

# Incidence and Predictors of Pre-Eclampsia Among Pregnant Women Attending Antenatal Care at Debre Markos Referral Hospital, North West Ethiopia: Prospective Cohort Study

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Molla Yigzaw Birhanu<sup>1</sup>  
Habtamu Temesgen<sup>2</sup>  
Gebreselassie Demeke<sup>3</sup>  
Moges Agazhe Assemie<sup>4</sup>  
Alehegn Aderaw Alamneh<sup>2</sup>  
Melaku Desta<sup>5</sup>  
Milkiyas Toru<sup>3</sup>  
Daniel Bekele Ketema<sup>4</sup>  
Cheru Tesema Leshargie<sup>1</sup>

<sup>1</sup>Department of Public Health, College of Health Sciences, Debre Markos University, Debre Markos, Ethiopia;

<sup>2</sup>Department of Human Nutrition and Food Sciences, College of Health Sciences, Debre Markos University, Debre Markos, Ethiopia; <sup>3</sup>Department of Medical Laboratory Sciences, College of Health Sciences, Debre Markos University, Debre Markos, Ethiopia;

<sup>4</sup>Department of Public Health, College of Health Sciences, Debre Markos University, Debre Markos, Ethiopia;

<sup>5</sup>Department of Midwifery, College of Health Sciences, Debre Markos University, Debre Markos, Ethiopia

**Background:** Pre-eclampsia is a pregnancy-induced hypertension that occurs after 20 weeks of gestation. It is the leading cause of maternal and perinatal morbidity and mortality globally, but it is higher in developing countries. In Ethiopia, conducting research on the incidence and predictors of pre-eclampsia is crucial due to the paucity of information.

**Methods:** A prospective cohort study was undertaken using 242 pregnant women between November 1, 2018 and March 30, 2019 at Debre Markos Referral Hospital. All eligible women who fulfilled the inclusion criteria were included in this study. Data were entered into the epic-data Version 4.2 and analyzed using the STATA Version 14.0 software. The Cox-proportional hazard regression model was fitted and Cox-Snell residual test was used to assess the goodness of fit. Pre-eclampsia free survival time was estimated using the Kaplan-Meier survival curve. Both bivariable and multivariable Cox-proportional hazard regression models were fitted to identify predictors of pre-eclampsia.

**Results:** The overall incidence rate of pre-eclampsia was 3.35 per 100 person-years. Having a pre-existing history of diabetes mellitus [AHR=2.7 (95% CI=1.43–8.81)], having a history of multiple pregnancy [AHR=3.4 (95% CI=2.8–6.9)] and being  $\geq 35$  years old age [AHR=2.5 (95% CI=1.42–3.54)] were the significant predictors of pre-eclampsia.

**Conclusion:** The incidence of pre-eclampsia was high in this study. Having (pre-existing diabetes and multiple pregnancy) and being  $\geq 35$  years old age were the significant predictors of pre-eclampsia. Inspiring pregnant women's health-seeking behavior should provide a chance to diagnose pre-eclampsia early to prevent the medical complication of pre-eclampsia.

**Keywords:** pre-eclampsia, incidence, predictors, pregnant women, Debre Markos, Ethiopia

## Background

Pre-eclampsia is a pregnancy-induced hypertension, characterized by significant proteinuria, with or without edema, and resolves by the 12th post-partial weeks.<sup>1</sup> It is a life-threatening multisystem disorder of pregnant mothers and the leading cause of morbidity and mortality of perinatal.<sup>2–4</sup> About ten million mothers each year develop pre-eclampsia worldwide.<sup>5</sup> The World Health Organization (WHO) estimated that the incidence rate of pre-eclampsia in developing countries is 7-times higher (2.8%) than in developed countries (0.45%).<sup>6</sup>

Globally, maternal mortality due to pre-eclampsia and related hypertensive disorders were 76,000 per year<sup>5</sup> and 56% of mortality occurring in sub-Saharan

