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Family history of hypertension increases risk of preeclampsia in pregnant women: a case-control study

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ABSTRACT

BACKGROUND

Preeclampsia is one of the leading causes of maternal and fetal morbidity and mortalities worldwide. Despite extensive research, the underlying cause of preeclampsia remains poorly understood. This study aimed to offer compelling evidence on the important risk factors of preeclampsia in Amhara region, Ethiopia.

METHODS

A case control study was conducted in public health facilities of Bahir Dar city from September 2014 to January 2015. A total of 453 (151 cases and 302 controls) pregnant women were enrolled in this study. Hemoglobin level and urinary tract infection (UTI) status were collected from clinical notes. Oral examination was performed by a dentist for detection of periodontal diseases. Univariate and multiple logistic regression analysis was conducted to determine the relationship of all the independent variables with the outcome variable. A p-value <0.05 was declared statistically significant.

RESULT

Advanced maternal age (AOR=4.79;95% CI 1.031-22.18), family history of hypertension (AOR=11.16;95% CI 5.41-41.43), history of diabetes mellitus (AOR=6.17;95% CI 2.11-20.33), UTI in the current pregnancy (AOR=6.58;95% CI 2.93-14.73), failure to comply with iron and folic acid supplement during pregnancy (AOR=8.32;95% CI 3.35-20.62), lack of exercise (AOR=3.33;95% CI 1.35-8.17), multiple pregnancy (AOR=4.05;95% CI 1.57-12.27), anemia (AOR=4.19;95% CI 1.27-13.92), and periodontal disease or gingivitis (AOR =3.51;95% CI 1.14-10.83) were associated with preeclampsia.

CONCLUSION

Family history of hypertension was the most dominant risk factor for preeclampsia in pregnant women. Encouraging pregnant women to have health seeking behavior during pregnancy would provide a chance to diagnose preeclampsia as early as possible.

Keywords: Preeclampsia, risk factors, pregnancy, pregnant women, Bahir Dar city

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INTRODUCTION

Preeclampsia is a pregnancy complication recognized by new-onset gestational hypertension and proteinuria first detected after 20 weeks gestation with or without generalized edema.[1,2] Preeclampsia is a multisystem disorder of unknown etiology and unique to pregnancy.[3] In severe cases, it can present with hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome [4] or eclampsia, that is the occurrence of convulsions associated with a high rate of maternal mortality.[5] Preeclampsia, complicating 5% to 8% of pregnancies, has been traditionally defined by an elevated blood pressure (over 140/90 mmHg on at least 2 occasions at least 6 hours apart) and proteinuria, at or beyond 20 weeks' gestation.[6] The onset of preeclampsia is only 5% from 20 weeks to 34 weeks of gestation, 90% from 34 weeks to the time of labor and delivery and the remaining 5% occurs postpartum within 48 hours after delivery.[7]

Although the characteristic placental pathology of preeclampsia is established during early pregnancy,[2] there are no reliable tools for early clinical diagnosis and no effective therapies to treat the disease and improve maternal and fetal outcomes. In developed countries, surveillance for preeclampsia through prenatal care using risk factors allows for early identification and intervention via delivery. This management is very effective at reducing maternal mortality rate in developed countries. However in developing countries, where inadequate prenatal care limits preeclampsia surveillance, maternal mortality is common, accounting for 50,000 deaths yearly.[8] Ninety-nine (99%) percent of these deaths occur in the developing world and more than 50% in Sub Saharan Africa.[9] Therefore it is necessary to recognize the epidemiological and clinical risk factors to predict the disease before it threatens the survival of both mother and fetus.

Preeclampsia has remained a significant public health threat in both developed and developing countries contributing to maternal and perinatal morbidity and mortality globally.[8] The incidence of pre-eclampsia ranges from 3% to 7% for nulliparas and 1% to 3% for multiparas.[10,11] The World Health Organization (WHO) estimates the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%).[3]

Preeclampsia affects 5% to 10% of all pregnancies globally. The rates are lower in the developed world (about 3% to 5% of women), but the prevalence of preeclampsia in developing countries reaches up to 16.7% and it is estimated to account for about 40% to 60% of maternal deaths in developing countries.[12]

Maternal morbidity remains great with preeclampsia, which continues to be one of the leading causes for the admission of pregnant women to intensive care units in the world.[13] Fetal morbidity and mortality also increase substantially in women with preeclampsia and it is a major cause of stillbirths and early neonatal deaths in developing nations.[13,14]

Although the cause for pre-eclampsia is still unclear, there does appear to be certain risk factors which were identified by a number of studies such as advanced maternal age,[15] illiteracy,[16] nulliparity,[17] twin pregnancy,[18] high maternal body mass index (BMI),[19] family history of hypertension,[20] renal disease and diabetes mellitus.[21]

Other evidences also showed that preeclampsia is more common among women who have histories of certain health conditions, such as previous history of preeclampsia, [22] diabetes,[23] urinary tract infection (UTI),[24] periodontal disease,[25] anemia,[26,27] migraine headaches and sickle cell disease.[23] While smoking,[26] alcohol use,[28] partner change and lack of physical exercise during pregnancy [29] have been explained as risk factors. Fruit and vegetable intake,[26] adequate antenatal follow up [15] and periconceptual and ongoing regular use of folate containing multivitamins and induced abortion [30, 31] have been associated with primary prevention of preeclampsia.

