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Determinants of pre-eclampsia among pregnant women attending perinatal care in hospitals of the Omo district, Southern Ethiopia

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Abstract

Pre-eclampsia is estimated to cause 70 000 maternal death globally every year, with the majority of deaths in low- and middle-income countries. In Ethiopia, pre-eclampsia causes 16% of direct maternal deaths. Despite the high burden of disease, pre-eclampsia remains poorly studied in low and middle-income countries. In this study, we aimed to identify risk factors for pre-eclampsia in pregnant women attending hospitals in the Omo district of Southern Ethiopia. Data were collected via face-to-face interviews. Logistic regression analysis was computed to examine the relationship between the independent variable and pre-eclampsia. An adjusted odds ratio (AOR) with the corresponding 95% confidence interval (CI) excluding 1 in the multivariable analysis was considered to identify factors associated with pre-eclampsia at a p-value of <0.05. A total of 167 cases and 352 controls were included. Factors that were found to have a statistically significant association with pre-eclampsia were primary relatives who had a history of chronic hypertension (AOR 2.1, 95% CI: 1.06-4.21), family history of diabetes mellitus (AOR 2.35; 95% CI: 1.07-5.20), preterm gestation (AOR = 1.56, 95% CI: 1.05-2.32), and pre-conception smoking exposure (AOR = 4.16, 95% CI: 1.1-15.4). The study identified that a family history of chronic illnesses and diabetes mellitus, preterm gestation, and smoking exposure before conception were the risk factors for pre-eclampsia. Presumably, addressing the identified risk factors may give further insight into where interventions and resources should be focused, as well as having an understanding of the burden of disease.

1 | BACKGROUND

According to the classification of The International Society for the Study of Hypertension in Pregnancy (ISSPH), pre-eclampsia is gestational hypertension accompanied by proteinuria at or after 20 weeks of gestation.[1] World Health organization estimates the occurrence of pre-eclampsia to be seven time higher in low-income countries (2.8%) than the high-income counties (0.4%).[2] The global prevalence of pre-eclampsia ranges from 2.7% to 8.2% of pregnancies.[3] Its prevalence in the sub-Sarahran African countries was 5.6%.[4] A

study from Ethiopia indicated that the prevalence in Ethiopia is 5% to 12%.[5] In low-income countries, especially in sub-Saharan African countries, under-reporting influences the preventive measure to lower the burden of the disease.[6]

Nevertheless, the pathogenesis of different pre-eclampsia phenotypes has not been completely elucidated.[7] Research indicates that women who develop pre-eclampsia at earlier gestation exhibit impaired endothelial function.[8] If detection is delayed, its progress into a multi-organ dysfunction is more evident.[9] In women with severe pre-eclampsia, the risk of fetal morbidity and mortality was found to be high; indeed, it was the major cause of stillbirth and early neonatal death.[10] In Ethiopia, pre-eclampsia alone attributes 16% of pregnancy-related deaths. A report revealed an increasing trend of maternal morbidity and mortality due to pre-eclampsia.[11] Besides, pre-eclampsia has healthcare-related outcomes. For instance, women who have pre-eclampsia are at increased risk of chronic illness later in life.[12]

The common factors that have been suggested to increase the risk of pre-eclampsia among women include pre-existing chronic illnesses, excessive weight gain, primiparity, advanced maternal age, first or second-degree relatives with a history of pre-eclampsia, and other environmental genetic-related factors.[13] However, there is no single excellent factor to predict pre-eclampsia.[14,15] Understanding risk factors and prognostic factors for pre-eclampsia in low/middle-income settings is an important area of research as factors may differ from high-income settings. Highlighting the factors could have a role in reducing the burden of perinatal complications. But, published work of literatures emphasizing the determinants of pre-eclampsia in Ethiopia is scarce. Therefore, this study aimed to identify the risk factors for pre-eclampsia in pregnant women attending hospitals in the Omo district of Southern Ethiopia.

2 | METHODS

2.1 | Study area and period

A facility-based unmatched case–control study design was conducted in Omo districts in six public hospitals from February to August 2018. Based on the national 2007 census, the district houses an estimated total population of more than five and a half million.[16] The source population for this study was all women attending labor and delivery services in Arbaminch General, Konso district, Sawla district, Chencha district, Jinka General, and Gidole district hospitals. Data were collected from randomly selected pregnant women attending antenatal and delivery in all hospitals.

2.2 | Inclusion criteria

To make the study comparable, women who reviewed perinatal service in Omo district hospitals and confer informed consent were included.