Correspondence: Molla Yigzaw Birhanu  
College of Health Sciences, Debre Markos University, P.O. Box 269, Debre Markos, Ethiopia  
Email mollayigzaw33@gmail.com

countries.<sup>7</sup> In developing countries, pre-eclampsia accounted for 40–60% of maternal death.<sup>8–11</sup> In Ethiopia, maternal mortality due to pre-eclampsia was 10% per year.<sup>12</sup> The incidence rate of pre-eclampsia was 3.3 per 100 person-years in Australia<sup>13</sup> and 5.2 per 1,000 person-years in Yorkshire.<sup>14</sup> The incidence rate of pre-eclampsia in developing countries varies from 1.8–16.7%.<sup>6,–15–17</sup> Coming to Addis Ababa, pre-eclampsia increased from 2.2% in 2009 to 5.58% in 2013.<sup>18</sup> As the report of the previous studies, factors associated with pre-eclampsia were classified as socio-demographic,<sup>12,–19–24</sup> obstetric,<sup>19–21,23–26</sup> and clinical factors.<sup>21,22,26,27</sup>

The result of this study is important for improving the quality-of-life and survival status of mothers and newborn babies and for social-capital and sustainable economic growth of the country at large. There is a paucity of information on the incidence and predictors of pre-eclampsia in Ethiopia; hence, this study aimed to determine the incidence and predictors of pre-eclampsia in Debre Markos referral hospital northwest Ethiopia.

## Methods

### Study Design, Area, and Periods

A hospital-based prospective cohort study was conducted at Debre-Markos Referral Hospital from November 1, 2018 to March 30, 2019. Debre Markos Referral Hospital is found in Debre Markos Town located at 299 km far from Addis Ababa, the capital city of Ethiopia, and 265 km far from Bahir-Dar, the capital city of Amhara Regional State.

### Population

All pregnant women who received antenatal care at Debre Markos Referral Hospital were the target population. Pregnant women who were  $\geq 20$  weeks of gestational age during the recruitment period were the study population. All pregnant women having  $\geq 20$  weeks of gestational age and not developing pre-eclampsia were the eligible population. Pregnant women free of pre-eclampsia were selected using their antenatal registration number. About 242 pre-eclampsia free pregnant women were drawn using computer generated simple random sampling method.

### Sample Size Determination and Sampling Procedure

The minimum required sample size was calculated using a survival sample size determination formula. To calculate

the sample size we used the following information and assumptions: level of significance ( $\alpha$ )=5%,  $Z_{\alpha/2}$ =value at 95% confidence interval=1.96, HR: hazard ratio=1.49,<sup>19</sup> and power of 80%. We applied sample size calculation for each predictor variable, and the one with the maximum sample size selected for this study. Then, we randomly selected 242 pregnant women using a computer-generated simple random sampling method among those mothers having antenatal care follow-up at Debre Markos referral Hospital since November 1, 2018 to March 30, 2019.

### Variables of the Study

The dependent variable of this study was the time to pre-eclampsia. There were three sets of explanatory variables. First, socio-demographic characteristics included age, occupation, physical activity, residence, and educational status. The second set was obstetric factors including history of abortion, null parity, and absence of antenatal care, family history of pre-eclampsia, multigravida, cesarean section, induced delivery, multiple pregnancy, and gestational age. The third set of explanatory variables was clinical factors such as chronic hypertension, diabetes mellitus, gestational diabetes mellitus, renal and cardiac disease, severe anemia, urinary tract infection, smoking, pyelonephritis, body mass index, pre-existing hypertension, and use of alcohol.

### Operational Definition

Pregnant women who experienced pre-eclampsia during their ANC visit were considered as an event and those who did not experience pre-eclampsia (including those who died, lost to follow-up, transferred out, continued on a visit, and gave birth without experience of pre-eclampsia at the end of the study) were censored.

Gestational age was calculated from the last normal menstrual period (LNMP) and, for those women who did not recall their last menstrual period, fundal height and/or ultrasound result was used.

Gravidity was the total number of pregnancies, including abortion, ectopic pregnancy, and any other pregnancies recorded on the follow-up chart.

Parity was recorded as the number of deliveries after 28 weeks of gestation, including stillbirth and IUFD documented in the chart.

Pre-eclampsia represents pregnant women with blood pressure of  $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic on two separate readings taken at least 4–6 hours apart after 20 weeks gestation in an individual with previously normal blood pressure and proteinuria.<sup>28,29</sup>

Proteinuria is detected using the urine dipstick technique. Those women having protein in the urine +1 level and above are classified as proteinuria.