Studies on the determinant factors of preeclampsia are non-existent in Ethiopia. Hence,

we aimed to identify risk factors for the occurrence of preeclampsia in the study area.

METHODS

Study design

A multi-center unmatched case-control study was conducted among pregnant women who attended antenatal care (ANC) or skilled delivery service in public health facilities in Bahir Dar city from September 2014 to January 2015.

Study area

The study was conducted in Bahir Dar city, one of the three administrative cities and the capital city of the Amhara region. Amhara region is the second largest and second most populous region in Ethiopia, with a population of nearly 20 million. The city is located 565 km Northwest of Addis Ababa. According to Bureau of Finance and Economic Development report, the city hosts a population of 277,566 with a male to female ratio of 0.92. The average fertility rate in the region is 4.8. Currently, 70% and 26% of pregnant women in the region are attending ANC and skilled delivery services respectively.[32,33] The city has one referral hospital and six public health centers serving approximately 5 million people within and outside the city. The study involved all of these public health facilities in Bahir Dar city.

Study population

All pregnant women who stayed at least 6 months in the region and attended antenatal care follow up and/or delivery during the study period at any of the public health facilities of Bahir Dar city, and met the inclusion criteria comprised the study population.Cases were pregnant women diagnosed to have any form of preeclampsia/ eclampsia during ANC follow up or delivery care by an obstetrician. Preeclampsia was diagnosed after 20 weeks of pregnancy if they had a blood pressure of 140/90 mmHg or higher measured at least twice with 6 hours separation and protein in their urine confirmed by a laboratory test.

Controls were normotensive women delivered in the same health facilities at the same time as cases were enrolled. Hence, to avoid misclassification of potential cases as controls, we waited to see the outcome of all the controls until 48 hours post-partum. Cases were enrolled consecutively as they were diagnosed to have preeclampsia/eclampsia until the required sample size was obtained. For each case, two controls were selected by using a simple random sampling technique from the same health facility on the same day.

Sample size determination

The sample size was determined using EPI info version 3.5.3 stat calc calculator for two populations based on all the necessary assumptions for case control study by taking power of 85% and significance level of 5% and control to case ratio of 2:1. In Ethiopia there are only few descriptive studies conducted concerning the prevalence of hypertensive disorders of pregnancy,[32,33] but no previous study has been done on determinant factors of preeclampsia in the country. Therefore the sample size was determined by using the results of a previous study to identify risk factors of preeclampsia and select a variable that would yield maximum sample size [34] which was advanced maternal age. Based on the assumption, the total sample size required for cases and controls, including 10% for non-response, was 156 and 312 respectively.

Measurements

Gingivitis and periodontitis were diagnosed based on the American Academy of Periodontology (AAP)/American Dental Association (ADA) classification, using the measurement method of Ramfjord by a calibrated periodontal probe.[35] Clean catch urine specimens were collected from each of the study participants. From all subjects recruited into the study a specimen of clean catch midstream urine was collected during ANC follow up that was subjected to a dipstick test and urine microscopy for UTI. Maternal anemia was defined as hemoglobin

concentration less than 11 g/dl. If a woman had been taking iron and folic acid (IFA) supplement daily, she would be considered compliant to IFA supplement as per the WHO recommendations.[37] Exercise was defined as at least a conscious effort to stroll around participant's home for not less than 20-30 minutes daily.[29]

Data analysis

IBM SPSS version 20 was used for data entry and cleaning. Then, univariate logistic regression analysis was conducted using STATA version 12.0. Backward stepwise unconditional logistic regression analysis was employed to determine the strength of association between predictive variables and the outcome variable and to control for the effect of confounding variables. Crude odds ratio (COR) was reported for bivariate logistic regression and adjusted odds ratio (AOR) was reported for the multivariate logistic regression model. A p-value <0.05 was declared statistically significant.

Ethical clearance

Ethical clearance was obtained from the Bahir Dar University School of Public Health Ethical Review Board. The person in charge of each facility and care providers were informed and their agreement received before the onset of data collection. Moreover, the purposes and importance of the study was explained and informed consent was secured, confidentiality was maintained at all levels of the study, and participant's involvement in the study was on a voluntary basis.