TABLE 1 Diagnostic criteria used for the study on determinants of pre-eclampsia among women attending hospitals in Omo district, Southern Ethiopia, 2018

Diagnostic criteria for pre-eclampsia[19]
The onset of symptoms after 20 weeks' gestation with remission by 6-12 weeks postpartum[a]
Pre-eclampsia:
Hypertension (systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg), may be superimposed on chronic hypertension
Proteinuria (proteinuria ≥ 300 mg/24 h, or significant increase from baseline)
Severe pre-eclampsia if one or more of the following:
Sustained systolic blood pressure (SBP) ≥160 mmHg or diastolic blood pressure (DPB)≥ 110 mmHg (measured twice at sitting and left lateral position, at least 6 h apart)
Evidence of other end-organ damage
Deteriorating renal function including nephrotic range proteinuria ≥ 3 g/24 h or 3 + on urine dipstick or sudden oliguria, especially with elevated creatinine[b]
Central nervous system (CNS) disturbance (altered vision, headache)
Pulmonary edema (3% of patients)
Liver dysfunction
Epigastric/right upper quadrant pain (stretching of hepatic capsule)
Thrombocytopenia (15%–30% of patients)
HELLP syndrome is characterized by hemolysis elevated liver enzymes and low platelet count which may occur without proteinuria
Evidence of fetal compromise (intrauterine growth restriction-IUGR, oligohydramnios, non-reasoning fetal testing)

Cases were defined in two alternative ways. First, when a woman was confirmed to have an elevated blood pressure of 140/90 mmHg, measured at rest sitting and left lateral position or 5 min after arrival, was detected at least 4-6 h apart.[2] Plus, a urine dipstick value of 2 + proteinuria and/or two random urine concentrations of 100 mg/dl collected 4 h apart after 20 completed weeks of gestation in a previously normotensive client,[17] (Table 1).

Second, if the urine dipstick value became negative, the data collector also asked for the presence of severity signs. Women with elevated blood pressure and having one of the following symptoms (severe fronto-occipital headache unresponsive to antipain, right upper quadrant tenderness, epigastric pain, oliguria, upper extremity edema, facial edema, and blurring of vision) were used as an alternative to diagnose pre-eclampsia. Only if it was confirmed by a physician. For new cases, the data collector had observed for proper measurement of blood pressure. Participants in the labor and delivery ward, it was measured on the right arm, with the patient lying on her side at an estimated 45° to the horizontal. In the antenatal room, a measurement was taken on a sitting position. In either case, the brachial artery was kept at the level of the heart. Blood pressure was taken five minutes with an appropriate sized cuff. The functionality of the blood pressure cuff was observed every time before the start of measurement. General practitioners had given the responsibility
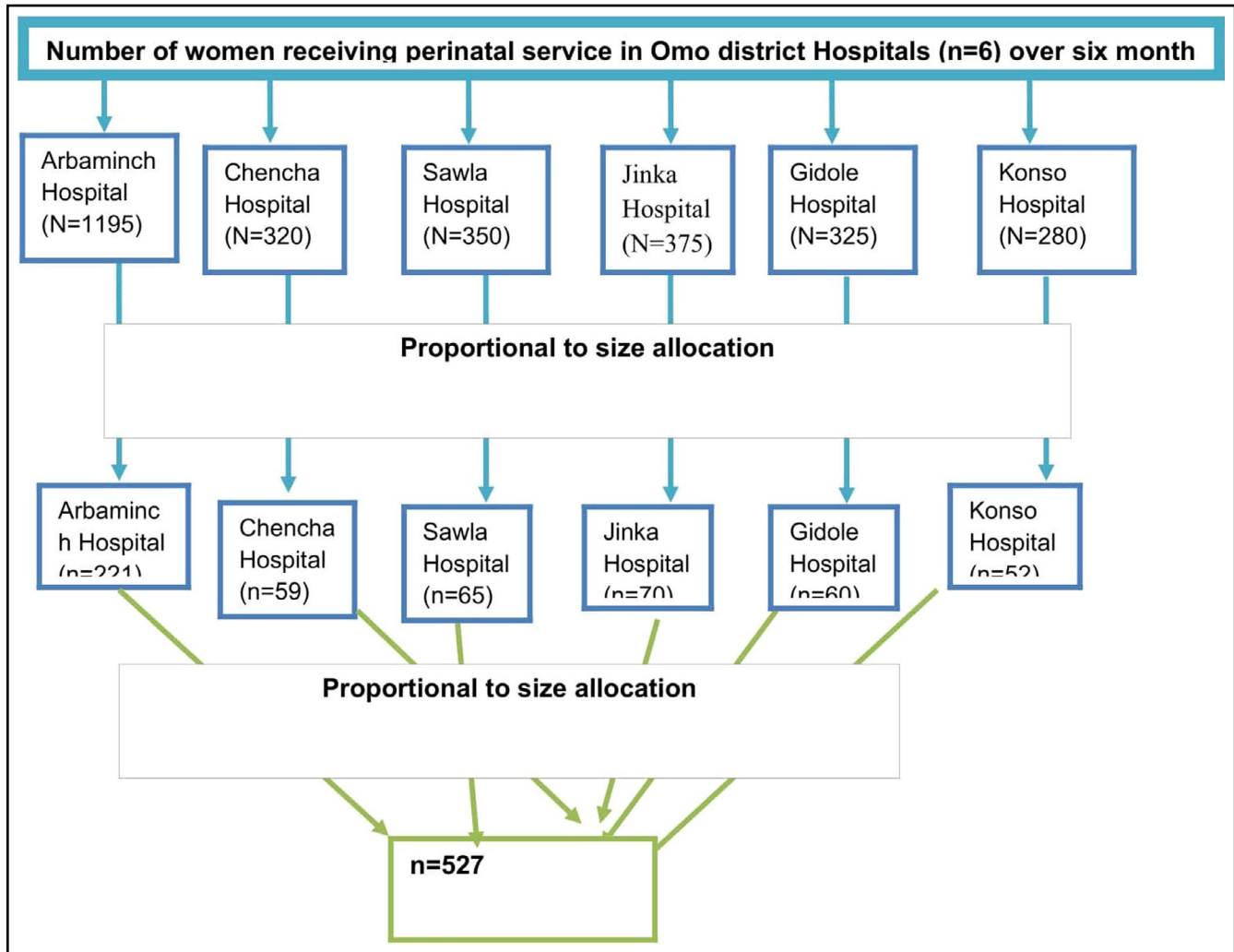
FIGURE 1 Pictorial presentation of women enrolled for a case–control study on determinants of pre-eclampsia among pregnant women, Omo district hospitals, southern Ethiopia [Color figure can be viewed at wileyonlinelibrary.com]

