	
Parity				
Nullipara	12(3.3)	5(1.4)	17(2.3)	P>0.05
1	37(10.2)	94(25.6)	131(17.9)	
2-3	264(72.4)	222(60.5)	486(66.6)	
≥4	50(13.8)	46(12.5)	96(13.2)	
Interpregnancy Interval (IPI)				
<24 months (short (IPI)	8(2.2)	4(1.1)	12(1.6)	
24-59 months (optimal IPI)	180(49.6)	263(71.7)	443(60.7)	P<0.001
60+ months (long IPI)	115(31.7)	35(9.5)	150(20.5)	
Not applicable (prim)	60(16.5)	65(17.7)	125(17.1)	
Gestational age at admission				
<34 weeks	103(28.4)	91(24.5)	194(26.6)	P<0.05
34-37 weeks	260(71.6)	276(75.5)	536(73.4)	
Maternal ICU admission				
Yes	5(1.4)	1(0.3)	6(0.8)	P>0.05
No	358(98.6)	366(99.7)	724(99.2)	
GA at delivery (week)				

Extremely preterm (<28)	10(2.8)	5(1.4)	15(2.1)	
Very preterm (28-32)	24(6.6)	1(0.3)	25(3.4)	P<0.001
Moderate to late preterm (32-37)	123(33.9)	67(18.3)	190(26)	
Term+(≥37)	206(56.7)	294(80)	500(68.5)	
Hospitals				
Adare general hospital	60(16.5)	109(29.7)	169(23.2)	
Hawassa referral hospital	53(14.6)	47(12.8)	100(13.7)	
Yirgalem general hospital	148(40.8)	131(35.7)	279(38.2)	P<0.001
Hula primary hospital	7(1.9)	7(1.4)	12(1.6)	
Bona general hospital	51(14)	29(7.9)	80(11)	
Chuko primary hospital	11(3)	6(1.6)	17(2.3)	
Daye primary hospital	33(9.1)	40(10.9)	73(10)	

||GA=Gestational age, ¶NICU=Neonatal Intensive Care Unit, ††g=gram, †††IPI=Interpregnancy Interval

Incidence of adverse perinatal outcomes among women with preeclampsia

There were 224 adverse perinatal outcomes was observed in the preeclampsia group compared to 136 deaths in the normotensive group (P<0.001). There were 23 early neonatal deaths was reported in the preeclampsia group compared to 6 deaths in the normotensive group (P<0.001). Although there were 96 preterm births was observed in the preeclampsia group compared to 17 preterm births in the normotensive group (P< 0.001). There were 35 perinatal deaths was reported in the preeclampsia group compared to 16 deaths in the normotensive group (P<0.05) (Table 3).

Table 3: Neonatal outcomes among women with preeclampsia and normotensive women in Sidama region southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Women with preeclampsia (n=363)	Normotensive women(n=367)	Total (n=730)	P-value
Birth weight of neonate (††g)				
<15000	33(9.1)	6(1.6)	39(5.3)	
15000-2499	103(28.4)	31(8.4)	134(18.4)	P<0.001
2500-3999	211(58.1)	302(82.3)	513(70.3)	
≥4000	16(4.4)	28(7.6)	44(6)	
Apgar score <7 at 1 minutes				
Yes	64(17.6)	52(14.2)	116(15.9)	
No	299(82.4)	315(85.8)	614(84.1)	P<0.05
Apgar score <7 at 5 minutes				
Yes	62(17.1)	54(14.7)	116(15.9)	P>0.05

No	301(82.9)	313(85.3)	614(84.1)	
Intrauterine growth restriction				
Yes	22(6.1)	4(1.1)	26(3.6)	P<0.001
No	341(93.9)	363(98.9)	704(96.4)	
Still birth				
Yes	21(5.8)	11(3)	32(4.4)	P<0.05
No	342(94.2)	356(97)	698(95.6)	
Early neonatal death				
Yes	23(6.3)	6(1.6)	29(4)	P<0.001
No	340(93.7)	361(98.4)	701(96)	
Preterm birth				
Yes	96(26.4)	17(4.6)	113(15.5)	P<0.001
No	267(73.6)	350(95.4)	617(84.5)	
Perinatal death				
Yes	35(9.6)	16(3.8)	49(6.7)	P<0.05
No	328(90.4)	353(96.2)	681(93.3)	
Low birth weight				
Yes	98(27)	73(19.9)	171(23.4)	P<0.05
No	265(73)	294(80.1)	559(76.6)	
Small for gestational age				
Yes	66(18.2)	30(8.2)	96(13.2)	P<0.001
No	291(46.4)	336(53.6)	624(68.8)	
Birth asphyxia				
Yes	39(10.7)	15(4.1)	54(7.4)	P<0.05
No	324(89.3)	352(95.9)	676(92.6)	
Admission to ¶NICU				
Yes	88(24.2)	39(10.6)	127(17.4)	P<0.001
No	275(75.8)	328(89.4)	603(82.6)	
Adverse perinatal outcomes				
Yes	224(61.7)	136(37.1)	360(49.3)	P<0.001
No	139(38.3)	231(62.9)	370(50.7)	

Effect of preeclampsia with or without a severity feature on adverse perinatal outcomes and other risk factors

In the bivariable log-binomial logistic regression model, fourteen risk factors for adverse perinatal outcomes were identified as: maternal age, maternal and husband education, maternal and husband occupation, parity, gravidity, wealth index, women with preeclampsia, mode of delivery, women with severe features of preeclampsia, maternal ICU admission, systolic and diastolic blood pressure.

After controlling for confounders, women in the preeclampsia group had a 38% (aRR: 1.38, 95%CI: 1.20–1.58) higher risk for adverse perinatal outcomes compared to normotensive group. Women with severe features of preeclampsia had a 45% (aRR: 1.45, 95% CI: 1.37–2.76) higher risk for adverse perinatal outcomes compared to women without severe features of preeclampsia. Women who admitted to the hospital at <34 weeks had a 14% (aRR: 1.14, 95% CI: 1.02–1.27) higher risk for adverse perinatal outcomes compared to women who were admitted between 34–37 weeks (Table 4).

Table 4: A multivariable log-binomial logistic regression model for risk factors for adverse perinatal outcomes among women with preeclampsia in Sidama region southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Adverse perinatal outcomes		Unadjusted RR* (95%Cl)	Adjusted RR (95%Cl†)	AF (95%CI)
	Yes (%)	No (%)			
Parity					
Nullipara	11(64.7)	6(35.3)	0.94[0.64–1.78]	0.86[0.65– 1.78]	–
1	139(43.7)	179(56.3)	0.68***[0.57–0.80]	0.86[0.60–1.22]	–
2-3	148(51.7)	138(48.3)	0.83*[0.70–0.97]	0.93[0.72–1.19]	–
≥4	62(56.9)	47(43.1)	1	1	1
Maternal age (year)					
16-24	223(66)	115(34)	1.71***[1.48–1.23]	1.57***[1.36–1.82]	47% [42–53%]
25-34	123(34.2)	237(65.8)	1	1	1
≥35	14(43.8)	18(56.2)	1.38[0.99–1.92]	1.49*[1.09–2.03]	21% [9–33%]
Maternal education					
No formal education	32(63.3)	17(34.7)	1.52**[1.19–1.93]	1.40**[1.14– 1.72]	30% [17–54%]
Primary education	175(56.6)	134(43.4)	1.30**[1.08–1.57]	1.23*[1.05– 1.46]	21% [10–37%]
Secondary education	84(40.4)	124(59.6)	0.99[0.79–1.23]	0.56[0.44–1.25]	–
College/university	69(42.1)	95(57.9)	1	1	1
Husband education					
No formal education	17(77.3)	5(22.7)	1	1	1
Primary education	123(58.9)	86(41.1)	0.76*[0.59– 0.98]	0.92(0.76–1.97)	–
Secondary education	105(48.6)	111(51.4)	0.62**[0.48– 0.81]	0.83(0.67–1.04)	–
College/university	115(40.6)	168(59.4)	0.52***[0.40–0.68]	0.74[0.57–2.97]	–
Wealth index					
Low	176(69.6)	77(30.4)	1.77***[1.48–2.12]	1.72[0.44–2.06]	–
Middle	98(40.2)	146(59.8)	1.03[0.83–1.29]	1.02[0.82–1.28]	–
Rich	86(36.9)	147(63.1)	1	1	1
Gravidae					
1	127(42.6)	171(57.4)	0.81[0.91– 1.96]	0.84 [0.72–1.97]	–
2-3	154(52.4)	140(47.6)	0.96[0.80–1.15]	0.95[0.81–1.11]	–

≥4	79(57.2)	59(42.8)	1	1	1
Mode of delivery					
‡SVD	205(51.5)	193(48.5)	0.89[0.77–1.04]	0.12[0.78–1.16]	–
C/section	143(46.3)	166(53.7)	1.01[0.67–1.561]	1.32[0.85–2.34]	–
Vacuum assisted	12(52.2)	11(47.8)			
Gestational age at admission (week)					
<34	113(58.2)	81(41.8)	1.11[0.97–1.28]	1.14*[1.02–1.27]	20% [17–33%]
34-47	247(46.1)	289(53.9)	1	1	1
Maternal ICU admission					
Yes	4(80)	1(20)	1.67**[1.16– 2.41]	1.22[0.75– 3.19]	–
No	356(49.1)	369(50.9)	1	1	1
Women with preeclampsia					
Yes	224(61.7)	139(38.3)	1.57***[1.37–1.81]	1.38***[1.20–1.58]	40% [35–44%]
No	136(37.1)	231(62.9)	1	1	1
Women with severe features of preeclampsia					
Yes	105(78.9)	28(21.1)	1.58***[1.25–1.85]	1.45***[1.37–2.76]	44% [37–48%]
No	255(42.7)	342(57.3)	1	1	1
Eclampsia					
Yes	32(82.1)	7(17.9)	1.61***[1.38–1.92]	1.34[0.41–1.83]	–
No	328(47.5)	363(52.5)	1	1	1
Systolic blood pressure (mmHg)					
<140	136(37.1)	231(62.9)	1	1	1
140-159	162(62.3)	98(37.7)	1.56***[1.35–1.81]	1.38***[1.19–1.59]	38% [26–50%]
≥160	62(60.2)	41(39.8)	1.59***[1.33–1.91]	1.34**[1.13– 1.58]	36% [19–53%]
Diastolic blood pressure(mmHg)					
<90	136(37.1)	231(62.9)	1	1	1
90-109	180(62.3)	109(37.7)	1.68***[1.43–1.97]	1.12[0.21–2.03]	–
≥110	44(59.5)	30(40.5)	1.60***[1.27–2.02]	1.43[0.96–2.43]	–
Magnesium sulfate treatment					
Yes	74(43.8)	95(56.2)	0.65***[0.57–0.74]	0.56[0.36–1.23]	–
No	286(51)	275(49)	1	1	1
Antihypertensive drug treatment					
Yes	124(33.5)	178(49.4)	0.64***[0.56–0.73]	0.84[0.40– 1.75]	–
No	246(66.5)	182(50.6)	1	1	1
Dexamethasone treatment					
Yes	56(48.7)	59(51.3)	0.54[0.34–1.81]	0.45[0.23–1.98]	–
No	304(49.4)	311(50.6)	1	1	1

*RR=Relative Risk, † CI = Confidence Interval, ‡SVD= Spontaneous Vaginal Delivery, §C/section-Cesarean Section, *p-value <0.05, **p-value <0.001, ***p-value <0.0001

Discussion

In this study, a higher adverse perinatal outcome was observed in the preeclampsia group compared to normotensive group in the Sidama region. Preeclampsia had an effect on adverse

perinatal outcomes after controlling for confounders. Perinatal death, stillbirth, small for gestational age, preterm birth, birth asphyxia, and low birth weight were higher in the preeclampsia group compared to normotensive group. Risk factors for adverse perinatal outcomes were identified as women with severe features of preeclampsia, and women who were admitted to the hospital at<34weeks, younger women.

A higher adverse perinatal outcome was observed in the preeclampsia group compared to normotensive women. This finding was consistent with another studies (27, 28), but slightly lower than another study in Ethiopia (66.4% versus 22.2%) (15). This finding was also higher than a study in Uganda that found, 36.9%, 20.3%, and 1.1% of neonates were admitted to NICU, stillbirths, and neonatal deaths (29). This discrepancy might be since in Ethiopia in 2019, the universal health coverage index was low at 39% (12) leading to variations in the implementation of policies, strategies, and services delivery for maternal health among regions.

A higher perinatal death was reported in the preeclampsia group compared to normotensive group. This finding was lower than other study in southern Ethiopia in 2015 that also found that (49.4%) (2). Perinatal deaths can be reduced in a country if better access to quality maternal health care services is ensured. Thus, preventing and managing preeclampsia should become a priority to accelerate the progress of newborn survival.

A higher stillbirth was observed in the preeclampsia group compared to normotensive group. This finding was higher than other study in Tigray region in 2020 (10% versus 1.7%) (15) that found that women with preeclampsia was associated with placental insufficiency and placenta fails to provide adequate oxygen and nutrients to the growing fetus. This implies that maternity care provider should aware to detect and treat fetal complications before advancing to a severe stage. It also gives room for the pregnant woman to share her symptoms, feelings and worries with her health care provider before worsening.

A higher small for gestational age newborn was reported in the preeclampsia group compared to normotensive group. This finding was higher than other studies in Tigray regional state Ethiopia in 2020 (36.7% versus 10.7%) (15) and in Ghana in 2017 (6.3%) (14). Women with preeclampsia showed that blood flows are reduced and decreased placental exchange of important nutrients such as amino acids have been demonstrated in intrauterine growth restriction. Those who have been

born SGA had smaller diameter of coronary arteries compared to those born from normal gestational age. Thus, a higher risk for cardiovascular events in the future life (14).