## Data Collection Tool and Procedure

The data collection tool was prepared from studies conducted previously. The questionnaire contains socio-demographic factors, obstetric, and clinical characteristics.

To ensure data quality, before data collection, the data collection tool was prepared with care. Likewise, Two days of training were given for both data collectors and supervisor to standardize and agree on the way of interviewing. In addition, we verified, consistent understanding of the prepared questionnaire by study participants through randomly selecting and completing 24 samples, which resulted in slight amendments on the data collection tool. Furthermore, the supervisor and principal investigators supervised the data collectors throughout the entire data collection period.

Two BSc midwives who have been working in the gynecology and obstetrics ward of Debre Markos Referral Hospital were the data collectors. The data collectors had the list of 242 pregnant women with their cell phone numbers and appointment dates. Pregnant women were contacted by the data collectors when they came to Debre Markos referral hospital for their focused antenatal care visit or seeking medical care during the data collection period. Mothers who were missing their respective schedule visit were receiving a call from the data collectors.

## Statistical Analysis

Data were entered into the Epidata™ version 4.2, and analyzed using STATA™ version 14.0 statistical software. At the end of the data collection period, the outcome of each study subject was dichotomized into censoring and event. Moreover, to identify the predictor variables, a Cox-proportional hazard regression model was fitted. To check the assumption of the Cox-proportional hazard regression model, we used Schoenfeld residual test for continuous variables and Log–Log plot for categorical variables.

Furthermore, we checked the model fitness using a Cox-Snell residual test (see [Supplementary Figure 1](#)). We used the Kaplan–Meier curve to estimate the occurrence of time to pre-eclampsia. A Log rank test was estimated to compare the survival curves for different categorical explanatory variables.

In univariate analysis, we used mean with standard deviations to describe normally distributed continuous data and median with interquartile range for skewed continuous data. In another way, the categorical data collected from pregnant women were described using frequency distribution or percentages. Regarding bivariable analysis the outcome variable (pre-eclampsia) and explanatory variables were entered into the bivariable Cox-proportional hazard regression model to select variables for multivariable Cox-proportional hazard regression model. As a result, variables having a  $P$ -value  $\leq 0.25$  in the bi-variable analysis were fitted into the multivariable Cox-proportion regression model. Finally, adjusted risk ratio with its corresponding 95% confidence interval (CI) was used to declare the presence of a significant association between the explanatory and outcome variables.

## Results

### Socio-Demographic Characteristics

The mean (SD) age of the study participants was 28 ( $\pm 5$ ) years. Two hundred and eleven (87.19%) were married and 102 (42.15%) worked as a civil servant in their occupational status. Regarding educational status, 143 (50.09%) had college and above. Slightly less than three-quarters (70.66%) of the pregnant women were physically inactive ([Table 1](#) and [Figure 1](#)).

### Reproductive and Obstetric Characteristics

The median age at first menstruation was 15 (IQR=2.3) and the mean age at first pregnancy was 23 ( $\pm 5$ ) years old. During enrollment, the mean gestational age of pregnant women was 30 ( $\pm 5$ ) weeks and the median gestational age at the time of delivery was 38 weeks, with a 2-week interquartile range. Among study participants, 19 (7.85%) and 24 (9.92%) participants experienced pre-term delivery and pre-eclampsia, respectively. About 18 (7.44%), 35 (14.46%), and 26 (10.74%) of the pregnant women had a family history of pre-eclampsia, history of abortion, and history of cesarean section, respectively. About one-third (34.71%) of pregnant women had antenatal care follow-up and one-tenth (9.50) had a history of multiple pregnancy in the previous pregnancy. Approximately four of every ten women (40.50%) were null parity ([Table 1](#) and [Figure 2](#)).