to make sure the cuff reading was at the level of 0 mmHg. During measurement, the lower border of the cuff was taped up two to three centimeters above the elbow line. The systolic blood pressure was taken as pressure when the first two heart sounds were heard and detected. Whereas the diastolic blood pressure was measured at the point of the fifth Korotkoff sound or disappearance sound to the nearest whole number. The diagnostic value was the average of more than two measurements taken 6 h apart (using different parameters such as checking the functionality of the blood pressure apparatus, the tightness of the cuff comfortably over the study participant's arm, the lower edge of the cuff was 2-3 cm above the elbow line, and whether the patient's arm was at the level of the heart.

Controls were a woman with other cases after 20 completed weeks of gestation and who were not diagnosed with pre-eclampsia. All cases and controls were observed by the physician in the hospitals.

2.3 | Sample size determination

Epi-Info version 7.2 was used to compute the sample size using the double population proportion formula by assuming student occupation as a risk factor with an odds ratio of 2.65% and 5.79% among controls and exposed from the literature reviewed.[18] With corresponding assumptions of the 95% confidence interval, 5% marginal error, and 80% power, the calculated sample size was 494. Considering 5% possible non-respondents, the final sample size of 519 (167 cases and 352 controls) was estimated.

2.4 | Sampling techniques and procedures

All hospitals in Omo district, such as Konso primary Hospital, Arbaminch, and Jinka General Hospitals, Chencha, Gidole, and Sawla District Hospitals, were selected purposely because of a small

number of cases. For each identified hospitals, proportional to size allocation based on previous year hospital reports in a similar period of the study was considered to estimate the target population. However, due to the limited number of cases, all women who fulfilled the inclusion criteria were taken to be compared with systematically addressed controls.

According to the 2017 annual report, the average number of women who had attended perinatal service per month was 478, 128, 150, 130, 112, and 140 in Arbaminch General Hospital, Chencha General Hospital, Jinka Hospital, Gidole Hospital, Konso Hospital, and Sawla hospitals, respectively, (Figure 1). Considering the average number of pregnant women attending perinatal service per day in each hospital, control were selected using a systematic random sampling technique immediately.