A higher preterm birth was observed among women with preeclampsia compared with normotensive women. This finding was similar with another study in Ethiopia in 2020 (15) that also found that women with preeclampsia were at an increased risk of preterm births as shown as a significantly lower gestational age compared to term pregnancy. Thus, it needs improving the quality of maternal and child health care services to reduce adverse perinatal outcomes associated with preeclampsia. In addition, the Federal Ministry of Health and concerned bodies should work towards the prevention of preeclampsia and its adverse outcomes (12).

A higher incidence of newborn with birth asphyxia was reported among women with preeclampsia compared to normotensive women. This finding was higher than another study in in Tigray region in 2020 (46.5% versus 11.3%) (15) found also that women with preeclampsia is increased preterm births that might be vulnerable to the immaturity of lung that causes birth asphyxia and respiratory failure.

A higher incidence of newborn with low birth weight was observed among women with preeclampsia compared to normotensive. This finding was higher than another study in Ethiopia in 2020 (37.7% versus 6.1%) (15) this indicated that low birth weight could be the result of fetal malnutrition, prematurity, poor nutritional reserves of the mother, and inadequate flow of the blood in the uterus. Thus, reducing the risk of low birth weight by increasing attention to keeping the newborn warm, skin-to-skin care and assistance with early initiation of breast feeding.

Women with severe features of preeclampsia had higher risk for adverse-perinatal outcomes compared to women without severe features of preeclampsia. This finding was agreed with another study (30) that also found that severe preeclampsia was associated with neonatal complications (45.9%) (7). The chance of perinatal complication observed might be explained by the progression of preeclampsia to severe features and women who developed preeclampsia before 34 weeks.

Women who were admitted to the hospital at <34 weeks had a higher risk for adverse perinatal outcomes compared to women who admitted between 34–37 weeks. This finding was supported by another study (6) that also found that early onset of preeclampsia was associated with increased risk for adverse perinatal outcomes compared to late-onset of preeclampsia after 34 weeks (6). Early-

onset of preeclampsia is associated to have a more severe placental dysfunction, infant's growth restriction compared to late-onset of preeclampsia (6).

Limitations of the study

One limitation could be recall bias linked to gestational age which was calculated based on the women's recall of her last menstrual period. However, ultrasound scan used for those women who could not remember their last menstrual period.

Conclusion

A higher adverse perinatal outcome was observed among women with preeclampsia compared with normotensive women in Sidama region. In this study, preeclampsia had an effect on adverse maternal outcomes after controlling for confounders. These effects could be detected and controlled early in pregnancy. Similarly, women with severe features of preeclampsia, women who were admitted to the hospital at<34weeks, younger and older women, women with no formal education, primary school-educated women, and women with high systolic blood pressure were the risk factors for adverse perinatal outcomes.

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Competing interests: The authors declare that we have no competing interests

Author's contributions: This study was carried out in collaboration among all authors. BJ, MA and KA contributed to conceptualizing, and designing the study, contributed to the data curation, performed data analysis, and wrote the first draft. Although; BJ, MA, TA, and KA managed the investigation, literature searches, methodology review, writing, and contributed to data collection; BJ, MA, TA, and KA contributed to the manuscript review, resource, preparation, and editing. All the authors have read and agreed to the final manuscript.

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Availability of data and materials: The data that support the findings of this study is available from the corresponding author upon reasonable request in the form of STATA Version 14.

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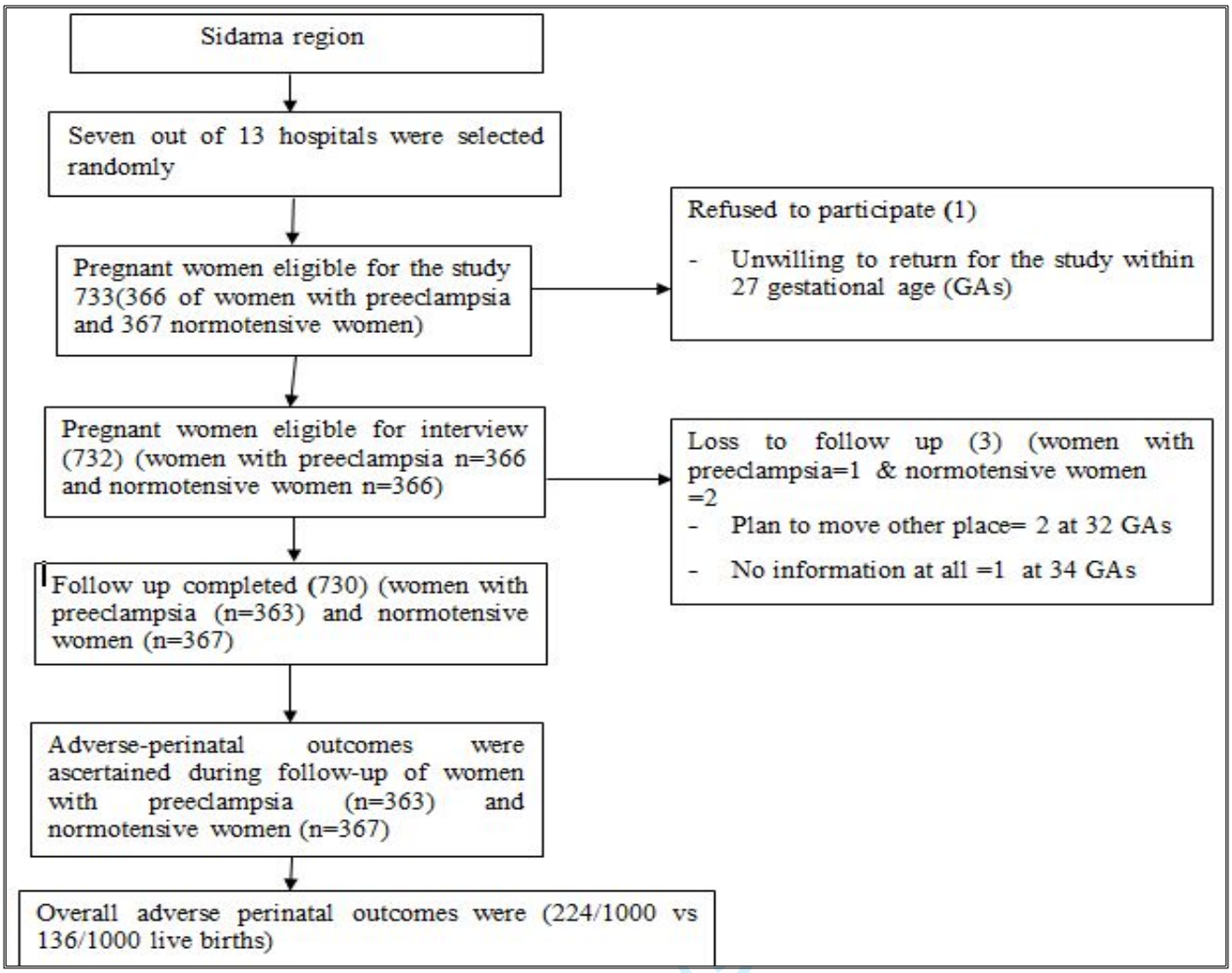
List of figures



Cover Letter to BMJ Pediatrics open

To: Professor Imti Choonara, Editor in Chief, BMJ Paediatrics Open

Dear Professor Imti Choonara,

We would like to thank you for re-considering our article as a new submission entitled "**The effect of preeclampsia on adverse perinatal outcomes in Sidama region, southern Ethiopia: a prospective open cohort study"** for publication in your journal**.** The following points were corrected in the revised manuscript: We also appreciate the editor's feedback and further suggestions to improve our manuscript.

We hope that the revision and the changes we've made in the revised manuscript will satisfy the editor's concerns for re-consideration of our manuscript as a new submission to BMJ Paediatrics Open. We look forward to getting the good news regarding the new submission.

Best regards!

Birhanu Jikamo

Corresponding author

Paper's originality

Thank you, Dear Professor Imti Choonara, for recommending us to briefly explain the findings of this study are similar to other studies from Ethiopia.

The following points were to show the originality of this paper

Our study differs from other study from southern Ethiopia

Studies in southern Ethiopia were limited in estimating the effect of preeclampsia on adverse perinatal outcomes because of poor ascertainment of exposures and outcomes and, 22.7% of the pregnant women did not know the causes of newborn deaths, though this study didn't measure the risk of outcomes of interest [1].

A single-site study conducted in southern Ethiopia found that more than one third of all stillbirths and perinatal deaths were due to obstructed labor with or without uterine rupture. This may mask the real association of other potential factors for perinatal death. Although a majority of babies die during labor in obstructed labor and uterine rupture, it was not possible to ascertain whether some of the babies died even before the onset of labor [2]. There may also be bias due to differences in the selection of women studied. This suggests it was a case-control study and therefore limited the assessment of confounders [1, 2, 3].

Furthermore, the other cross-sectional study conducted in southern Ethiopia, which was poor in evidence generation for policymakers and clinical practices, did not show cause and effect relationships [1]. In addition, other studies have used purposive sampling techniques to recruit study participants. This suggests that they did not represent the Sidama region's populations [3]. Previous research using a retrospective design and a single-center site study did not address our exposure interests, and obstruction of labor is linked to perinatal deaths [2]. The retrospective cross-sectional study conducted in Hawassa University Comprehensive Specialized and Yirgalem hospitals in southern Ethiopia, which may result in overstated numbers, could be due to record review and lack of relevant variables for study [4, 7].

Our study differs from other studies from Ethiopia

A prospective non-comparative observational study was conducted in a referral hospital in urban Ethiopia to determine the maternal and perinatal outcomes of pregnant women with preeclampsia without severity features. This indicated that they did not include a non-exposed (without preeclampsia) group that would have been important to controlling confounders like the quality of perinatal care and preterm birth associated morbidity and mortality [5]. Furthermore, this study aimed to consider only women without severe features in a hospital in urban Ethiopia and did not include women with severe features of preeclampsia [5]. In addition, they only considered urban residents and did not include rural pregnant women [5].

However, our study considered a non-exposed group (normotensive women) that would have been important for controlling confounders like the quality of perinatal care and perinatal outcomes associated with morbidity and mortality, including urban and rural pregnant women in the study.

Another prospective cohort study was conducted in the Tigray region, Ethiopia. This study differs from ours in that woman did not find an association between the time at which women developed preeclampsia and the occurrence of adverse perinatal outcomes, and the difference in cultural context between the two regions is that the way of life is different [6]. The exposure ascertainment is different because this study included women diagnosed with preeclampsia, eclampsia, and gestational hypertension between 28 and 35 weeks of gestation. In addition, they did not consider the effect of the early (28 weeks) and late (> 35 weeks) onset of pregnancy-induced hypertension on the adverse fetal outcomes [6]. However, our study considered and aimed to measure the effect of preeclampsia on adverse perinatal outcomes.

Another study, as the design was retrospective in nature, did not include control groups, possibly limiting the extent to which cause and effect can be attributed to the study findings. After adjustment for some of the potential factors considered, marked changes were observed between the unadjusted and adjusted odds ratios, suggesting that other confounding factors might be operating. However, the sample size available for this study was insufficient to support a more detailed statistical evaluation of this issue [8]. The other is a retrospective cross-sectional conducted in Addis Ababa, Ethiopia and facility-based from the record review, which may result in overstated numbers because it did not report relevant baseline demo-graphics defining the studied population [9].

Methodological Considerations in our study

We considered preeclampsia with or without severity features as the main exposure, which is recommended by the recent International Society for the Study of Hypertension in Pregnancy guideline [11]. although we ascertained exposure status based on this guideline [11]. Outcomes were ascertained by obstetricians/gynecologists and trained midwives. Client medical registration was also used to retrieve adverse perinatal outcome status. The perinatal condition was also determined at the follow-up appointment for those who were discharged, and a phone call was used for those who did not show up for this follow-up. The loss to follow up was computed to minimize its effects on the conclusion, including as missing completely at random, missing at random, and missing not at random. During the follow-up, we considered the early and late onset of preeclampsia and its effect on perinatal conditions. During the follow-up, 194 women with

preeclampsia and normotensive women were admitted to the hospital at 34 weeks of gestation, and 536 women with preeclampsia and normotensive were admitted to the hospital at 34–37 weeks of gestation. During the follow-up, eight normotensive women developed preeclampsia. We included them in exposed groups.

We validated the tool before data collection. We used proper exposure and outcome ascertainments (10). We followed the recommended tool validation steps and procedures. Two bilingual (in Sidamic and English) forward translators who were capable of translating the original (English) version into the Sidamic version were selected. Translations into the Sidamic language more accurately reflected the tones of the language. The translations were compared and discrepancies were noted during the translation process. The poorer wording choices were identified and resolved in a discussion between the translators.

The back translations were performed by two translators in the source language (English). This was a validity checking process to ensure that the translated version reflected the same item content as the original versions. Face and content validation of the tool was done by the panel of experts (midwife experts, epidemiologists, and gynecologists). The panel of experts independently assessed the tool for readability, understanding, clarity, and ease of use. The internal consistency for each dimension was checked using Cronbach's alpha (Cronbach's alpha=0.98) (10).

All participants responded to all items in the local Sidamic version and marked them correctly. No missing items were found. Data collectors reported no difficulties in asking the questions, and no participants reported having any problems understanding the items. The tool was tested for the second time two weeks later after the first measurement. The two-week test-retest reliability result was shown to have an excellent correlation between reliable strategy to assess these point scores (ICC for agreement 0.78; $p< 0.001$).