**Table 1** The Characteristics of Pregnant Women

Characteristics	Frequency	Percentage
Age		
15–24	62	25.62
25–34	144	59.50
≥35	36	14.88
Marital status		
Single	15	6.20
Married	211	87.19
Divorced	8	3.31
Widowed	8	3.31
Having physical activity		
Yes	72	29.34
No	170	70.66
Educational status		
Can read and write	29	11.98
Primary	19	7.85
Secondary	51	21.07
College and above	143	59.09
Occupation		
Merchant	29	11.99
Government	110	45.46
Private employee	19	7.85
Housewife	84	34.71
Experience of preterm		
Yes	19	7.85
No	223	92.15
History of pre-eclampsia		
Yes	15	6.20
No	227	93.80
Family history of pre-eclampsia		
Yes	22	9.1
No	220	90.9
Experience of cesarean section		
Yes	26	10.74
No	216	89.26
History of abortion		
Yes	35	14.46
No	207	85.54
Experience of previous ANC follow-up		
Yes	84	34.71
No	158	65.29

(Continued)

**Table 1** (Continued).

Characteristics	Frequency	Percentage
Experience of molar pregnancy		
Yes	21	8.68
No	221	91.32
History of infertility		
Yes	84	34.71
No	158	65.29
History of chronic hypertension		
Yes	16	6.61
No	226	93.39
Family history of hypertension		
Yes	25	10.33
No	217	89.67
Experience of diabetes mellitus		
Yes	14	5.79
No	228	94.21
History of renal disease		
Yes	21	8.67
No	221	91.33
Experience of anemia		
Yes	135	55.79
No	107	44.21
Family history of diabetes mellitus		
Yes	35	14.46
No	207	85.54

### Clinical Characteristics

Fifteen (6.20%) and 16 (6.61%) participants had a family history of chronic hypertension and chronic hypertension themselves, respectively. Less than one in five of the study participants experienced pre-existing diabetes mellitus (14.05%) and renal disease (17.36%), respectively. Slightly more than half of the study women were anemic (55.79%) or experienced urinary tract infections (51.24%) (Table 1).

### Measured Value of Variables

The mean with the range of systolic blood pressure at baseline was 150±16 mmHg with 129±225 mmHg, and diastolic blood pressure was 105±14.5 mmHg with 85 ±133 mmHg, respectively. The mean with the range of

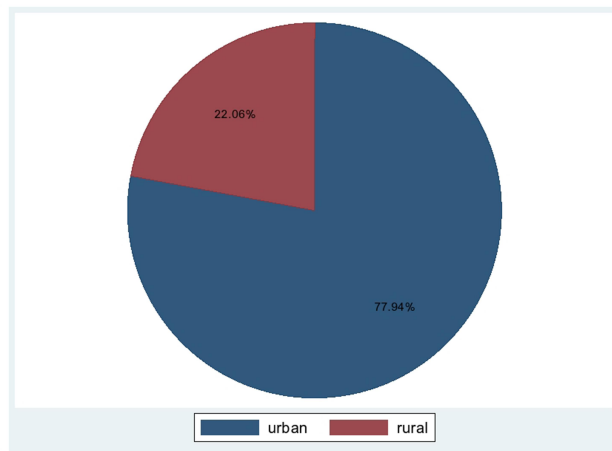


Figure 1 Pregnant women over their residence.

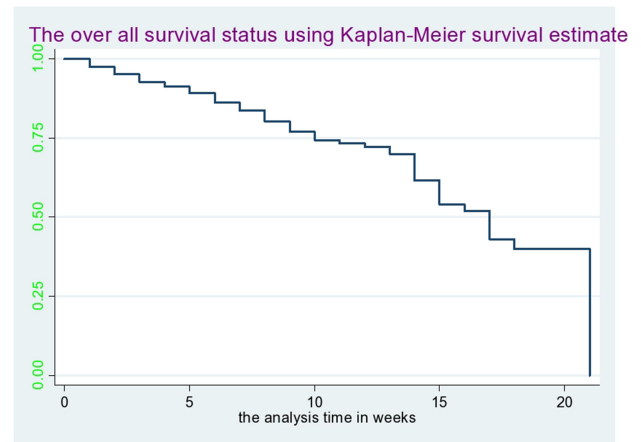


Figure 3 The overall survival status of pregnant women.

proteinuria of pregnant women at baseline were  $2.8 \pm 0.9$  and 1–3, correspondingly.

Regarding the follow-up value of blood pressure, the mean with a range of systolic blood pressure was  $163.3 \pm 18$  mmHg and  $1234 \pm 220$  mmHg retrospectively. The mean with the range of proteinuria of pregnant women at baseline were  $2.8 \pm 0.6$  and 1–2.8, correspondingly.