2.5 | Data collection procedure

Data were collected using a pre-tested, structured, and interview administered questionnaire. Besides, patient cards were also reviewed further for the variables listed in the diagnostic criteria and to extract laboratory investigation results. The questionnaire encompasses different parts of questions related to sociodemographic variables, obstetric, medical, and behavioral-related variables. All the aforementioned variables were adopted by referring to different scholarly articles.[19-23] The questionnaires were prepared in English, translated into Amharic (Federal Government Working Language), and then translated back to English by a language expert to keep uniformity. Twelve fluent Amharic speaking Bachelor degree midwives from the health center of each town were used as data collectors. Upon arrival at the data collection site, the enumerator identified the case from antenatal and delivery booking. Then, it was cross-checked for the assurance of the diagnosis by the duty physician. The data collector also had a duty to crosscheck the diagnosis with the case definition used for this study, particularly for newly diagnosed ones.

Data were collected after the women stabilized (within 4-6 h of childbirth) and comfortable to respond. Six general practitioners (medical doctors) had supervised the data collection process. The principal investigator coordinated the data collection team and give the necessary support. After the pre-test, the questionnaire was corrected for illogically ordered and some ambiguous and miss-leading terminologies.

2.6 | Data quality assurance

Data collectors were trained on the purpose of the study, selection of exposed and unexposed, how to keep confidentiality of patient information, the contents of the questionnaire, and data quality management by the principal investigators. The training was based on the guide that was developed for clarifying the interview administered questionnaires.

Throughout data collection, the supervisors checked the questionnaire for completeness, clarity, and consistency daily. The data collectors were oriented to correct missing data before the discharge of the patient from the hospital. Fully completed data with a few missing items were coded and duly reported to the investigator. The reliability coefficient of the tool was checked and it was 0.76. Data were entered by a trained and experienced clerk on a priory created Epi-info template.

2.7 | Data management, analysis, and interpretation

The collected data were cleaned, coded, and entered into Epi-Info version 7.2 and exported to SPSS version 26.0 for further analysis. The frequency was checked to see the accuracy, consistency, variables, and missed values. Descriptive statistics were computed and used to describe the study population using tables compared between cases and controls.

Binary and multivariable logistic regression models were fitted to identify the association between explanatory and outcome variables. In model one, we want to see if there is a difference in the outputs of multivariable logistic regression when the model is controlled for gestational age. This is based on the hypothesis that gestational age and pre-eclampsia are inversely related, where the probability of pre-eclampsia is more as gestational age close to 20 weeks. In the second model, the gestational age was included. Variables with a p-value of <0.20, biological plausibility, and previous study findings were considered for inclusion in the multivariable logistic regression analysis where confounders can be controlled. Multi-collinearity was checked among independent variables using a variance inflation factor.

The necessary assumptions of logistic regression were made by checking Hosmer and Lemeshow goodness of fit test statistics. Variables with a p-value of <0.05 in the multivariable logistic regression analysis were considered as a statistically significant determinant. The adjusted odds ratio (AOR) with the 95% confidence interval (CI) was calculated to measure the strength of the association between the explanatory variables and the outcome variable.

3 | RESULTS

3.1 | Sociodemographic characteristics of the study participants

A total of 527 women were enrolled. Nine of the items had missed important variables, this gives a response rate of 98.3%. The mean age of the cases was 25 years with SD (±5.5). The majority of 110 (65.9%) of cases were between 20 and 34 years of age, followed by 45 (26.9%) of cases whose ages < 20 years. The majority of 236 (67.3%) of the control groups fell in these age groups. More than 161 (96%) and 234 (66%) cases and controls were married. Regarding

educational status, the majority of the cases (28.14%) and 30.2% of controls had completed primary education. Nearly, one-fourth of cases (28.1%) and 25.3% of controls had higher education. Ninety-three 55.7% of cases were housewives compared with one hundred eighty controls, on which they had a similar role (Table 2).

3.2 | Personal and family history-related characteristics

In this study, approximately 24% of cases had a family history of chronic hypertension compared with 16.8% of controls. Regarding the family history of diabetes mellitus, cases and controls had only a 3% difference, where 7.2% (12) and 10% (32) of the cases and controls had a family history of diabetes mellitus, respectively. On the other hand, the difference in the percentage of the personal history of diabetes mellitus during the last pregnancy in both cases and controls was not significant. Approximately 7% and 5% of cases and controls had diabetes mellitus during the last pregnancy, respectively. Similarly, the proportion of cases who had asthma during their last pregnancy had a 2.1 difference. Regarding the personal history of severe pre-eclampsia or eclampsia, 24 (14.4%) were accounted for cases while 34 (9.7%) of the controls had symptoms due to the preceding confirmed diagnosis of pre-eclampsia (Table 3).