We collected clinical and laboratory variables prospectively in each hospital. One strength of this study was that it was based on a prospective cohort, which minimized the risk of selection and recall bias. We checked confounder and interaction effects among predictors. We also checked the multicollinearity among predictors using the variance inflation factor at a cutoff point of ten. The goodness of the fit was tested using the Hosmer-Lemeshow test. The one that was greater than the significance level (p-value > 0.05) was accepted.

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The effect of preeclampsia on adverse perinatal outcomes in Sidama region, southern Ethiopia: a prospective open cohort study

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Abstract

Background: In Ethiopia, in 2020, more than 80% of newborn deaths are caused by preventable and treatable conditions. This study aimed to measure the effect of preeclampsia on adverse perinatal outcomes and its risk factors in the Sidama region of southern Ethiopia.

Methods: A prospective open cohort study was conducted from August 8, 2019 to October 1, 2020. We enrolled a total of 730 pregnant women with preeclampsia and normotensive women at >20 weeks of gestation and followed until the 37th week. We followed them until the seventh day from their delivery up to the last perinatal outcome status was ascertained. A log-binomial logistic regression model was used to estimate the effects of preeclampsia on adverse perinatal outcomes and identify risk factors for adverse perinatal outcomes. Relative risk with a 95% confidence interval was reported. A P-value<0.05 was considered statistically significant.

Results: There were 224 adverse perinatal outcomes observed in the preeclampsia group compared to 136 adverse perinatal outcomes in the normotensive group (P<0.001). There were 23 early neonatal deaths in the preeclampsia group compared to 6 deaths in the normotensive group (P<0.001). There were 35 perinatal deaths in the preeclampsia group compared to 16 deaths in the normotensive group (P<0.05). Women with preeclampsia had a 38% (aRR=1.38, 95% CI=1.20–1.58) higher risk for adverse perinatal outcomes compared to the normotensive group.

Conclusions: In this study, a higher adverse perinatal outcome occurred among women with preeclampsia. Preeclampsia affected perinatal outcomes, after controlling confounders. Women with severe features of preeclampsia, women who were admitted to a hospital at <34 weeks, younger and older women, women with no formal education, women with primary school education, and women with high systolic blood pressure were the risk factors for adverse perinatal outcomes.

Keywords: Adverse Perinatal Outcome, Preeclampsia, Pregnant Women, southern Ethiopia

What is already known on this topic?

- Previous studies conducted in southern Ethiopia were limited in estimating the effect of preeclampsia on adverse perinatal outcomes because of poor ascertainment of exposures and outcomes. Likewise, the studies did not compare the adverse perinatal outcomes among women with preeclampsia and normotensive women.

- In 2020, in the Sidama region, 22.7% of the pregnant women did not know the causes of newborn deaths, and this study didn't measure the risk of outcomes of interest.

What this study adds?

- In this study, there were 224 adverse perinatal outcomes observed in the preeclampsia group compared to 136 adverse perinatal outcomes in the normotensive group (P<0.001).

- Women in the preeclampsia group had a 38% higher risk of adverse perinatal outcomes compared to the normotensive group.

How this study might affect research, practice or policy

- This study helps provide epidemiological evidence for the effect of preeclampsia on adverse perinatal outcomes in clinical and public health practices. Future research should consider the effects of all types of hypertensive disorders of pregnancy on adverse perinatal outcomes.

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Introduction

The incidence proportion of hypertensive disorders of pregnancy (HDP) has increased from 16.30 million in 1990 to 18.08 million from 1990 to 2019 globally (1). Similarly, the proportion varied from country to country (1). In Ethiopia, in 2018, preeclampsia occurred in 2.4–67.4% of all pregnancies, and severe preeclampsia occurred in 10.7–82.5% of the pregnancies (2–5). A higher proportion of preeclampsia and eclampsia (10.13%) was observed in southern Ethiopia compared to Addis Ababa (5.41%) (6).

Maternal mortality which is related to HDP was 27.83 thousand in 2019, which accounted for a 30.05% decrease from 1990 (1). Globally, preeclampsia was responsible for 500,000 perinatal deaths in 2019 (7). Similarly, in low-and middle-income countries (LMICs), 10%-15% of direct maternal mortalities are associated with preeclampsia and eclampsia (8). HDP were the second leading cause of maternal deaths (22.1%) in sub-Saharan Africa in 2022 (9). HDPs were the third leading cause of maternal deaths (16% of HDPs) in southern Ethiopia in 2019 (10).

In Ethiopia, in 2020, more than 80% of newborn deaths were caused by preventable and treatable conditions (11). According to the 2019 Ethiopia Mini Demographic and Health Survey report, the overall <5 child mortality rate was 55 deaths per 1,000 live births, and neonatal mortality was 30 deaths per 1,000 live births (12). In 2021, women with preeclampsia had a higher rate of adverse perinatal outcomes than normotensive women (64.1% versus 32.8%) (13).

An uneven distribution of health resources; suboptimal quality of care; availability of anesthesia, magnesium sulphate, and intensive care unit; low child healthcare-seeking behavior; shortage of kangaroo mother care and essential health commodities; gestational age at delivery; lack of antenatal care; women who did not attend school; low birth weight; nulliparity, preterm birth, asphyxia, women who didn't have decision-making power on health care, didn't attend postnatal care; and breastfed immediately; neonatal sepsis, neonatal tetanus, and neonatal pneumonia were identified as common risk factors for adverse perinatal outcomes (11, 12, 14-16).

A significant improvement has been made by the government of Ethiopia in reducing maternal mortality (17). However, the reduction of mortality is still a challenge. In line with this, Ethiopia is replacing the previous four-visit focused antenatal care (ANC) model with the new ANC eight-

contacts model (18). Additional contact may be required to detect a complication (18). Poor infrastructure, scarcity of supplies and skilled labor, weak referral system, poor quality of care, and lack of timely obstetric care contributed to a higher proportion of adverse perinatal mortality in Ethiopia (19). The government of Ethiopia has taken steps to strengthen engagement with key local and international sectors and stakeholders to address determinants of health (18).

Studies conducted in southern Ethiopia were limited in estimating the effect of preeclampsia on adverse perinatal outcomes because of poor ascertainment of exposures and outcomes using purposive sampling techniques, and 22.7% of the pregnant women did not know the causes of newborn deaths. What is more, the studies were poor in generating evidence that could be used by policymakers and in clinical practices, did not include control group, and didn't measure the risk of outcomes of interest (20-23). Another study in Ethiopia found that these studies did not include a non-exposed group that would have been important to controlling confounders like the quality of perinatal care associated morbidity and mortality (24). Thus, this study aimed to measure the effect of preeclampsia on adverse perinatal outcomes and its risk factors in the Sidama region of southern Ethiopia. The findings from this study could be used for early detection of preeclampsia during ANC visits and improvement of the care and treatment for women who experience adverse perinatal outcomes that are associated with preeclampsia.

Methods

Study design and setting

A prospective open cohort study was conducted from August 8, 2019 to October 1, 2020 in the Sidama region. In 2020, the population of the region was approximately 4 million. There were thirteen public hospitals, 138 health centers, and 540 health posts in the region that provided maternal, newborn, and child health services. In 2020, approximately 132,031 pregnant women attended ≥4 antenatal care visits (ANC) and 127, births were assisted by skilled birth attendants. Out of the 13 hospitals that are found in the region, we enrolled participants from seven hospitals namely Adare, Hawassa, Yirgalem, Hula, Bona, Chuko, and Daye hospitals.

Patient and public involvement

The participants of this study were women with preeclampsia and normotensive women who were enrolled at ≥20 weeks of gestation until the 37th week. We followed them until the seventh day after delivery and waited for the last enrolled woman's perinatal outcome status to be ascertained. During the follow-up, 194 women with preeclampsia and normotensive women were admitted to a hospital at <34 weeks of gestation, and 536 women with preeclampsia and normotensive women were admitted to hospitals at 34–37 weeks of gestation. During the follow-up, eight normotensive women developed preeclampsia. We included these eight women in the exposed group. Pregnant women with hypertension plus proteinuria, women with mild hypertension and evidence of organ dysfunction, severe hypertensive patients without proteinuria and evidence of organ dysfunction were included in the study.

Operational definitions

Birth asphyxia was defined as the condition of a baby with trouble in breathing (gasping or breathing very irregularly or no breathing). Small for gestational age of pregnancy was defined as a birth weight of a newborn below the tenth percentile of weight distribution at the specified gestational age of pregnancy. Stillbirth refers to a baby born with no sign of life at or after 28 weeks of gestation. Preterm delivery is defined as the delivery of a baby before 37 weeks gestation. Low birth weight describes a baby with a birth weight of less than 2.5 kg. A low Apgar score refers to a newborn baby with an Apgar score of less than seven at 1 and 5 minutes (25).

Perinatal death was defined as a stillbirth or an early neonatal death. Early neonatal death was defined as the death of a live newborn in the first seven days of life. Intrauterine growth restriction of newborn is defined as birth weight and/or birth length below the 10th percentile for their gestational age and whose abdominal circumference was below the 2.5th percentile with pathologic restriction of fetal growth (25).

Sample size and sampling

The sample size was calculated using EPI INFO version 7. We considered the following assumptions for sample size calculations: early neonatal death (15), the ratio of exposed to unexposed group (1 to 1), the proportion of early neonatal death among women with preeclampsia

(5%), and the proportion of early neonatal death among normotensive women (1%). The sample size was estimated to be 733 (366 women with preeclampsia and 367 normotensive women), accounting for a design effect of two and 10% loss to follow-up. We also assumed a two-sided confidence level of 95% with a power of 80%.

A two-stage cluster sampling technique was used to recruit study participants. In the first stage, seven of the thirteen hospitals were selected using a simple random sampling technique. In the second stage, perinatal conditions were selected from women with preeclampsia and normotensive women using a simple random sampling technique.

Exposure ascertainments

The main exposure variable in this study was preeclampsia (preeclampsia with or without severity features). Preeclampsia with severe features was defined as the presence of one or more of the following conditions: blood pressure (BP) of ≥160mmHg systolic or ≥110mmHg diastolic, ≥3+protein on two urine samples taken four hours or more apart or 5gm of protein in a 24hr urine sample (25). Preeclampsia without severe features was defined as raised BP>140/90 mmHg plus 24-hour urine protein >300mg/24 hour or urine dipstick >+1 after 20 weeks of gestation in previously normotensive women (25). Normotensive women were pregnant women having a (BP)<140/90 mmHg with ≥20 weeks of gestation or who did not develop preeclampsia and proteinuria (25). Gestational age was calculated based on a woman's recall of her last menstrual period. However, an ultrasound scan was used for those women who could not remember their last menstrual period (25).

Outcome variable

Adverse-perinatal outcomes were defined as a newborn with the occurrence of at least one of the following outcomes: birth asphyxia, low birth weight, small for gestational age, preterm delivery, admission to the neonatal intensive care unit, and perinatal death.

Data collection

We validated the data collection tool before data collection (26). Accordingly, we followed the recommended tool validation steps and procedures. Two bilingual translators (speakers of both Sidamic and English languages) who were capable of translating the original tool in the English

version into the Sidamic version were selected. Translations into the Sidamic language more accurately reflected the tones of the language. The translations were compared and discrepancies were noted during the translation process. The poorer wording choices were identified and resolved in a discussion between the translators.

The back translations were done by two experts of the source language (English). This was a validity checking process to ensure that the translated version reflected the same item content as the original version did. Face and content validation of the tool was done by a panel of experts (midwife experts, epidemiologists, and gynecologists). The panel of experts independently assessed the tool for readability, intelligibility, clarity, and ease of use. The internal consistency for each dimension was checked using Cronbach's alpha (Cronbach's alpha=0.98) (26).

All participants responded to all items in the local, Sidamic, version and marked them correctly. No missing item was found. Data collectors reported no difficulty in asking the questions, and no participant reported having any problem understanding the items. The tool was tested for the second time two weeks after the first measurement. The two-week test-retest reliability result was shown to have an excellent correlation between reliable strategies to assess these point scores (ICC for agreement 0.78; $p< 0.001$) (26).

Trained midwives conducted face-to-face interviews at antenatal care clinics using a locally translated and validated tool. A checklist was used to collect information from the maternal and neonatal records of women with preeclampsia and normotensive women in each hospital. Similarly, socio-demographic variables such as maternal age, religion, residence, parity, marital status, education, and maternal and husband's occupation were collected.

We collected clinical and laboratory variables prospectively in each hospital through medical records and using a check list: blood pressure, urine protein, gestational age, acute kidney injury, platelet count, creatinine, serum glutamic oxaloacetic transaminase, number of maternal intensive care unit admissions (ICUs), convulsion, parity, gravidity and sonographic scan. Pregnant women were selected by health care providers: general medical practitioners, emergency surgical officers, or obstetricians/gynecologists during antenatal care follow-up, and the data collection procedures were supervised by three maternity and reproductive health professionals.

Outcome ascertainment

Adverse perinatal outcomes were ascertained by obstetricians/gynecologists and trained midwives. Client medical registration was also used to retrieve adverse perinatal outcome status. The perinatal condition was determined at the follow-up appointment for those who were discharged, and a phone call was made for those who did not show up for this follow-up.

Missing data

Pregnant women's loss means dropout of women who had complications during the follow-up period. Those women with adverse perinatal outcomes had their status determined at a later time and were contacted by phone. The loss to follow up was computed to minimize its effects on the conclusion, including as missing completely at random, missing at random, and missing not at random.