### Incidence of Pre-Eclampsia

The study participants had 20–40 weeks gestational age during their recruitment. The overall pre-eclampsia free survival time of pregnant women was 1970 person-years. Out of 66 women diagnosed as developing pre-eclampsia, 33 (50%) had mild pre-eclampsia, 20 (30.3%) had severe pre-eclampsia, and 13 (19.69%) showed eclampsia. The overall incidence rate of pre-eclampsia was 3.35 (95% CI=0.026–0.043) per 100 person-

years (Figure 3), the incidence rate over the number of pregnancies (Figure 4) and the incidence rate over the diabetes status (Figure 5) were compared graphically.

### Bivariable and Multivariable Cox-Regression Analysis

Having physical activity, a history of infertility, a family history of pre-eclampsia, age at current pregnancy, multiple pregnancy, having a family history of diabetes mellitus, history of hypertension, family history of hypertension, presence of renal disease, pre-existing diabetes mellitus, antenatal follow-up, and history of abortion were the variables having a  $P$ -value < 0.25 in the bivariable Cox-regression analysis and were eligible for multivariable analysis. In the multivariable Cox-regression analysis, having a history of pre-existing

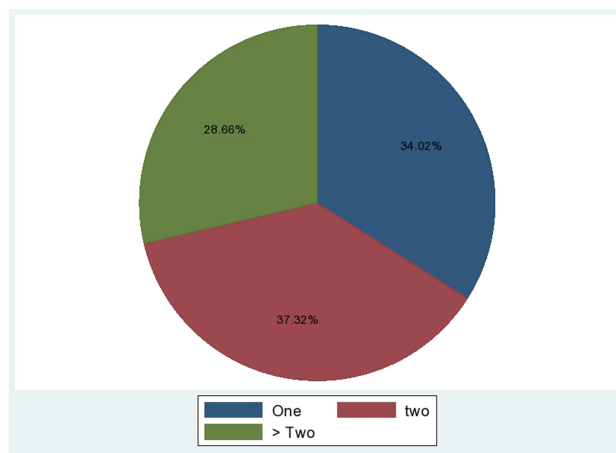


Figure 2 Pregnant women over their gravidity.

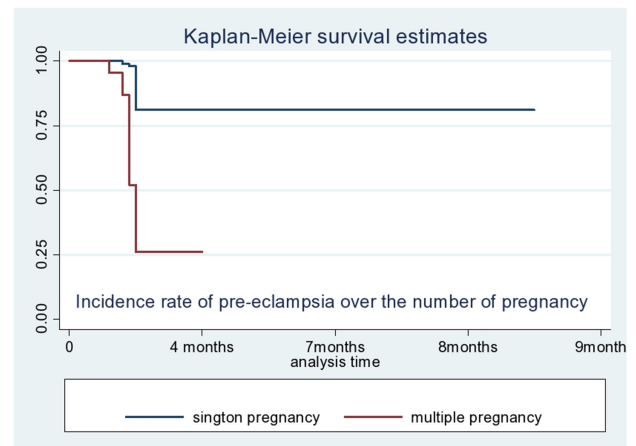
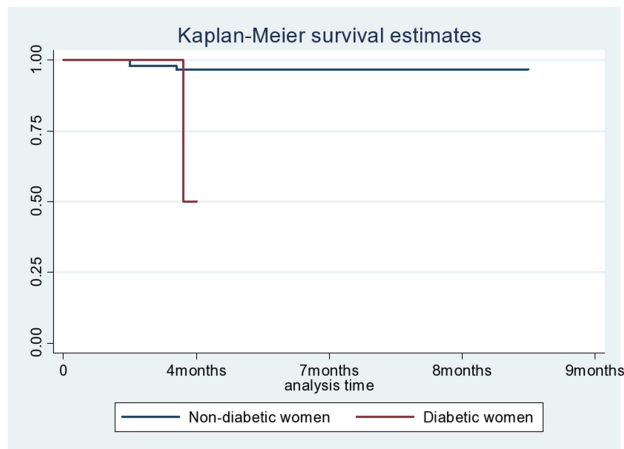


Figure 4 The incidence rate of pre-eclampsia over the number of pregnancies.



**Figure 5** Incidence rate of pre-eclampsia over diabetic status of women.

diabetes mellitus, having a history of multiple pregnancies, and age  $\geq 35$  years old were statistically significant predictors of pre-eclampsia.