3.3 | Reproductive-related characteristics

More than half (50.3%) of the cases had a history of pregnancy twice comparable to 57.3% of controls. The difference in the proportion of cases and controls was equivalent to 1%. Most of the 68.9% of cases and 57.8% of the controls had preterm birth before the data collection period. The number of having had ANC follow-up at least ones during the last pregnancy was 31.7% among cases with new ANC follow-up, while it became 34.5% in controls (Table 4).

3.4 | Behavioral- and nutritional-related characteristics

It was indicated that the percentage of cases who had a history of smoking before conception was 4.2%. Concerning alcohol intake during pregnancy, 48 (28.7%) of cases and 89 (25.4%) controls had consumed at least once. The majority (110 [65.9%] of cases and 239 [68.1%] of controls had taken a cup of coffee during their course of pregnancy at least. More than 92% of both cases and controls had a habit of snack fruit while they were pregnant. Similarly, 158 (94.6%) cases and 342 (97.4%) controls were taken as green leafy vegetables at least once during their pregnancy. A habit to have non-strenuous physical exercise during pregnancy was responded, 83 (49.7%) of cases, and 174 (49.6%) controls were engaged in non-strenuous physical exercise during pregnancy.

3.5 | Determinants of pre-eclampsia identified

The degree of relatives with a history of diabetes mellitus, gravidity, and seasonality was not incorporated in the multivariable analysis due to collinearity. In model one, a family history of hypertension, women with a history of smoking before pregnancy, and a family history of diabetes were variables that found to have a significant statistical association with pre-eclampsia. However, marital status, a habit of green leaf vegetable intake during pregnancy, and personal stories of hypertension showed no association with pre-eclampsia. In the second model, similar variables with model one remained to have a significant statistical association with pre-eclampsia together with gestational age.

Primary relatives who had a history of chronic hypertension were more than two times at increased risk for developing pre-eclampsia (AOR 2.1, 95% CI: 1.08-4.28).

The probability of developing pre-eclampsia among women with a family history of diabetes mellitus increases more than twice (AOR 2.35; 95% CI: 1.07-5.20).

Referring to gestational age at admission, the odds of having pre-eclampsia increased among women who had preterm gestation (AOR = 1.57, 95% CI: 1.05-2.33) and pre-conception smoking exposure (AOR = 4.25, 95% CI: 1.15-15.7) (Table 5).

4 | DISCUSSION

This study aimed to assess sociodemographic, medical disease, obstetric history, and behavioral determinants of pre-eclampsia. We found that a family history of hypertension and diabetes mellitus and a history of smoking appeared to be a risk factor for pre-eclampsia. A population-based study reported that pre-eclampsia has a strong familial tendency.[24] As a single gene hypothesis indicated, it remains an interplay of multiple factors where the effect of close relatives can be considered.[25] Besides, a study had indicated that maternal predisposition to pre-eclampsia because of genetic inheritance.[26] For instance, a daughter born from a pre-eclamptic mother may carry the risk for a genetic predisposition in which a gene from parents operate during uterine life through the offspring.[27]

Further, relatives who were not born after a pregnancy complicated by pre-eclampsia carries more risk.[28,29] But, women born from mothers with the previous episode of pre-eclampsia were more likely to trigger severe pre-eclampsia in their pregnancy.[26] A stronger genetic predisposition may explain the clinical severity of pre-eclampsia.[30] Besides, strong single gene expression from the maternal side has more influence on pre-eclampsia than its relationship to the fetal association.

Like other studies,[31,32] this research has found a positive association with a family history of chronic hypertension and diabetes mellitus. In this study, women with a previous family history of hypertension and diabetes Mellitus had more than twice more likely to develop pre-eclampsia, respectively. Many population-based studies found a significant statistical association between pre-eclampsia

TABLE 2 Sociodemographic characteristics of women attending public health hospitals in Omo District for antenatal and delivery services, Southern Ethiopia, 2018 (n = 519)