Statistical analysis

Data were cleaned, coded and analyzed using STATA 14. Besides, identification of outliers and missing values was performed. Data consistency was checked using the original questionnaire for the responses using participants' code numbers. Frequencies and percentages were computed for categorical variables. Mean and standard deviations were computed for continuous variables. An incidence proportion of adverse perinatal outcomes was conducted about women who had preeclampsia and normotensive women. Cross tabulation was also performed to test the relationship of exposure variables with the outcome variable. A chi-squared test was used to compare categorical variables between women with preeclampsia and normotensive women. From the last normal menstrual period or from an ultrasound report, gestational age was calculated.

Principal component analysis was computed and used for wealth index computation and was ranked in three groups as low, middle, and high. Different items for urban and rural areas were computed separately. The suitability of data was computed by using Bartlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) measure of sample adequacy (27). The KMO > 0.6 was used to confirm the sample adequacy for factor analysis (27).

A multivariable log-binomial logistic regression model was performed to identify the risk factors for adverse perinatal outcomes. Variables with a p-value<0.25 were included in the multivariable log-binomial logistic regression analysis (28). Multivariable log-binomial logistic regression

analysis was performed by estimating the risk ratios with a 95% confidence interval. Attributable fractions (AF) were calculated from the adjusted risk ratio to evaluate to what extent the occurrence of adverse perinatal outcomes could have been reduced if a particular risk factor was prevented. A p-value of <0.05 was considered a significant risk factor for adverse perinatal outcomes.

We checked the multicollinearity among predictors using a variance inflation factor at a cutoff point of ten. The goodness of the fit was tested using the Hosmer-Lemeshow test. The predictor that was greater than the significance level (p-value >0.05) was accepted.

Ethical considerations

This study was reviewed and ethically approved by the Institutional Review Board of the University of Gondar R.No: (O/V/P/RCS/044/2019 in March 2019). All participants signed an informed consent document before study participation began. Pregnant women having abnormal clinical and laboratory results were referred for treatment. Women with severe hypertension were provided with antihypertensive drugs; those with convulsions were given magnesium sulphate.

Results

Socio-demographic and economic characteristics of study participants

Of all the 733 women with preeclampsia and normotensive women, we enrolled 730 women with preeclampsia and normotensive women. Two (0.27%) of the participants were lost to follow-up and one of these two participants was from the normotensive group and one from the preeclamptic group. During the follow-up, eight normotensive women developed preeclampsia. We included these eight women in the exposed group (Figure 1).

The mean gestational age at the diagnosis of women with preeclampsia was 32.85 (SD± 3.25) weeks and that of normotensive women was 33.90 (SD± 2.75) weeks. The mean duration of follow-up of women with preeclampsia was 6.51 (SD± 3.15) weeks and that of normotensive women was 5.68 (SD± 2.97) weeks (Figure 1).

The mean age of the preeclamptic women was 25.42 (SD±4.76) years, and 24.6 (SD±4.48) years for the normotensive group. More than half of the women with preeclampsia (56.7%, 206/363, P < 0.001) were 16–24 years old, compared to the normotensive group (35.9%, 132/367, P<0.001). A higher proportion of women with preeclampsia was observed (81%, 294/363), P<0.001) among

women who resided in rural areas compared to urban residents (19%, 69/363), P<0.001) (Table 1).

Table 1: Socio-demographic and economic characteristics of women with preeclampsia and normotensive women in Sidama region, southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Women with preeclampsia (n=363)	Normotensive women (n=367)	Total (n=730)	P-value
Age group (in year)	mean 25.42(±4.76)	mean 24.6 (±4.48)		
16-24	206(56.7)	132(35.9)	338(46.3)	
25-34	147(40.5)	213(58)	360(49.3)	P<0.001
≥35	10(2.8)	22(6)	32(6)	
Maternal education				
No formal education	33(9.1)	16(4.3)	49(6.7)	
Primary education	164(45.2)	145(39.5)	309(42.3)	P<0.05
Secondary education	98(27)	110(30)	208(28.5)	
College/University	68(18.7)	96(26.2)	164(22.5)	
Husband education				
No formal education	15(4.1)	7(1.9)	22(3)	
Primary education	122(33.6)	87(23.7)	209(28.5)	P<0.05
Secondary education	99(27.3)	117(31.9)	216(29.6)	
College/University	127(35)	156(42.5)	283(38.8)	
Maternal occupation				
House wife	191(52.6)	163(44.4)	354(48.5)	
Merchant	70(19.3)	76(20.7)	146(20)	
Employed	64(17.6)	88(24)	152(20.8)	P>0.05
Student	23(6.3)	21(5.7)	44(6)	
Farmer	10(2.8)	10(2.7)	20(2.7)	
Daily laborer	5(1.4)	9(2.5)	14(1.9)	
Husband occupation				
Employed	116(32)	149(40.6)	265(36.3)	
Merchant	126(34.7)	136(37.1)	262(35.9)	
Farmer	75(20.7)	45(12.3)	120(16.4)	P<0.05
Daily laborer	31(8.5)	23(6.3)	54(7.4)	
Student	7(1.9)	10(2.7)	17(2.3)	
Unemployed	8(2.2)	4(1.1)	12(1.6)	
Place of residence				
Rural	294(81)	331(90.4)	104(14.3)	P<0.001
Urban	69(19)	35(9.6)	625(85.7)	
Wealth Index				
Low	157(43.3)	95(26)	252(34.6)	
Middle	105(28.9)	139(28)	244(33.5)	P<0.001
Rich	101(27.8)	132(36.1)	233(32)	

‡‡Others= widowed or single

Obstetric characteristics of women with preeclampsia and normotensive

Compared to the normotensive group (35.7%, 131/367, P < 0.001), a higher proportion of women with preeclampsia (40.8%, 148/363, P<0.001) was observed in Yirgalem hospital. A higher proportion of very preterm births was reported in the preeclampsia group (6.6%, 24/363, P<0.001) compared to the normotensive group (0.3%, 1/367, P< 0.05). A higher proportion of women with preeclampsia (28.4%, 103/363), P<0.05) was reported among women who were admitted at < 34 weeks compared to the normotensive group (24.5%, 91/367, P<0.05) (Table 2).

Table 2: Obstetrics factors for women with preeclampsia and normotensive women in Sidama region, southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Women with preeclampsia (n=363)	Normotensive women(n=367)	Total (n=730)	P-value
Fetal sex				
Male	202(55.6)	195(53.1)	397(54.4)	P>0.05
Female	161(44.4)	172(46.9)	333(45.6)	
Number of neonates delivered				
Singleton	337(92.8)	350(95.4)	687(95.4)	
Twin	26(7.2)	17(4.6)	43(5.9)	P>0.05
Gravida				
1	46(12.7)	77(21)	123(16.8)	
2-3	253(69.7)	208(56.7)	461(63.2)	P>0.05
≥4	64(17.6)	82(22.3)	146(20)	
Parity				
Nullipara	12(3.3)	5(1.4)	17(2.3)	P>0.05
1	37(10.2)	94(25.6)	131(17.9)	
2-3	264(72.4)	222(60.5)	486(66.6)	
≥4	50(13.8)	46(12.5)	96(13.2)	
Interpregnancy Interval (¶¶IPI)				
<24 months (short IPI)	8(2.2)	4(1.1)	12(1.6)	
24-59 months (optimal IPI)	180(49.6)	263(71.7)	443(60.7)	P<0.001
60+ months (long IPI)	115(31.7)	35(9.5)	150(20.5)	
Not applicable (prim)	60(16.5)	65(17.7)	125(17.1)	
Gestational age at admission (week)				
<34	103(28.4)	91(24.5)	194(26.6)	P<0.05
34-37	260(71.6)	276(75.5)	536(73.4)	
Maternal ¶ICU admission				
Yes	5(1.4)	1(0.3)	6(0.8)	P>0.05
No	358(98.6)	366(99.7)	724(99.2)	
||GA at delivery (week)				

Extremely preterm (<28)	10(2.8)	5(1.4)	15(2.1)	
Very preterm (28-32)	24(6.6)	1(0.3)	25(3.4)	P<0.001
Moderate to late preterm (32-37)	123(33.9)	67(18.3)	190(26)	
Term+(≥37)	206(56.7)	294(80)	500(68.5)	
Hospitals				
Adare general hospital	60(16.5)	109(29.7)	169(23.2)	
Hawassa referral hospital	53(14.6)	47(12.8)	100(13.7)	
Yirgalem general hospital	148(40.8)	131(35.7)	279(38.2)	P<0.001
Hula primary hospital	7(1.9)	7(1.4)	12(1.6)	
Bona general hospital	51(14)	29(7.9)	80(11)	
Chuko primary hospital	11(3)	6(1.6)	17(2.3)	
Daye primary hospital	33(9.1)	40(10.9)	73(10)	

||GA=Gestational age, ¶ICU= Intensive Care Unit, ††g=gram, ¶¶IPI=Interpregnancy Interval

Incidence of adverse perinatal outcomes among women with preeclampsia and normotensive women

There were 224 adverse perinatal outcomes observed in the preeclampsia group compared to 136 adverse perinatal outcomes in the normotensive group (P<0.001). There were 23 early neonatal deaths reported in the preeclampsia group compared to 6 deaths in the normotensive group (P<0.001). Also, there were 96 preterm births observed in the preeclampsia group compared to 17 preterm births in the normotensive group (P<0.001). There were 35 perinatal deaths reported in the preeclampsia group compared to 16 deaths in the normotensive group (P<0.05) (Table 3).

Table 3: Neonatal outcomes among women with preeclampsia and normotensive women in Sidama region southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Women with preeclampsia (n=363)	Normotensive women(n=367)	Total (n=730)	P-value
Birth weight of neonate (††g)				
<1500	33(9.1)	6(1.6)	39(5.3)	
1500-2499	103(28.4)	31(8.4)	134(18.4)	P<0.001
2500-3999	211(58.1)	302(82.3)	513(70.3)	
≥4000	16(4.4)	28(7.6)	44(6)	
Apgar score <7 at 1 minutes				
Yes	64(17.6)	52(14.2)	116(15.9)	P<0.05
Apgar score <7 at 5 minutes				
Yes	62(17.1)	54(14.7)	116(15.9)	P>0.05
Intrauterine growth restriction				
Yes	22(6.1)	4(1.1)	26(3.6)	P<0.001

Still birth				
Yes	21(5.8)	11(3)	32(4.4)	P<0.05
Early neonatal death				
Yes	23(6.3)	6(1.6)	29(4)	P<0.001
Preterm birth				
Yes	96(26.4)	17(4.6)	113(15.5)	P<0.001
Perinatal death				
Yes	35(9.6)	16(3.8)	49(6.7)	P<0.05
Low birth weight				
Yes	98(27)	73(19.9)	171(23.4)	P<0.05
Small for gestational age				
Yes	66(18.2)	30(8.2)	96(13.2)	P<0.001
Birth asphyxia				
Yes	39(10.7)	15(4.1)	54(7.4)	P<0.05
Admission to ¶¶NICU				
Yes	88(24.2)	39(10.6)	127(17.4)	P<0.001
Adverse perinatal outcomes				
Yes	224(61.7)	136(37.1)	360(49.3)	P<0.001

††g=gram, ¶¶NICU=Neonatal Intensive Care Unit

Effect of preeclampsia with or without a severity feature on adverse perinatal outcomes and other risk factors

In the bivariable log-binomial logistic regression model, fourteen risk factors for adverse perinatal outcomes were identified: maternal age, maternal and husband's education, maternal and husband's occupation, parity, gravidity, wealth index, presence of preeclampsia, mode of delivery, presence of severe features of preeclampsia, maternal ICU admission, systolic and diastolic blood pressure.

After controlling for confounders, women in the preeclampsia group had a 38% (aRR: 1.38, 95%CI: 1.20–1.58) higher risk for adverse perinatal outcomes compared to women in the normotensive group. Women with severe features of preeclampsia had a 45% (aRR: 1.45, 95% CI: 1.37–2.76) higher risk for adverse perinatal outcomes compared to women without severe features of preeclampsia. Women who were admitted to the hospital at <34 weeks had a 14% (aRR: 1.14, 95% CI: 1.02–1.27) higher risk for adverse perinatal outcomes compared to women who were admitted between 34–37 weeks (Table 4).