The risk of developing pre-eclampsia among pregnant mothers who had a history of pre-existing diabetes mellitus were 2.7- [AHR=2.7 (95% CI=0.43–0.85)] times higher than those who had no history of pre-existing diabetes mellitus. The chances of developing pre-eclampsia among pregnant women who were  $\geq 35$  years old were 2.5- [AHR=2.5 (95% CI=1.42–3.54)] times greater than those who were in the rang of 5–24 years old. Pregnant women who had a history of multiple pregnancy were 3.4- [AHR=3.4 (95% CI=2.8–6.9)] times more likely to experience pre-eclampsia than those who had no history of multiple pregnancy (Table 2).

## Discussions

Pre-eclampsia is a pregnancy-induced hypertension and defined as high blood pressure with a significant amount of protein in the urine. Pre-eclampsia is noted as the global leading cause of maternal mortality. This study aimed to determine the incidence and predictors of pre-eclampsia using 242 pregnant women who had an antenatal follow-up visit at Debre Markos Referral Hospital. The incidence of pre-eclampsia among pregnant women who had an antenatal follow-up visit at Debre Markos Referral Hospital was 3.35 (95% CI=0.026–0.043) per 100 person-years. The incidence of pre-eclampsia of this study is higher than in Yorkshire, England (5.2 per 1,000 person-years) and Zimbabwe (1.7 per 100 person-years).<sup>14,16</sup> This might be due to 29 (11.98%) of the study participants not being formally educated in this study. This might limit

their health-seeking behavior and level of understanding, finally creating stress on their current pregnancy, which in turn leads to increasing the occurrence of pre-eclampsia. This finding might have again resulted due to the socio-economic and demographic differences in the study population.

According to the findings of this study, the risk of developing pre-eclampsia among older women ( $\geq 35$  years old) was 2.5- [AHR=2.5 (95% CI=1.42–3.54)] times higher than their counterparts (15–25 years old women). It is supported by a study conducted in Washington state.<sup>19,20</sup> This might be a cardiovascular disorder increased in old age due to increment in cholesterol deposition and high level of lipid profiles, which leads to increasing the risk of pre-eclampsia occurrence due to a narrowing effect on the blood vessels.<sup>24,30,31</sup> Likewise, it could be that more old pregnant women experience pre-eclampsia than young pregnant women due to a hemodynamic adaptation problem.<sup>32</sup> Furthermore, this could be the gradual loss of cardiovascular vessel compliance due to aging of uterine blood vessels and increased arterial stiffness causing endothelial dysfunction.<sup>22,33</sup>

This study identified that mothers who had a history of multiple pregnancy were at 3.4- [AHR=3.4 (95% CI=2.8–6.9)] times higher risk of experiencing pre-eclampsia than those pregnant women who had no history of multiple pregnancy. This is supported by studies conducted previously.<sup>25,34,35</sup> This might be because experiencing multiple pregnancies can encourage the occurrence of psychological stress, which might lead to placing the woman at risk of developing pre-eclampsia.<sup>36</sup> This could be again because women with multiple pregnancy have a large placenta, which has decreased placental perfusion. The excess of placenta tissues, which could not perfuse adequately leads to develop pre-eclampsia.

The risk of developing pre-eclampsia among pregnant women who had a history of pre-existing diabetes mellitus was 2.7- [AHR=2.7 (95% CI=1.43–8.81)] times higher than those pregnant women who had no history of pre-existing diabetes mellitus. The finding of this study is in line with the studies conducted previously.<sup>21,27</sup> It could be that diabetic pregnant women develop pre-eclampsia because high levels of blood sugar (diabetes mellitus) cause narrowing of blood vessels and interfere with the normal physiological response during pregnancy according to the World Health Organization evidence.<sup>37</sup>