Variables	Case, n = 167 N (%)	Control, n = 352 N (%)	p-value
Age			
Less than 20	45 (26.9)	80 (22.7)	0.19
20-34	110 (65.9)	237 (67.3)	0.39
Above 34	12 (7.2)	35 (10)	1:00
Marital status			
Married	161 (96.4)	325 (92.3)	0.08
Unmarried	6 (3.6)	27 (7.7)	1:00
Residence			
Urban	89 (53.3)	201 (57.1)	0.41
Rural	78 (46.7)	151 (42.9)	1:00
Educational status			
No formal education	41 (24.6)	77 (21.9)	1:00
Primary	47 (28.0)	106 (30.1)	0.48
Secondary	39 (23.4)	97 (27.6)	0.30
College and above	40 (24.0)	72 (20.4)	0.88
Religion			
Orthodox	85 (50.9)	180 (51.1)	0.14
Protestant	66 (39.5)	142 (40.3)	0.10
Muslim	9 (5.4)	24 (6.9)	0.11
Others	7 (4.2)	6 (1.7)	1:00
Maternal occupation			
Housewife	94 (56.3)	180 (51.1)	0.47
Merchant	26 (15.6)	49 (13.9)	0.49
Gov't employee	15 (8.9)	49 (13.9)	0.67
Private worker	8 (4.8)	25 (7.1)	0.76
Student	16 (9.6)	28 (8.0)	0.44
Others	8 (4.8)	21 (6.0)	1:00
Paternal occupation			
Gov't employee	45 (22.8)	98 (29.63)	0.30
Merchant	43 (33.5)	114 (28.77)	0.13
Farmer	59 (31.7)	96 (29.10)	0.74
Private	8 (6.6)	27 (6.84)	0.12
Others	12 (5.4)	17 (5.70)	1:00

TABLE 3 Personal and family history-related characteristics of women attending public health hospitals in Omo District for antenatal and delivery services, Southern Ethiopia, 2018 (n = 519)

Variables	Case, n = 167 N (%)	Control, n = 352 N (%)	p-value
Family history of hypertension			
No relatives history	126 (75.4)	293 (83.3)	1.00
1st degree relatives history	19 (11.4)	23 (6.5)	0.05
2nd degree relatives history	22 (13.2)	36 (10.2)	0.23
Family history of diabetes mellitus			
Yes	12 (7.2)	35 (9.90)	0.31
No	155 (92.8)	317 (90.1)	1.00
Personnel history of diabetes mellitus			
Yes	11 (6.6)	19 (5.4)	0.59
No	156 (93.4)	333 (94.6)	1.00
Personnel history of asthma			
Yes	13 (7.8)	20 (5.7)	0.36
No	154 (92.2)	332 (94.3)	1.00
Personnel history of Pre-eclampsia			
Yes	24 (14.4)	34 (9.7)	0.11
No	143 (85.6)	318 (90.3)	1.00

and family history of chronic hypertension and diabetes mellitus. This finding is in line with studies conducted in Brazil,[33] Sudan,[34] Pakistan,[35] Sweden,[36] and Uganda.[37] The possible explanation could be because the number of cares in the current study and the previous studies are relatively similar. Recent studies done during pregnancy noted that diabetes mellitus may involve in the development of pre-eclampsia in which insulin resistance may play a role in the cause of pre-eclampsia.[38] Other studies revealed that women with a family history of diabetes mellitus were more likely to develop pre-eclampsia.[23,39] It shows that family history of diabetes mellitus could be a considerable risk factor of pre-eclampsia.

This study showed that women at earlier gestations are at an increased risk of pre-eclampsia. Preterm gestational age attributes a higher probability of developing a severe form of pre-eclampsia than the later gestational age. The findings of this result are consistent with another study.[40] This is supported by other research findings,[41,42] in which women at preterm gestation reported as a factor to develop pre-eclampsia. In this study, the percentage of pre-eclampsia cases who were admitted at preterm gestational age was higher than its counterparts. It was indicated that 68.9% of women who had pre-eclampsia were admitted before 37 weeks of gestation than 57.3% of women without pre-eclampsia. Similar findings were observed in different parts of the world such as China[43] and Portuguese.[44] For example, a study conducted in China indicated that the difference in the rate of pre-eclampsia among preterm gestation was more than 22% compared to those without. This is supported because the risk of pre-eclampsia is inversely correlated with gestational age; the closer the gestation to 20 weeks, the more pregnant women could develop pre-eclampsia.[45] This is evidenced by a hypothesis that a common pathophysiologic mechanism, suggesting that a significant proportion of preterm births are caused by improper remodeling of the uterine

TABLE 4 Obstetric characteristics of women attending public health hospitals in Omo District for antenatal and delivery services, Southern Ethiopia, 2018 (n = 519)