Table 4: A multivariable log-binomial logistic regression model for risk factors for adverse perinatal outcomes among women with preeclampsia in Sidama region southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Adverse perinatal outcomes		Unadjusted RR* (95%Cl)	Adjusted RR (95%Cl†)	AF (95%CI)
	Yes (%)	No (%)			
Parity					
Nullipara	11(64.7)	6(35.3)	0.94[0.64–1.78]	0.86[0.65– 1.78]	–
1	139(43.7)	179(56.3)	0.68***[0.57–0.80]	0.86[0.60–1.22]	–
2-3	148(51.7)	138(48.3)	0.83*[0.70–0.97]	0.93[0.72–1.19]	–
≥4	62(56.9)	47(43.1)	1	1	1
Maternal age (year)					
16-24	223(66)	115(34)	1.71***[1.48–1.23]	1.57***[1.36–1.82]	47% [42–53%]
25-34	123(34.2)	237(65.8)	1	1	1
≥35	14(43.8)	18(56.2)	1.38[0.99–1.92]	1.49*[1.09–2.03]	21% [9–33%]
Maternal education					
No formal education	32(63.3)	17(34.7)	1.52**[1.19–1.93]	1.40**[1.14– 1.72]	30% [17–54%]
Primary education	175(56.6)	134(43.4)	1.30**[1.08–1.57]	1.23*[1.05– 1.46]	21% [10–37%]
Secondary education	84(40.4)	124(59.6)	0.99[0.79–1.23]	0.56[0.44–1.25]	–
College/university	69(42.1)	95(57.9)	1	1	1
Husband education					
No formal education	17(77.3)	5(22.7)	1	1	1
Primary education	123(58.9)	86(41.1)	0.76*[0.59– 0.98]	0.92(0.76–1.97)	–
Secondary education	105(48.6)	111(51.4)	0.62**[0.48– 0.81]	0.83(0.67–1.04)	–
College/university	115(40.6)	168(59.4)	0.52***[0.40–0.68]	0.74[0.57–2.97]	–
Wealth index					
Low	176(69.6)	77(30.4)	1.77***[1.48–2.12]	1.72[0.44–2.06]	–
Middle	98(40.2)	146(59.8)	1.03[0.83–1.29]	1.02[0.82–1.28]	–
Rich	86(36.9)	147(63.1)	1	1	1
Gravidae					
1	127(42.6)	171(57.4)	0.81[0.91– 1.96]	0.84 [0.72–1.97]	–
2-3	154(52.4)	140(47.6)	0.96[0.80–1.15]	0.95[0.81–1.11]	–
≥4	79(57.2)	59(42.8)	1	1	1
Mode of delivery					
ǂSVD	205(51.5)	193(48.5)	0.89[0.77–1.04]	0.12[0.78–1.16]	–
C/section	143(46.3)	166(53.7)	1.01[0.67–1.561]	1.32[0.85–2.34]	–
Vacuum assisted	12(52.2)	11(47.8)			
Gestational age at admission (week)					
<34	113(58.2)	81(41.8)	1.11[0.97–1.28]	1.14*[1.02–1.27]	20% [17–33%]
34-47	247(46.1)	289(53.9)	1	1	1
Maternal ICU admission					
Yes	4(80)	1(20)	1.67**[1.16– 2.41]	1.22[0.75– 3.19]	–
No	356(49.1)	369(50.9)	1	1	1

Women with preeclampsia					
Yes	224(61.7)	139(38.3)	1.57***[1.37–1.81]	1.38***[1.20–1.58]	40% [35–44%]
No	136(37.1)	231(62.9)	1	1	1
Women with severe features of preeclampsia					
Yes	105(78.9)	28(21.1)	1.58***[1.25–1.85]	1.45***[1.37–2.76]	44% [37–48%]
No	255(42.7)	342(57.3)	1	1	1
Eclampsia					
Yes	32(82.1)	7(17.9)	1.61***[1.38–1.92]	1.34[0.41–1.83]	–
No	328(47.5)	363(52.5)	1	1	1
Systolic blood pressure (mmHg)					
<140	136(37.1)	231(62.9)	1	1	1
140-159	162(62.3)	98(37.7)	1.56***[1.35–1.81]	1.38***[1.19–1.59]	38% [26–50%]
≥160	62(60.2)	41(39.8)	1.59***[1.33–1.91]	1.34**[1.13– 1.58]	36% [19–53%]
Diastolic blood pressure(mmHg)					
<90	136(37.1)	231(62.9)	1	1	1
90-109	180(62.3)	109(37.7)	1.68***[1.43–1.97]	1.12[0.21–2.03]	–
≥110	44(59.5)	30(40.5)	1.60***[1.27–2.02]	1.43[0.96–2.43]	–
Magnesium sulfate treatment					
Yes	74(43.8)	95(56.2)	0.65***[0.57–0.74]	0.56[0.36–1.23]	–
No	286(51)	275(49)	1	1	1
Antihypertensive drug treatment					
Yes	124(33.5)	178(49.4)	0.64***[0.56–0.73]	0.84[0.40– 1.75]	–
No	246(66.5)	182(50.6)	1	1	1
Dexamethasone treatment					
Yes	56(48.7)	59(51.3)	0.54[0.34–1.81]	0.45[0.23–1.98]	–
No	304(49.4)	311(50.6)	1	1	1

*RR=Relative Risk, † CI = Confidence Interval, ‡SVD= Spontaneous Vaginal Delivery, §C/section-Cesarean Section, *p-value <0.05, **p-value <0.001, ***p-value <0.0001, ††AF-Attributable fraction

Discussion

In this study, a higher adverse perinatal outcome was observed in the preeclampsia group compared to the normotensive group in the Sidama region. Preeclampsia affected perinatal outcomes after controlling for confounders. Perinatal death, stillbirth, small for gestational age, preterm birth, birth asphyxia, and low birth weight were higher in the preeclampsia group compared to the normotensive group. Women with severe features of preeclampsia and women who were admitted to the hospital at<34 weeks were identified as risk factors for adverse perinatal outcomes.

A higher adverse perinatal outcome was observed in the preeclampsia group compared to the normotensive group. This finding is consistent with other studies (29, 30), but slightly lower than other studies conducted in southwest Ethiopia in 2021 (64.1% versus 32.8%) (32) and in Ethiopia in 2020 (66.4% versus 22.2%) (15). This finding of the current study is higher than that of a Ugandan study, which indicated that 36.9%, 20.3 percent, and 1.1 percent of neonates were admitted to NICUs, stillbirths, and neonatal deaths, respectively (31). This discrepancy might be since, in Ethiopia, in 2019, the universal health coverage index was low at 39% (13), leading to variations in the implementation of policies, strategies, and service delivery for maternal health among regions.

A higher perinatal death was reported in the preeclampsia group compared to the normotensive group. This finding is lower than the finding of a study conducted in southwest Ethiopia in 2021(21.2% and 6.2%) (31). Perinatal deaths can be reduced in a country if better access to quality maternal health care services is ensured. Thus, preventing and managing preeclampsia should become a priority to accelerate the progress of newborn survival.

A higher stillbirth was observed in the preeclampsia group compared to the normotensive group. This finding is lower than the findings of other studies conducted in southwest Ethiopia in 2021 (11.2% versus 4.1%) (31) and the Tigray region in 2020 (10% versus 1.7%) (15), which found that women with preeclampsia were associated with placental insufficiency and that the placenta fails to provide adequate oxygen and nutrients to the growing fetus. This difference could be due to the quality of antenatal care services and obstetrics care across health institutions and the study design used. This implies that maternity care providers should be aware of how to detect and treat fetal complications before the complication advance to a severe stage. It also gives room for the pregnant woman to share her symptoms, feelings, and worries with her health care provider before her condition worsen.

A higher small for gestational age newborns was reported in the preeclampsia group compared to the normotensive group. This finding is higher than findings of other studies conducted in Tigray regional state of Ethiopia in 2020 (36.7% versus 10.7%) (15) and Ghana in 2017 (6.3%) (14). Women with preeclampsia show that blood flow is reduced and placental exchange of important nutrients such as amino acids has been demonstrated in intrauterine growth restriction. Those babies who were born at SGA had smaller diameters of coronary arteries compared to those born

at normal gestational age. Thus, the finding indicates a higher risk for cardiovascular events in the future (14).

A higher preterm birth was observed in the preeclampsia group compared to the normotensive group. This finding is similar to the finding of another study conducted in Ethiopia in 2020 (15), which found that women with preeclampsia were at an increased risk of preterm births, as shown by a significantly lower gestational age compared to term pregnancy. The similarity in the incidence of preterm birth across the studies might be due to the similar quality of antenatal care services and the similar guidelines used for the management of preeclampsia. Thus, it is important to improve the quality of maternal and child health care services to reduce adverse perinatal outcomes associated with preeclampsia. In addition, the Federal Ministry of Health and concerned bodies should work towards the prevention of preeclampsia and its adverse outcomes (12).

A higher newborn with birth asphyxia was reported in the preeclampsia group compared to the normotensive group. This finding is higher than the finding of another study conducted in Tigray region, Ethiopia in 2020 (46.5% versus 11.3%) (15), which discovered that women with preeclampsia have more preterm births, which may be vulnerable to lung immaturity, which causes birth asphyxia and respiratory failure. The lungs of a preterm baby may be deficient in surfactant, which makes it more difficult to the lung to ventilate. Thus, newborn resuscitation techniques shall be improved and treatment of newborns with birth-related asphyxia shall be paid due attention for it reduces mortality.

A higher newborn with low birth weight was observed in the preeclampsia group compared to the normotensive group. This finding is higher than other studies conducted in Ethiopia, particularly in southwestern Ethiopia in 2021 (39.8% versus 12.7%) (32) and in Tigray region in 2020 (37.7% versus 6.1%) (15). This indicated that low birth weight could be the result of fetal malnutrition, prematurity, poor nutritional reserves of the mother and inadequate flow of blood in the uterus. The disparity between the studies could be attributed to antenatal care service quality and preeclampsia management. Thus, reducing the risk of low birth weight by increasing attention to keeping the newborn warm, skin-to-skin care, and assistance with early initiation of breast feeding is essential.

Women with severe features of preeclampsia had a higher risk for adverse perinatal outcomes compared to women without severe features of preeclampsia. This finding was in agreement with

another study that reported an association between severe preeclampsia with neonatal complications (45.9%) (8). The increased risk of perinatal complication may be explained by preeclampsia progressing to severe features, and women developing preeclampsia before 34 weeks.

Women who were admitted to a hospital at <34 weeks had a higher risk of adverse perinatal outcomes compared to women who were admitted between 34–37 weeks. This finding is supported by another study (6) whose finding indicated that early onset of preeclampsia was associated with an increased risk for adverse perinatal outcomes compared to late-onset of preeclampsia after 34 weeks (6). Early-onset of preeclampsia is associated with having more severe placental dysfunction and infant growth restriction compared to late-onset of preeclampsia (6).

Limitations of the study

One limitation could be recall bias linked to gestational age, which was calculated based on a woman's recall of her last menstrual period. However, an ultrasound scan was used for those women who could not remember their last menstrual period.

Conclusion

A higher adverse perinatal outcome was observed among women with preeclampsia compared with normotensive women in the Sidama region. In this study, preeclampsia was found to have an effect on adverse maternal outcomes after controlling for confounders. These effects could be detected and controlled early in pregnancy. Women with severe features of preeclampsia, women who were admitted to a hospital at <34 weeks, younger and older women, women with no formal education, primary school-educated women, and women with high systolic blood pressure were the risk factors for adverse perinatal outcomes. Preeclampsia awareness and health promotion at antenatal care clinics and in the community focusing on preeclampsia risk factors could reduce the adverse perinatal outcomes and consequences.

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Author's contributions: This study was carried outby all authors collaboratively. BJ, MA and KA contributed to conceptualizing and designing the study, curating and analyzing data, and writing the first draft. Also, BJ, MA, TA, and KA managed the investigation, literature searches, methodology review, writing, and contributed to data collection; BJ, MA, TA, and KA contributed to the manuscript review, resource, preparation, and editing. All the authors have read and agreed to the final manuscript.

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List of figures

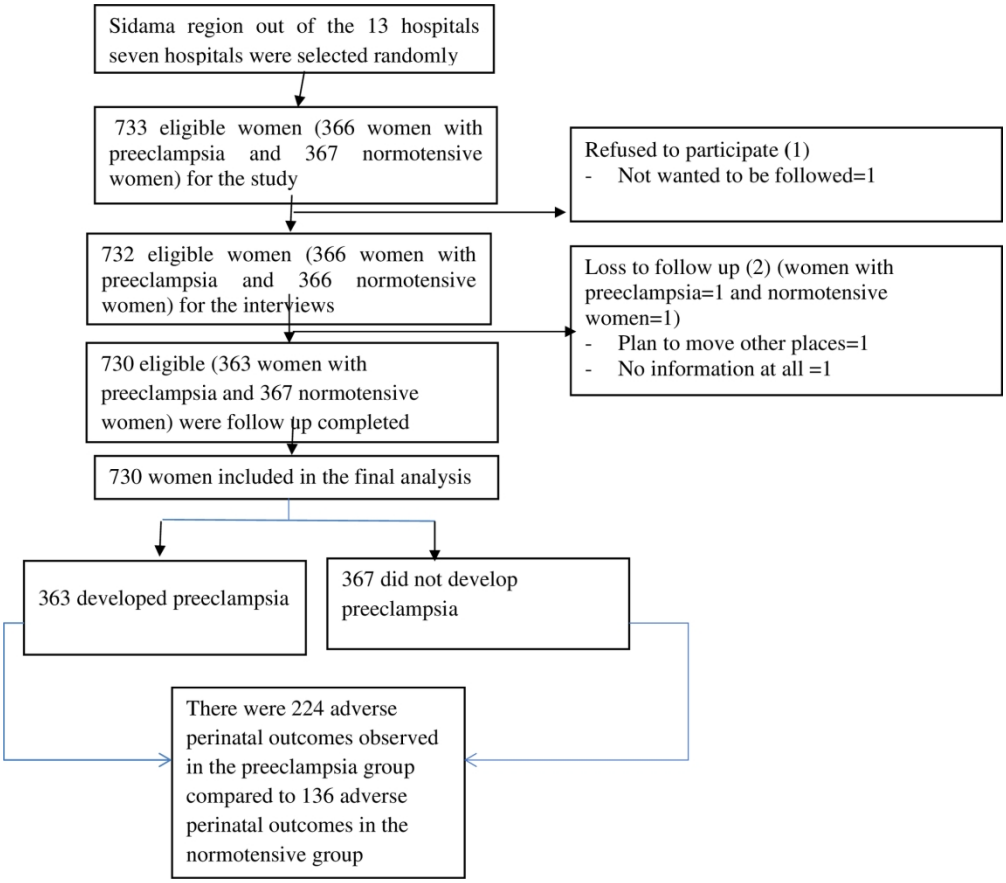

Figure 1: Flow-diagram of the overall study process in Sidama region, southern Ethiopia, August 8, 2019, to October 1, 2020

190x166mm (300 x 300 DPI)

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Incidence of adverse perinatal outcomes and risk factors among women with preeclampsia, southern Ethiopia: a prospective open cohort study

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Abstract

Background: In Ethiopia, in 2021, more than 80% of all newborn deaths were caused by preventable and treatable conditions. This study aimed to measure the incidence of adverse perinatal outcomes and risk factors among women with preeclampsia in the Sidama region of southern Ethiopia.