**Table 2** Multivariable Cox Regression Analysis

Variables	Last Status		CHR (95% CI)	AHR, (95% CI)	P-value
	Event	Censored			
Having physical activity					
No	44	126	1.0	1.0	0.59
Yes	22	50	1.26 (0.38–2.89)	3.4 (3.3–7.42)	
History of infertility					
No	54	155	1.0	1.0	0.38
Yes	12	21	0.61 (0.34–1.12)	1.6 (0.6–3.9)	
Having antenatal follow-up					
No	38	120	1.0	1.0	0.20
Yes	28	56	0.65 (0.34–1.23)	0.34 (0.54–0.9)	
Family history of pre-eclampsia					
No	56	164	1.0	1.0	0.45
Yes	10	12	0.42 (0.25–1.36)	0.7 (0.42–2.85)	
History of molar pregnancy					
No	56	165	1.0	1.0	0.46
Yes	8	13	0.55 (0.21–1.34)	0.2 (0.37–0.99)	
Family history of diabetes mellitus					
No	51	156	1.0	1.0	0.36
Yes	15	20	0.45 (0.25–0.81)	1.2 (1.4–3.4)	
Family history of hypertension					
No	57	160	1.0	1.0	0.20
Yes	10	15	0.53 (0.22–1.25)	1.2 (1.5–7.95)	
History of multiple pregnancy					
No	58	166	1.0	1.0	0.003*
Yes	6	10	0.68 (0.34–1.29)	3.4 (2.8–6.9)	

(Continued)

**Table 2** (Continued).

Variables	Last Status		CHR (95% CI)	AHR, (95% CI)	P-value
	Event	Censored			
Pre-existing diabetes mellitus					
No	55	166	1.0	1.0	0.01*
Yes	6	10	1.36 (2.36–6.94)	2.7 (1.43–8.81)	
Age at current pregnancy					
15–24	15	47	1.0	1.0	0.11
25–34	41	102	1.43 (0.78–2.63)	1.59 (0.9–2.8)	
≥35	10	26	2.32 (1.3–5.34)	2.5 (1.42–3.54)	
History of abortion					
No	53	154	1.0	1.0	0.73
Yes	13	22	0.58 (0.34–2.35)	1.6 (1.74–2.15)	
Having antenatal follow-up					
Yes	38	120	1.0	1.0	0.25
No	28	56	0.75 (0.46–1.23)	0.34 (0.89–1.98)	

**Note:** \*Used to show the presence of statistical association.

### Limitations of This Study

Even though this study provided a clue for the policymakers and clinical purpose towards the decrement of the maternal morbidity and mortality, it has its own constraints. First, this study did not consider some essential predictors, like complete blood cell count, electrolyte, and hormonal tests, because it was not considered a laboratory investigation as a data collection method. Second, the incidence rate of pre-eclampsia might be underestimated if mothers who had a tendency to develop pre-eclampsia were lost to their antenatal care visit during the study period.

### Recommendations

To overcome stress as well as normalize cardiac output and blood pressure, health professionals should provide health education for pregnant women to have monstrous

physical exercise. Inspiring pregnant women's health-seeking behavior should provide a chance to diagnose pre-eclampsia early to prevent its medical complication.

## Conclusion

The incidence rate of pre-eclampsia was high in this study. Pre-existing diabetes mellitus, a history of multiple pregnancy, and being  $\geq 35$  years old were statistically significant predictors of pre-eclampsia. Inspiring pregnant women's health-seeking behavior should provide a chance to diagnose pre-eclampsia early to prevent the medical complication of pre-eclampsia.

## Abbreviations

PE, pre-eclampsia; WHO, World Health Organization; LMIC; low- and middle-income countries; ANC, Antenatal care; DM, Diabetes Mellitus; IUFD, Intrauterine fetal death; RR, Relative Risk.

## Data Sharing Statement

No additional data are required; all information is stated in the main manuscript.

## Ethics Approval and Consent to Participate

Ethical clearance was given from Debre Markos University, health sciences college review committee. During data collection, informed written consent was obtained from all pregnant women who were greater than 18 years old and above, and there were no pregnant women below the age of 18 years old participating in this study. To keep the confidentiality, the information of the study participants was not disclosed to anyone other than the principal investigators. Generally, this study was conducted in accordance with the World Medical Association Declaration of Helsinki.

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## Author Contributions

MYB: conception of the research idea, study design, data collection, analysis and interpretation, and manuscript write-up. HT, GD, MAA, AAA, MD, MT, DBK, CTL: data collection, analysis and interpretation, and manuscript write-up. All authors contributed to data analysis, drafting or revising the

article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. All authors have read and approved the final manuscript.

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## Disclosure

The authors have declared that they have no competing interests.

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