Variable	Case (n = 167) N (%)	Control (n = 352) N (%)	p-value
Gravidity			
Primigravida	71 (42.5)	127 (36.2)	0.12
Multigravida	84 (50.3)	187 (57.3)	0.32
Gravid multigravida	12 (7.2)	38 (10.5)	1.00
Number of gestation			
Singleton	156 (93.4)	326 (92.9)	0.74
Multiple	11 (6.6)	26 (7.1)	1.00
Gestational age			
Less than 37 weeks	115 (68.9)	201 (57.3)	0.01
37 and above weeks	52 (31.1)	151 (42.7)	1.00
ANC follow-up			
New	53 (31.7)	121 (34.5)	0.55
Repeated	114 (68.3)	232 (65.5)	1.00
Pregnancy interval			
No interval	63 (37.7)	115 (32.7)	0.13
Less than 2 years	33 (19.8)	58 (16.5)	0.16
2 years and above	71 (42.5)	179 (50.9)	1.00
Abortion			
Yes	31 (18.6)	69 (19.7)	0.78
No	136 (81.4)	283 (80.3)	1.00
Contraceptive before conception			
No modern contraception used	88 (52.7)	178 (50.7)	1.00
Injectable	53 (31.7)	104 (29.5)	0.89
Long acting reversible	17 (10.2)	49 (13.9)	0.25
Oral pills	9 (5.4)	22 (5.9)	0.73
Conception from a new partner			
Yes	34 (20.4)	66 (18.8)	0.66
No	133 (79.6)	286 (81.2)	1.00
Counseling during pregnancy			
Yes	148 (88.6)	327 (93.2)	0.11
No	19 (11.4)	25 (6.8)	1:00
Body mass index			
Normal	100 (59.9)	230 (65.3)	1.00
Underweight	18 (10.8)	22 (6.2)	0.06
Overweight	42 (25.1)	94 (26.8)	0.90
Obese	7 (4.2)	6 (1.7)	0.08

spiral arteries in earlier gestation and pre-eclampsia may happen for a similar reason.[46]

Statistically speaking, our data suggest that being an active smoker before conception increases the probability of pre-eclampsia. Women who had smoked before conception were more than four times more likely to exhibit pre-eclampsia. In support of this, women who stopped smoking after a pregnancy recognition but had smoked before had an increased risk of pre-eclampsia compared with those who never did.[47] On the other hand, women who had previous smoking exposure before pregnancy compared with non-smokers were about six times more likely to develop pre-eclampsia.[48] Research has also speculated that the probability of developing hypertension was increased among women whose ages were above 35 years.[49]

The underlying mechanism that increased the risk of pre-eclampsia among women who smoked before pregnancy remains unclear. Evidence indicates that the absence of a temporary protective factor-like carbon monoxide due to low tobacco exposure could be the possible reason.[48] A decreased mRNA and protein expression of the Nitric oxide synthase activity in endothelial cells are the suggested mechanism in research from pre-eclamptic pregnancies.[50] Women who smoke before conception may have lower nitric oxide levels,[51] leads to increased vascular tension, smoking may act through this mechanism to increase the risk of pre-eclampsia.

Moreover, pre-eclamptic women have reported having more release of syncytiotrophoblastic cellular particles and syncytial cellular debris in maternal circulation, this could result from endothelial dysfunction.[52] In the placentas of pre-eclamptic women, the rate of syncytiotrophoblastic proliferation and apoptosis is higher.[53] In women with smoking exposure before conception, it has reported that an increased focal syncytial apoptosis, cytotrophoblastic hyperplasia, loss or distortion of the placental barrier, decreased syncytial pinocytotic vessels, loss of the microvilli, decreased degeneration of cytoplasmic organelles, and increased collagen in the vascular stroma are related to pre-eclampsia.[54] Evidence of syncytial damage, knots, and focal necrosis is higher in smokers.[54]

Any understanding must consider the multifactorial and complex nature of pre-eclampsia pathogenesis involving genetic, environmental, and immunologic-related factors. Although there is much evidence in favor of this finding, due to the smallness of cases reported smoking.[55] But, the association between smoking and pre-eclampsia should be interpreted consciously. As smoking before conception is subject to recall bias, misreporting is likely. In this regard, the true effect of smoking on pre-eclampsia may be masked.[56]

4.1 | Strengths of the study and limitations of the study

We used a clear, understandable, variety of diagnostic criteria to make the diagnosis of pre-eclampsia more accurate. We triangulate observations with a patient card review for a detailed overview of the information needed to reach the diagnosis, other than a senior physician consultation, was used. Also, we take all cases attending the hospitals included in this study during the study period.