Methods: A prospective open cohort study was conducted from August 8, 2019 to October 1, 2020. We enrolled 363 women with pre-eclampsia and 367 normotensive women at ≥20 weeks of gestation and followed them until the 37th week. We then followed them until the seventh day after delivery up to the last perinatal outcome status was ascertained. A log-binomial logistic regression model was used to estimate the incidence of adverse perinatal outcomes and its risk factors among women with preeclampsia. Relative risk with a 95% confidence interval was reported. A p-value of <0.05 was considered statistically significant.

Results: There were 224 adverse perinatal outcomes observed in the 363 women with preeclampsia compared to 136 adverse perinatal outcomes in the 367 normotensive women (P<0.001). There were 23 early neonatal deaths in the preeclampsia group compared to 6 deaths in the normotensive group (P<0.001). There were 35 perinatal deaths in the preeclampsia group compared to 16 deaths in the normotensive group (P<0.05). Women with severe features of preeclampsia had a 46% [aRR: 1.46, 95%CI: 1.38–2.77] higher risk for adverse perinatal outcomes compared to women without severe features of preeclampsia.

Conclusions: In this study, more adverse perinatal outcomes occurred among women with preeclampsia after controlling for confounders. A higher perinatal outcome observed among women with preeclampsia, especially among women with severe features of preeclampsia, and those admitted to hospital at <34 weeks. This paper highlights the significantly elevated perinatal risks associated with pre-eclampsia, especially when it has severe features.

Keywords: Adverse Perinatal Outcome, Incidence, Preeclampsia, Risk factors, Ethiopia

What is already known on this topic?

- Studies conducted in Ethiopia on maternal and perinatal outcomes related to preeclampsia have not generated evidence that could be used by policymakers or implemented in clinical practices because of study design. Most studies did not include control groups or measure the risk of outcomes of interest and there were missing socio-demographic variables such as maternal education level. A study in southern Ethiopia aiming to estimate the risk of preeclampsia on adverse perinatal outcomes did not include exposures and outcomes.

What does this study add?

- There were 224 adverse perinatal outcomes observed in the 363 women with preeclampsia compared to 136 adverse perinatal outcomes in the 367 normotensive women (P<0.001).
- Women with severe features of preeclampsia had a 46% [aRR: 1.46, 95%CI: 1.38–2.77] higher risk for adverse perinatal outcomes compared to women without severe features of preeclampsia.
- Women without severe features of preeclampsia had a 39% [aRR: 1.39, 95%CI: 1.21–1.56] higher risk for adverse perinatal outcomes compared to women in the normotensive group.

How does this study use on research, practice or policy?

- This study provides epidemiological evidence for the incidence of adverse perinatal outcomes and risk factors among women with preeclampsia. Early detection and management of pre-eclampsia may improve maternal and infant outcomes. So, this could support clinical and public health practitioners to be aware of early signs and symptoms of preeclampsia. A cohort study should be conducted to evaluate other types of hypertensive disorders of pregnancy on the incidence of adverse perinatal outcomes and its risk factors among pregnant women.

Introduction

Preeclampsia and eclampsia are two of the most common hypertensive disorders of pregnancy (HDPs) (1). It is the second leading cause of direct maternal death and is directly responsible for 70,000 maternal deaths annually at the global level (2). In low-and middle-income countries (LMICs), 10–15% of direct maternal mortalities were associated with preeclampsia and eclampsia in 2018 (1). In Ethiopia in 2019, the pooled prevalence of maternal death was 4% (3).

In Ethiopia, in 2018, the overall pooled prevalence of HDPs was 6.07% (4). In the same study, a higher pooled prevalence of HDPs was observed in southern Ethiopia (10.13%), with the lowest prevalence observed in Addis Ababa, the capital city of Ethiopia (5.41%) (4).

Adverse perinatal outcomes include an overall <5 child mortality rate of 55 deaths per 1,000 live births, and neonatal mortality was 30 deaths per 1,000 live births (5) and the pooled prevalence of low birth weight was 17.3% (6) and stillbirths was 6.7% (7). A study conducted in northwest Ethiopia in 2021 found that the overall prevalence of adverse perinatal outcomes was 19.4% (8). According to a 2019 study in northwest Ethiopia, 46.5% of newborns delivered to women had unfavorable outcomes of severe preeclampsia and eclampsia, with 28.1% of those being stillbirths (9).

A number of factors account for high rates of adverse perinatal outcomes, including poor infrastructure, scarcity of supplies and skilled labor, a weak referral system, poor quality of care, and lack of timely obstetric care contributed to a higher proportion of adverse perinatal mortality in Ethiopia (10).

In Ethiopia, in 2021, more than 80% of all newborn deaths were caused by preventable and treatable conditions (11). However, the reduction of mortality is still a challenge. The government of Ethiopia has taken steps to strengthen engagement with key local and international sectors and stakeholders to address determinants of health (12). Ethiopia recently replaced the previous four-visit focused antenatal care (ANC) model with the new ANC eight-contacts model (12).

Studies conducted in Ethiopia have poor in generating evidence that could be used by policymakers and in clinical practices because they did not include control groups or measure the risk of outcomes of interest and did not include socio-demographic variables such as maternal

education status (9, 13, 14). A study in southern Ethiopia was limited in estimating the risk of preeclampsia on adverse perinatal outcomes because of poor ascertainment of exposures and outcomes using purposive sampling techniques (15). Another study in Ethiopia did not include a non-exposed group that would have been important to controlling confounders like the quality of perinatal care associated with morbidity and mortality (16). This study's findings will provide epidemiological evidence for policy makers and implementers to reduce adverse perinatal outcomes among women with preeclampsia and normotensive women. This paper highlights the significantly elevated perinatal risks associated with pre-eclampsia, especially when it has severe features. We aimed to measure the incidence of adverse perinatal outcomes and risk factors among women with preeclampsia in Sidama region of southern Ethiopia.

Methods

Study design and setting

A prospective open cohort study was conducted from August 8, 2019 to October 1, 2020 in the Sidama region of Ethiopia. In 2020, the population of the region was approximately 4 million. There were thirteen public hospitals, 138 health centers, and 540 health posts in the region that provided maternal, newborn, and child health services. In 2020, approximately 132,031 pregnant women attended ≥4 antenatal care visits (ANC) and 127,585 births were assisted by skilled birth attendants. Out of the 13 hospitals that are found in the region, we enrolled participants from seven of the hospitals, including Adare, Hawassa, Yirgalem, Hula, Bona, Chuko, and Daye hospitals.

Participants

The participants were women with preeclampsia and normotensive women who were enrolled at ≥20 weeks of gestation up until the 37th week. We followed them until the seventh day after delivery and waited for the last enrolled woman's perinatal outcome status to be ascertained. During the follow-up, 194 women with preeclampsia and normotensive women were admitted to the hospitals at <34 weeks of gestation, and 536 women with preeclampsia and normotensive women were admitted to the hospitals at 34–37weeks of gestation. During the follow-up, eight normotensive women developed preeclampsia. We, thus, included these eight women in the exposed group. Pregnant women with hypertension plus proteinuria, mild hypertension and evidence of organ dysfunction, severe hypertensive without proteinuria and evidence of organ

dysfunction were included in the study (17, 18). Pregnant women with preeclampsia and normotensive women were selected by health care providers: general medical practitioners, emergency surgical officers, or obstetricians/gynecologists during the follow-up.

Operational definitions

We ascertained exposure of interest supported by guidelines of the Obstetrics Management Protocol for Hospitals in Ethiopia in 2021 and on the recent International Society for the Study of Hypertension in Pregnancy (17, 18). Birth asphyxia was defined as the condition of a baby with trouble in breathing (gasping or breathing very irregularly or no breathing). Small for gestational age of pregnancy was defined as a birth weight of a newborn below the tenth percentile of weight distribution at the specified gestational age of pregnancy (19). Stillbirth refers to a baby born with no sign of life at or after 28 weeks of gestation. Preterm delivery was defined as the delivery of a baby before 37 weeks gestation. Low birth weight describes a baby with a birth weight of less than 2.5 kg. A low Apgar score refers to a newborn baby with an Apgar score of less than seven at 1 and 5 minutes.

Perinatal death was defined as a stillbirth or an early neonatal death. Early neonatal death is defined as the death of a live newborn in the first seven days of life. Intrauterine growth restriction of newborn is defined as birth weight and/or birth length below the 10th percentile for their gestational age and whose abdominal circumference was below the 2.5th percentile with pathologic restriction of fetal growth (19). Gestational age at admission was defined as the time when the women were enrolled in the study. Skilled birth attendant was defined as a professionally trained health worker having the essential midwifery skills to manage normal labor and delivery, recognize complications early and perform any essential intervention including early referral (17).

Sample size and sampling

The sample size was calculated using EPI INFO version 7. We considered the following assumptions for sample size calculations: early neonatal death (20), the ratio of exposed to unexposed group (1 to 1), the proportion of early neonatal death among women with preeclampsia (5%), and the proportion of early neonatal death among normotensive women (1%). The sample size was estimated to be 733 (366 women with preeclampsia and 367 normotensive women),

accounting for a design effect of two and 10% loss to follow-up. We also assumed a two-sided confidence level of 95% with a power of 80%.

A two-stage cluster sampling technique was used to recruit study participants. In the first stage, seven of the thirteen hospitals were selected using a simple random sampling technique. In the second stage, perinatal conditions were selected from women with preeclampsia and normotensive women using a simple random sampling technique.

Exposure ascertainments

We ascertained exposure of interest supported by guidelines of the Obstetrics Management Protocol for Hospitals in Ethiopia in 2021 and on the recent International Society for the Study of Hypertension in Pregnancy (17, 18). The main exposure variable in this study was preeclampsia with or without severity features. Preeclampsia with severe features was defined as the presence of one or more of the following conditions: blood pressure (BP) of ≥160mmHg systolic or ≥110mmHg diastolic, ≥3+protein on two urine samples taken four hours or more apart or 5gm of protein in a 24hr urine sample (18). Preeclampsia without severe features was defined as raised BP>140/90 mmHg plus 24-hour urine protein >300mg/24 hour or urine dipstick >+1 after 20 weeks of gestation in previously normotensive women (18). Normotensive women were pregnant women having a (BP)<140/90 mmHg with ≥20 weeks of gestation or who did not develop preeclampsia and proteinuria. Gestational age was calculated based on a woman's recall of her last menstrual period. However, an ultrasound scan was used for those women who could not remember their last menstrual period (18).

Outcome variable

Adverse-perinatal outcomes were defined as a newborn with the occurrence of at least one of the following outcomes: birth asphyxia, low birth weight, small for gestational age, preterm delivery, admission to the neonatal intensive care unit, and perinatal death.

Data collection

We validated the data collection tool before data collection (21). Two bilingual translators (speakers of both Sidamic and English languages), who were capable of translating the original tool in the English version into the Sidamic version, were selected. Translations into the Sidamic

language more accurately reflected the tones of the language. The translations were compared and discrepancies were noted during the translation process. The poorer wording choices were identified and resolved in a discussion between the translators.

The back translations were done by two experts of the source language (English). This was a validity checking process to ensure that the translated version reflected the same item content as the original version did. Face and content validation of the tool was done by a panel of experts (midwife experts, epidemiologists, and gynecologists). The panel of experts independently assessed the tool for readability, intelligibility, clarity, and ease of use. The internal consistency for each dimension was checked using Cronbach's alpha (Cronbach's alpha=0.98) (21).

In the first pilot test, conducted in a non-study area, all participants responded to all items in the data collection tool and marked them correctly. No missing items were found. Data collectors also reported no difficulty in asking the questions, and no participant reported having any problem understanding the items. The tool was tested for the second time two weeks after the first measurement. The two-week test-retest reliability result was shown to have a good correlation with reliable strategies to assess these point scores (Intraclass Correlation Coefficients (ICC) for agreement 0.78; $p< 0.001$) because the ICC value was found to be in the range of 0.75 to 0.9, indicating good reliability (22). We also specified the kind of ICC was calculated we used the two-way mixed-effects model for calculating ICC as the model of choice for test-retest reliability measure (21, 22).

Trained midwives conducted face-to-face interviews at antenatal care clinics using the pre-tested validated tool. A checklist was used to collect information from the maternal and neonatal records of women with preeclampsia and normotensive women in each hospital. We collected socio-demographic information and clinical and laboratory variables linked to maternal and perinatal outcome status. The data collection procedures were supervised by three Maternal and Child Health maternity and reproductive health professionals.

Outcome ascertainment

Adverse perinatal outcomes were ascertained by obstetricians/gynecologists and trained midwives. Client medical registration was also used to retrieve adverse perinatal outcome status. The

perinatal condition was determined at the follow-up appointment for those who were discharged, and a phone call was made for those who did not show up for this follow-up.

Statistical analysis

Data were cleaned, coded and analyzed using Stata 14. We identified outliers and missing values and checked data consistency using the original questionnaire for the responses using participants' code numbers. Mean and standard deviations were computed for continuous variables. Frequencies and percentages were computed for categorical variables. An incidence proportion of adverse perinatal outcomes was conducted on women who had preeclampsia and normotensive women. Cross tabulation was also performed to test the relationship of exposure variables with the outcome variable. A chi-squared test was used to compare categorical variables between women with preeclampsia and normotensive women.

Principal component analysis was computed and used for wealth index computation and was ranked in three groups as low, middle, and high. It was a composite measure of household cumulative living standard, and calculated by using data on household ownership of selected assets, like various household assets and means of transportation. Different items for urban and rural areas were computed separately. We included 21 items for rural residents and 16 items for urban residents. The suitability of data was computed by using Bartlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) measure of sample adequacy (23). The KMO >0.6 was used to confirm the sample adequacy for factor analysis (23).

A multivariable log-binomial logistic regression model was performed to identify the risk factors for adverse perinatal outcomes. According to Hosmer and Lemeshow, a variable with a P-value <0.25 was recommended as a screening criterion for the selection of candidate variables used in a multivariable log-binomial logistic regression model (24). This confirmed that insignificant variables from the first step were reanalyzed in later steps (24). Moreover, the candidate variables were also considered based on subject matter expertise, such as gynecologists, obstetricians, epidemiologists, and statisticians who were working as a supervisor, and who provided more subject matter expertise to improve the modeling process substantially. This insight from subject matter experts substantially improved the modeling process (24). A variable with <0.05 was used to identify statistically significant risk factors for adverse perinatal outcomes. Maternal age was

treated as a continuous variable and reported using the beta-coefficient with a 95% confidence interval.

We checked the multicollinearity among predictors using a variance inflation factor at a cutoff point of ten (25). We confirmed that there was no collinearity among predictors. The goodness of the fit was tested using the Hosmer-Lemeshow test (26). The predictor that was greater than the significance level (p-value >0.05) was accepted (26). This indicates that the observed model did not significantly differ from the expected model.

Ethical considerations

This study was reviewed and ethical approval was issued by the Institutional Review Board of the University of Gondar with R.No.O/V/P/RCS/044/2019 in March 2019. All participants signed an informed consent document before study participation began. Pregnant women having abnormal clinical and laboratory results were referred for treatment. Women with severe hypertension were provided with antihypertensive drugs; those with convulsions were given magnesium sulphate.

Results

Socio-demographic and economic characteristics of study participants

Of the 733 women eligible for this study, 730 were enrolled. Two (0.27%) of the participants were lost to follow-up. Of these two participants, one was from the preeclamptic group and one from the normotensive group. One participant refused to participate in the study. During the follow-up, eight normotensive women developed preeclampsia. We thus included these eight women in the exposed group (Figure 1).

The mean gestational age at the diagnosis of preeclampsia was 32.85 ± 3.25 weeks and that of normotensive women was (33.90± 2.75) weeks. The mean duration of follow-up of women with preeclampsia was 6.51± 3.15 weeks and that of normotensive women was 5.68± 2.97weeks (Figure 1).

The mean age of the women with preeclampsia was 25.42±4.76 years, and 24.6±4.48 years for the normotensive group. Nearly half of the women had preeclampsia (45.2%, 164/363) were attended

primary school education, compared to the normotensive group (39.5%, 145/367, P<0.05). A higher proportion of women with preeclampsia was observed (81%, 294/363) among women who resided in rural areas compared to urban residents (19%, 69/363), P<0.001) (Table 1).

Table 1: Socio-demographic and economic characteristics of women with preeclampsia and normotensive women in Sidama region, southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Women with preeclampsia (n=363)	Normotensive women (n=367)	Total (n=730)	P-value
Maternal age (in year)	25.42±4.76	24.6 ±4.48	25.02 ±4.64	
Maternal education				
No formal education	33(9.1)	16(4.3)	49(6.7)	
Primary education	164(45.2)	145(39.5)	309(42.3)	P<0.05
Secondary education	98(27)	110(30)	208(28.5)	
College/University	68(18.7)	96(26.2)	164(22.5)	
Husband education				
No formal education	15(4.1)	7(1.9)	22(3)	
Primary education	122(33.6)	87(23.7)	209(28.5)	P<0.05
Secondary education	99(27.3)	117(31.9)	216(29.6)	
College/University	127(35)	156(42.5)	283(38.8)	
Maternal occupation				
House wife	191(52.6)	163(44.4)	354(48.5)	
Merchant	70(19.3)	76(20.7)	146(20)	
Employed	64(17.6)	88(24)	152(20.8)	P>0.05
Student	23(6.3)	21(5.7)	44(6)	
Farmer	10(2.8)	10(2.7)	20(2.7)	
Daily laborer	5(1.4)	9(2.5)	14(1.9)	
Husband occupation				
Employed	116(32)	149(40.6)	265(36.3)	
Merchant	126(34.7)	136(37.1)	262(35.9)	
Farmer	75(20.7)	45(12.3)	120(16.4)	P<0.05
Daily laborer	31(8.5)	23(6.3)	54(7.4)	
Student	7(1.9)	10(2.7)	17(2.3)	
Unemployed	8(2.2)	4(1.1)	12(1.6)	
Place of residence				
Rural	294(81)	331(90.4)	104(14.3)	P<0.001
Urban	69(19)	35(9.6)	625(85.7)	
Wealth Index				
Low	157(43.3)	95(26)	252(34.6)	
Middle	105(28.9)	139(28)	244(33.5)	P<0.001
Rich	101(27.8)	132(36.1)	233(32)	

p-value <0.05 was considered statistically significant

Obstetric characteristics of women with preeclampsia and normotensive

Compared to the normotensive group (35.7%, 131/367), a higher proportion of women with preeclampsia (40.8%, 148/363, P<0.001) was observed in Yirgalem hospital. A higher proportion of twins was reported in the preeclampsia group (7.2%, 26/363) compared to the normotensive group (4.6%, 17/367, P>0.05). However, there was no significant difference between the two groups. A higher proportion of women with preeclampsia (28.4%, 103/363) was observed among women who were admitted at<34 weeks compared to the normotensive group (24.5%, 91/367, P<0.05) (Table 2).

Table 2: Obstetrics factors for women with preeclampsia and normotensive women in Sidama region, southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Women with preeclampsia (n=363)	Normotensive women(n=367)	Total (n=730)	P-value
Fetal sex				
Male	202(55.6)	195(53.1)	397(54.4)	P>0.05
Female	161(44.4)	172(46.9)	333(45.6)	
Number of neonates delivered				
Singleton	337(92.8)	350(95.4)	687(95.4)	
Twin	26(7.2)	17(4.6)	43(5.9)	P>0.05
Gravida				
1	46(12.7)	77(21)	123(16.8)	
2-3	253(69.7)	208(56.7)	461(63.2)	P>0.05
≥4	64(17.6)	82(22.3)	146(20)	
Parity				
Nullipara	12(3.3)	5(1.4)	17(2.3)	P>0.05
1	37(10.2)	94(25.6)	131(17.9)	
2-3	264(72.4)	222(60.5)	486(66.6)	
≥4	50(13.8)	46(12.5)	96(13.2)	
Interpregnancy Interval (IPI)				
<24 months (short (IPI)	8(2.2)	4(1.1)	12(1.6)	
24-59 months (optimal IPI)	180(49.6)	263(71.7)	443(60.7)	P<0.001
60+ months (long IPI)	115(31.7)	35(9.5)	150(20.5)	
Not applicable (prim)	60(16.5)	65(17.7)	125(17.1)	
Gestational age at admission (week)				
<34	103(28.4)	91(24.5)	194(26.6)	P<0.05
34-37	260(71.6)	276(75.5)	536(73.4)	

Maternal intensive care unit admission				
Yes	5(1.4)	1(0.3)	6(0.8)	P>0.05
No	358(98.6)	366(99.7)	724(99.2)	
Gestational age at delivery (week)				
Extremely preterm (<28)	10(2.8)	5(1.4)	15(2.1)	
Very preterm (28-32)	24(6.6)	1(0.3)	25(3.4)	P<0.001
Moderate to late preterm (32-37)	123(33.9)	67(18.3)	190(26)	
Term+(≥37)	206(56.7)	294(80)	500(68.5)	
Hospitals				
Adare general hospital	60(16.5)	109(29.7)	169(23.2)	
Hawassa referral hospital	53(14.6)	47(12.8)	100(13.7)	
Yirgalem general hospital	148(40.8)	131(35.7)	279(38.2)	P<0.001
Hula primary hospital	7(1.9)	7(1.4)	12(1.6)	
Bona general hospital	51(14)	29(7.9)	80(11)	
Chuko primary hospital	11(3)	6(1.6)	17(2.3)	
Daye primary hospital	33(9.1)	40(10.9)	73(10)	

p-value <0.05 was considered statistically significant

Incidence of adverse perinatal outcomes women with preeclampsia

There were 224 adverse perinatal outcomes observed in the 363 preeclampsia women compared to 136 adverse perinatal outcomes in the 367 normotensive women (P<0.001). There were 23 early neonatal deaths reported in the preeclampsia group compared to 6 deaths in the normotensive group (P<0.001). Also, there were 96 preterm births observed in the preeclampsia group compared to 17 preterm births in the normotensive group (P<0.001). There were 35 perinatal deaths reported in the preeclampsia group compared to 16 deaths in the normotensive group (P<0.05) (Table 3).

Table 3: Neonatal outcomes among women with preeclampsia and normotensive women in Sidama region southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Women with preeclampsia (n=363)	Normotensive women(n=367)	Total (n=730)	P-value
Birth weight of neonate (gram)				
<1500	33(9.1)	6(1.6)	39(5.3)	
1500-2499	103(28.4)	31(8.4)	134(18.4)	P<0.001
2500-3999	211(58.1)	302(82.3)	513(70.3)	
≥4000	16(4.4)	28(7.6)	44(6)	
Apgar score <7 at 1 minutes	64(17.6)	52(14.2)	116(15.9)	P<0.05
Apgar score <7 at 5 minutes	62(17.1)	54(14.7)	116(15.9)	P>0.05
Intrauterine growth restriction	22(6.1)	4(1.1)	26(3.6)	P<0.001
Still birth	21(5.8)	11(3)	32(4.4)	P<0.05

Early neonatal death	23(6.3)	6(1.6)	29(4)	P<0.001
Preterm birth	96(26.4)	17(4.6)	113(15.5)	P<0.001
Perinatal death	35(9.6)	16(3.8)	49(6.7)	P<0.05
Low birth weight	98(27)	73(19.9)	171(23.4)	P<0.05
Small for gestational age	66(18.2)	30(8.2)	96(13.2)	P<0.001
Birth asphyxia	39(10.7)	15(4.1)	54(7.4)	P<0.05
Admission to ¶¶NICU	88(24.2)	39(10.6)	127(17.4)	P<0.001
Adverse perinatal outcomes	224(61.7)	136(37.1)	360(49.3)	P<0.001

¶¶NICU=Neonatal Intensive Care Unit, p-value <0.05 was considered statistically significant

Women with or without severity features of preeclampsia on adverse perinatal outcomes and other risk factors

In the bivariable log-binomial logistic regression model, the following variables were identified as candidate variables for multivariable log-binomial logistic regression analysis: maternal age, maternal and husband's education, maternal and husband's occupation, parity, gravidity, wealth index, women without severe features of preeclampsia, mode of delivery, women with severe features of preeclampsia, maternal ICU admission, systolic and diastolic blood pressure.

After controlling for confounders, we identified significant risk factors for adverse perinatal outcomes as women with severe features of preeclampsia, those admitted to hospital at <34 weeks, women without severe features of preeclampsia, maternal age, women with no formal education or with only primary school education, and women with high systolic blood pressure.

Women with severe feature of preeclampsia had a 46% [aRR: 1.46, 95%CI: 1.38–2.77] higher risk for adverse perinatal outcomes compared to women without severe features of preeclampsia. Women without severe features of preeclampsia had a 39% [aRR: 1.39, 95%CI: 1.21–1.56] higher risk for adverse perinatal outcomes compared to women in the normotensive group. Maternal age was found to have a significantly higher risk on adverse perinatal outcomes of women with preeclampsia [β=1.9, 95% CI: 1.5–3.3] compared to normotensive women, while other factors were kept constant. Women who were admitted to the hospital at <34weeks had a 15% (aRR: 1.15, 95% CI: 1.03–1.28) higher risk for adverse perinatal outcomes compared to women who were admitted between 34–37 weeks (Table 4).