Considering the design of the study, we have taken all cases that appeared to Omo district hospitals during the study period which minimize selection bias. On the other hand, due to the retrospective nature of part the information which has been collected via

TABLE 5 Bivariable and multivariable analysis on determinants of pre-eclampsia women attending public health hospitals in Omo District for antenatal and delivery services, Southern Ethiopia, 2018 (n = 519)

	Outcome variable		COR-95% confidence interval	AOR-95% confidence interval	p-value
Variable	Pre-eclampsia	Controls			
Family history of hypertension					
No family history®	126 (75.4%)	293 (83.3%)	1:00	1.00	–
1st degree relatives history	19 (11.4%)	23 (6.5%)	1.92 (1.01-3.65)	2.15 (1.08-4.28)	0.03
2nd degree relatives history	22 (13.2%)	36 (10.2%)	1.42 (0.80-2.51)	1.44 (0.79-2.63)	0.23
Personel history of pre-eclampsia					
Yes	24 (14.4%)	34 (9.7%)	1.6 (0.89-2.74)	0.59 (0.31-1.08)	0.09
No®	143 (85.6%)	318 (90.3%)	1:00	1.00	
Family history of diabetes mellitus					
Yes	12 (7.2%)	35 (9.90%)	0.70 (0.35-1.13)	2.35 (1.07-5.20)	0.03
No®	155 (92.8%)	317 (90.1%)	1:00	1.00	
Marital status					
Married	161 (96.4%)	325 (92.3%)	2.23 (0.90-5.51)	0.45 (0.17-1.15)	0.08
Unmarried®	6 (3.6%)	27 (7.7%)	1:00	1:00	
Green-leafy vegetable intake					
Yes	158 (94.6%)	343 (97.4%)	2.17 (0.85-5.57)	2.29 (0.67-5.98)	0.09
No	9 (5.39%)	9 (2.6%)	1:00	1.00	
Gestational age					
Less than 37 weeks	115 (68.9%)	201 (57.3%)	1.7 (1.13-2.45)	1.57 (1.05-2.33)	0.03
37 and above weeks®	52 (31.1%)	151 (42.7%)	1:00	1.00	–
History of smoking before pregnancy					
Never smoker®	96 (57.5%)	216 (61.4%)		1.00	–
Passive smoker	64 (38.3%)	132 (37.5%)	1.09 (0.74-1.60)	1.13 (0.76-1.68)	0.53
Active smoker	7 (4.3%)	4 (1.14%)	3.94 (1.13-13.8)	4.25 (1.15-15.7)	0.03

Note: Abbreviations: "AOR", adjusted odds ratio; "CI", confidence interval; ®, reference.

face-to-face interviews; therefore, recall bias is expected to some extent, but, we tried to minimize through limiting the time laps within the one-year duration. First, we were unable to evaluate the risk of pre-eclampsia with some factors such as maternal physical activity during pregnancy, length of the sexual relationship after marriage, mechanical contraceptives before conception, health setting, and smoking status during pregnancy. Thus, this has to be noted for future work.

Second, multicenter nature in this study may make the study population heterogeneous, therefore the results may not be reflective of the real condition, particularly for each setting. Besides, thirdly, this study did not consider hospitals as a factor, and there may be a difference in care provision. Thus, this has to be noted for future work.

Last, we did not consider women who might develop pre-eclampsia after 48 h to 6 weeks after delivery for two reasons. First, it was difficult to trace women after discharge because most of them had their postpartum care visits at the health center. Second, women may be delayed both from home to the health center and during

referral; therefore, they may develop eclampsia fits by the time they had arrived at the hospital, which was not incorporated in this study. Due to logistic reasons, we needed to focus on pre-eclampsia alone.

5 | CONCLUSIONS

Family history of chronic hypertension and diabetes mellitus, preterm gestational age, and pre-conception smoking exposure were statistically significant determinants of pre-eclampsia in the Omo district hospitals.

Careful examination of women who had primary relatives with a history of chronic hypertension and diabetes mellitus starting from 20 completed weeks of gestation would be helpful in the diagnosis, monitoring, and timely management of women with pre-eclampsia and its complications. Obstetric care providers need to prompt women to avoid smoking exposure before pregnancy recognition. A clinician who is an expert in giving psycho-social support for pregnant women with a habit of smoking, need to approach the woman

enthusiastically and work with the case on ways to cease smoking. However, researchers should have the insight to conduct further studies on the link between smoking status before conception and pre-eclampsia.

DECLARATIONS

We, the undersigned, agree to accept responsibility for the scientific, ethical, and technical conduct of the research project mentioned below and for the provision of required progress reports and financial settlements as per the terms and conditions of the University if the grant is awarded as the result of this application.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

KF has a role in the conceptualization, data cure, formal analysis, research administration and resources, development of methodology, visualization of the research output, oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team, original draft preparation and writes up, approval of the manuscript. FG, FG, NC, and DM contributed to data collection, editing, and revision of the final manuscript. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

On presumable requests, the data sets used for analysis during the current study are available from the corresponding author.

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