Table 4: A multivariable log-binomial logistic regression model for risk factors for adverse perinatal outcomes among women with preeclampsia in Sidama region southern Ethiopia from August 8, 2019, to October 1, 2020

Variables	Adverse perinatal outcomes		Unadjusted RR* (95%CI)	Adjusted RR (95%CI†)
	Yes (n=360)	No (n=370)		
Maternal age (in year)	25.42±4.76	24.6 ±4.48	2.2**[1.8–3.9]	1.9*[1.5–3.3]
Parity				
Nullipara	11(64.7)	6(35.3)	0.94[0.64–1.78]	0.86[0.65– 1.78]
1	139(43.7)	179(56.3)	0.68***[0.57–0.80]	0.86[0.60–1.22]
2-3	148(51.7)	138(48.3)	0.83*[0.70–0.97]	0.93[0.72–1.19]
≥4	62(56.9)	47(43.1)	1	1
Maternal education				
No formal education	32(63.3)	17(34.7)	1.52**[1.19–1.93]	1.41**[1.14– 1.73]
Primary education	175(56.6)	134(43.4)	1.30**[1.08–1.57]	1.22*[1.06– 1.46]
Secondary education	84(40.4)	124(59.6)	0.99[0.79–1.23]	0.56[0.44–1.25]
College/university	69(42.1)	95(57.9)	1	1
Husband education				
No formal education	17(77.3)	5(22.7)	1	1
Primary education	123(58.9)	86(41.1)	0.76*[0.59– 0.98]	0.92(0.76–1.97)
Secondary education	105(48.6)	111(51.4)	0.62**[0.48– 0.81]	0.83(0.67–1.04)
College/University	115(40.6)	168(59.4)	0.52***[0.40–0.68]	0.74[0.57–2.97]
Wealth index				
Low	176(69.6)	77(30.4)	1.77***[1.48–2.12]	1.72[0.44–2.06]
Middle	98(40.2)	146(59.8)	1.03[0.83–1.29]	1.02[0.82–1.28]
Rich	86(36.9)	147(63.1)	1	1
Gravidity				
1	127(42.6)	171(57.4)	0.81[0.91– 1.96]	0.84 [0.72–1.97]
2-3	154(52.4)	140(47.6)	0.96[0.80–1.15]	0.95[0.81–1.11]
≥4	79(57.2)	59(42.8)	1	1
Mode of delivery				
Spontaneous vaginal delivery	205(51.5)	193(48.5)	0.89[0.77–1.04]	0.12[0.78–1.16]
Cesarean section	143(46.3)	166(53.7)	1.01[0.67–1.561]	1.32[0.85–2.34]
Vacuum assisted delivery	12(52.2)	11(47.8)	1	1
Gestational age at admission (week)				
<34	113(58.2)	81(41.8)	1.11[0.97–1.28]	1.15*[1.03–1.28]
34-47	247(46.1)	289(53.9)	1	1
Maternal ICU admission				
Yes	4(80)	1(20)	1.67**[1.16– 2.41]	1.22[0.75– 3.19]
No	356(49.1)	369(50.9)	1	1
Women without severe feature of preeclampsia				
Yes	159(66.8)	79(33.2)	1.67***[1.39–1.93]	1.39***[1.21–1.56]
No	201(40.9)	291(59.1)	1	1

Women with severe feature of preeclampsia				
Yes	99(79.2)	26(20.8)	1.58***[1.25–1.85]	1.46***[1.38–2.77]
No	261(43.1)	344(56.9)	1	1
Eclampsia				
Yes	32(82.1)	7(17.9)	1.61***[1.38–1.92]	1.34[0.41–1.83]
No	328(47.5)	363(52.5)	1	1
Systolic blood pressure (mmHg)				
<140	136(37.1)	231(62.9)	1	1
140-159	162(62.3)	98(37.7)	1.55***[1.35–1.85]	1.37***[1.19–1.59]
≥160	62(60.2)	41(39.8)	1.60***[1.33–1.92]	1.34**[1.13– 1.58]
Diastolic blood pressure(mmHg)				
<90	136(37.1)	231(62.9)	1	1
90-109	180(62.3)	109(37.7)	1.68***[1.43–1.97]	1.12[0.21–2.03]
≥110	44(59.5)	30(40.5)	1.60***[1.27–2.02]	1.43[0.96–2.43]
Magnesium sulfate treatment				
Yes	74(43.8)	95(56.2)	0.65***[0.57–0.74]	0.56[0.36–1.23]
No	286(51)	275(49)	1	1
Antihypertensive drug treatment				
Yes	124(33.5)	178(49.4)	0.64***[0.56–0.73]	0.84[0.40– 1.75]
No	246(66.5)	182(50.6)	1	1
Dexamethasone treatment				
Yes	56(48.7)	59(51.3)	0.54[0.34–1.81]	0.45[0.23–1.98]
No	304(49.4)	311(50.6)	1	1

*RR=Relative Risk, † CI = Confidence Interval, *p-value <0.05, **p-value <0.001, ***p-value <0.0001

Discussion

In this study, more adverse perinatal outcomes occurred among women with preeclampsia compared to normotensive women after controlling for confounders. Perinatal death, stillbirth, small for gestational age, preterm birth, birth asphyxia, and low birth weight were higher in the preeclampsia group compared to the normotensive group. We identified significant risk factors for adverse perinatal outcomes such as women with severe feature of preeclampsia and women who were admitted to the hospital at <34 weeks.

A higher adverse perinatal outcome was observed in the preeclampsia group compared to the normotensive group. This finding was similar to another study conducted in southwest Ethiopia in 2021, which found that a higher rate of adverse perinatal outcomes was observed among women with HDPs (64.1%) compared to normotensive women (32.8%) (27). This finding was lower than the finding of a study conducted in Tigray Ethiopia in 2020 (66.4% versus 22.2%) (20). A

reduction in the utilization gaps of ANC practice is needed to end preventable deaths of newborns (28). Women who had not had ANC attendance were three times more likely to have unfavorable perinatal outcomes as compared to women who had attended antenatal care (14).

A higher perinatal death rate was reported in the preeclampsia group compared to the normotensive group. This finding was consistent with another study conducted in southwest Ethiopia in 2021, which found that a higher perinatal death rate occurred in women with HDPs (21.2%) compared to normotensive women (6.2%) (27). This finding of the current study was also lower than a study conducted in Ethiopia in 2020 (15.0% versus 2.5%) (20). Women who attended at least one ANC were found to have a 58% lower risk of perinatal mortality as compared to women who did not receive any ANC follow-up in Ethiopia (29).

A higher stillbirth rate was observed in the preeclampsia group compared to the normotensive group. This finding was slightly lower than the findings of another study conducted in Ghana in 2015, which found that a higher stillbirth rate was observed among women with preeclampsia (6.2%) compared to normotensive women (1.3%) (30). Similarly, this finding was lower than the finding of a study conducted in Multicounty survey in 2014 (6.4% versus 1.9%) (31). Women who attended at least one ANC session were found to have a 66% lower risk of stillbirth rate as compared to mothers who did not receive any ANC follow-up in Ethiopia (29).

A higher small for gestational age rate was observed in the preeclampsia group compared to the normotensive group. This finding was higher than another study conducted in Ghana in 2015, that found that a small for gestational age rate was observed among more women with preeclampsia (14.3%) compared to normotensive women (2.3%) (30) and in Southwest Ethiopia in 2021 (9.3% versus 2.3%) (27). This finding was lower than the finding of another study conducted in Ethiopia in 2020 (36.7% versus 10.7%) (20). Early detection and management of pre-eclampsia may reduce small for gestational age rate among newborns.

A higher preterm birth rate was observed in the preeclampsia group compared to the normotensive group. This finding was lower than a study conducted in Ethiopia, which found that a higher preterm birth rate was observed among women with pregnancy-induced hypertension (PIH) (40.8%) compared to normotensive women (5.6%) (20). This finding was also lower than the findings of a study conducted in southwest Ethiopia in 2021 (39.4% versus 10.6%) (27).

Furthermore, this finding was slightly lower than a study conducted in Haiti in 2019 (27.9% versus 9.9%) (32). The difference in incidence of preterm birth across the studies might be due to the difference in quality of antenatal care services and the difference in guidelines used for the management of preeclampsia.

A higher birth asphyxia rate was reported in the preeclampsia group compared to the normotensive group. This finding was higher than the finding of another study conducted in Ethiopia in 2020, particularly in the Tigray region, which found that the birth asphyxia rate was higher among women with PIH (39.6%) compared to normotensive women (10.9%) (20). This finding was slightly higher than the birth asphyxia rate reported (10.7%), compared with the study conducted in North West Ethiopia in 2018 (10.1%) (9). Monitoring the fetus for signs of asphyxia, usually by assessing the fetal heart rate either during prenatal care for fetuses at risk or during labor, can determine which fetuses are at risk of stillbirth (33).

A higher low birth weight rate was observed in the preeclampsia group compared to the normotensive group. This finding was higher than findings of the Multicounty Survey in 2014, which found that a higher low birth weight rate was reported among women with preeclampsia (26.1%) compared to normotensive women (9.4%) (31) and a study conducted in southwestern Ethiopia in 2021, which found that a higher low birth weight rate was observed among women with HDP (39.8% versus 12.7%) (27). This finding was lower than the findings of another study conducted in Ghana in 2015 (46.2% versus 6.8%) (30). One study in Ethiopia found that women who did not attend ANC follow-up were three times more likely to deliver low birth weight babies compared to those who had at least one ANC follow-up (34).

Women with severe features of preeclampsia had a higher risk for adverse perinatal outcomes compared to women without severe features of preeclampsia. A study from Brazil in 2018 found that in terms of preeclampsia with severity, severe preeclampsia was associated with birth weight <2,500gram in 59% of cases, and mild PE was associated with birth weight ≥ 2,500 gram in 85.5% of cases (1). In 2015, one study from India found that those women with severe pre-eclampsia had a higher perinatal mortality when compared to those with mild pre-eclampsia (35).

Women who were admitted to a hospital at<34 weeks had a higher risk of adverse perinatal outcomes compared to women who were admitted between 34–37weeks. This finding was similar to another study conducted in Ethiopia in 2020 that patients with early onset of preeclampsia

without severe feature were 25.9 times more likely to develop perinatal complication as compared to late-onset preeclampsia after 34 weeks (16). These increased perinatal complications might be explained by the progression of preeclampsia to severe diseases in those women who developed preeclampsia before 34 weeks, which is associated with high preterm birth (36).

Limitations of the study

One limitation could be recall bias linked to gestational age, which was calculated based on the women's recall of their last menstrual period. However, women who could not remember the approximate gestational age were given an ultrasound scan. Social desirability could have been present because data were collected in face-to-face interviews, which could have led to socially acceptable answers. This study is not generalizable as it was limited to one region of the country, and it was limited to women who received hospital care. It also only measured short-term morbidity in infants, so it did not assess the risk of pre-eclampsia on later mortality, growth, neurodevelopment or other important health outcomes. one strength that could be linked to this study was based on a prospective cohort, which minimized the risk of selection and recall bias.

Conclusion

In this study, more adverse perinatal outcomes occurred among women with preeclampsia after controlling for confounders. Early detection and management of pre-eclampsia may improve maternal and infant outcomes. We identified significant risk factors for adverse perinatal outcomes as women with severe features of preeclampsia, those admitted to hospital at <34 weeks, women without severe features of preeclampsia, maternal age, women with no formal education or with only primary school education, and women with high systolic blood pressure. This paper highlights the significantly elevated perinatal risks associated with pre-eclampsia, especially when it has severe features.

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Author's contributions: This study was carried outby all authors collaboratively. BJ, MA and KA contributed to conceptualizing and designing the study, curating and analyzing data, and

writing the first draft. Also, BJ, MA, TA, and KA managed the investigation, literature searches, methodology review, writing, and contributed to data collection; BJ, MA, TA, and KA contributed to the manuscript review, resource, preparation, and editing. All the authors have read and agreed to the final manuscript.

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Availability of data and materials: The data that support the findings of this study is available from the corresponding author upon reasonable request in the form of STATA Version 14.

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List of figure

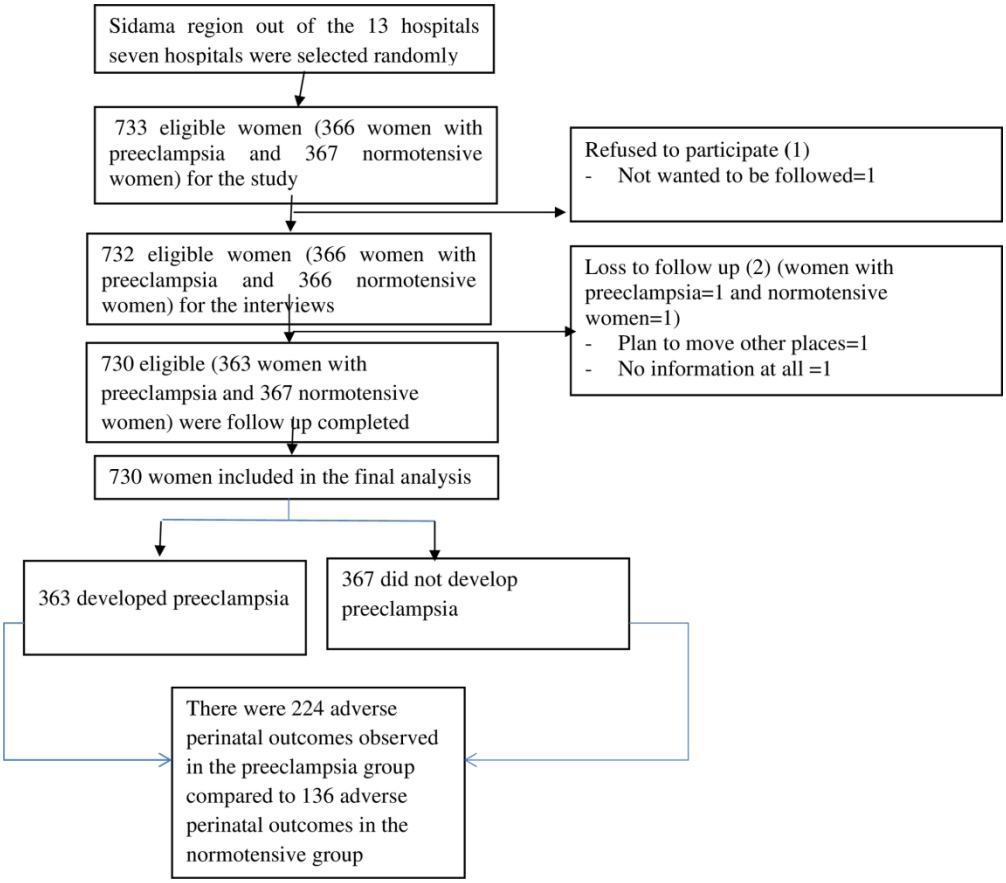

Figure 1: Flow-diagram of the overall study process in Sidama region, southern Ethiopia, August 8, 2019, to October 1, 2020

190x166mm (300 x 300 DPI)