RESULTS

A total of 453 verbally consented pregnant women who came for their antenatal follow up and skilled delivery service were enrolled in this study. The mean age of the study participants was 27.14 ± 5.73 years; the mean age for cases was 29.7 ± 6.28 years and for controls 24.6 ± 5.36 years. The age group of 25–29 years was the most

Table 1. Crude odds ratios for the associations between socio-demographic characteristics and preeclampsia among pregnant women

Variables	Cases (n=151)	Controls (n=302)
Age (years)		
<20	14 (9.3)	43 (14.2)
20-24	32 (21.2)	67 (22.2)
25-29	50 (33.1)	109 (36.1)
30-34	27 (17.9)	49 (16.2)
35 and above	28 (18.5)	34 (11.3)
Residence		
Rural	69 (45.7)	107 (35.8)
Urban	82 (54.3)	195 (64.2)
Marital status		
Currently married	141 (93.4)	281 (93.4)
Single*	10 (6.6)	21 (6.6)
Occupation		
Employed	33 (21.9)	72 (23.8)
Merchant	25 (16.6)	44 (14.6)
Housewife	93 (61.5)	186 (61.6)
Education		
No formal education	71 (47.0)	122 (40.4)
Primary	15 (9.9)	39 (12.9)
Secondary	42 (27.8)	80 (26.5)
Higher education	23 (15.3)	61 (20.2)
Income in US$		
< $75 **	88 (58.3)	170 (56.3)
≥ $75	63 (41.7)	132 (43.7)

*unmarried, divorced and widowed; **median monthly income: $1=21 Ethiopian Birr (ETB) based on the current exchange rate

common age group for cases and controls. There was a difference in area of residence for cases and controls, in that the percentage from urban areas was larger in the control group (64.2%) than in the cases group (54.3%). Other socio-demographic characteristics of the cases were similar to those of the controls (Table 1).

A higher proportion of cases than controls reported that they had taken alcohol during their pregnancy. The proportion of cases and controls who reported to have IFA regularly during pregnancy was 65.6% and 93.7% respectively. Similarly, the majority of cases (78.1%) and controls (84.1%) reported that they had engaged in physical exercise during their pregnancy. Comparable proportions of cases and controls had their first pregnancy while participating in this study. Almost all participants in both groups (96.0% of cases, 95.4% of controls) had visited an antenatal clinic during their pregnancy. An appreciably greater number of cases had family history of hypertension and history of diabetes mellitus than did the controls. Similarly, the proportion of women who had UTI, periodontal disease and anemia was higher among cases than controls (Table 2).

Table 2. Crude odds ratios for the associations between maternal life style, reproductive and medical risk factors and preeclampsia among pregnant women

Variables	Cases (n=151)	Controls (n
Alcohol intake		
Yes	80 (53.0)	122 (40.
No	71 (47.0)	180 (59.
Folate use		
Yes	99 (65.6)	283 (93.
No	52 (34.4)	19 (6.3
Exercise		
Yes	118 (78.1)	254 (84.
No	33 (21.9)	48 (15.9
Partner change		
Yes	31 (20.5)	33 (10.9
No	120 (79.5)	269 (89.
No. of pregnancy		
Primigravida	68 (45.0)	151 (50.
Multigravida	83 (55.0)	151 (50.
Type of pregnancy (n=416)		
Singleton	107 (91.5)	290 (97.
Multiple	10 (8.5)	9 (3.0)
Antenatal care follow up		
Yes	145 (96.0)	288 (95.
No	6 (4.0)	14 (4.6
Family history of hypertension		
Yes	52 (34.4)	16 (5.3
No	101 (65.6)	286 (94.
History of diabetes mellitus		
Yes	19 (12.6)	9 (3.0)
No	132 (87.4)	293 (97.
Urinary tract infection (current)		
Yes	48 (31.8)	19 (6.3
No	103 (68.2)	283 (93.
Periodontal disease		
Yes	19 (12.6)	14 (4.6
No	132 (87.4)	288 (95.

The simple binary logistic regression analysis in this study revealed several factors to be predictors of preeclampsia. Women who reported to have drunk alcohol at least weekly during the index pregnancy and those women who changed their partner had an increased risk of preeclampsia as compared with those women who did not (COR=1.66; 95% CI: 1.12- 2.46; and COR=2.10; 95% CI: 1.23-3.60, respectively) in the bivariate analyses, but the values turned out to be insignificant when adjusted in the multiple binary logistic regression model.

Women whose age was 35 years and above were almost five times more likely to develop preeclampsia than women whose age was less than 20 years. Inadequate use IFA was found to be a risk factor for the development of preeclampsia (AOR=8.32; 95% CI: 3.35-20.62). In addition, lack of exercise was found to be a risk factor for the occurrence of preeclampsia (AOR=3.33; 95% CI: 1.35-8.17). Similarly, those women who had a family history of hypertension and history of diabetes mellitus were more likely than their counterparts to develop preeclampsia (AOR=11.16; 95% CI: 5.41-41.43; AOR=6.17; 95% CI: 2.11-20.33, respectively). Likewise, presence of UTI, anemia and periodontal disease during pregnancy were independent risk factors for the incidence of preeclampsia (AOR=6.58; 95% CI: 2.93- 14.73; AOR=4.19; 95% CI: 1.27-13.92; AOR=3.51; 95% CI: 1.14-10.83, respectively). A family history of hypertension was the most dominant risk factor of preeclampsia. However, factors such as residence, education, marital status, monthly income, occupation, alcohol intake, primiparity, sexual partner change and ANC follow up did not show any significant association with the incidence of preeclampsia in our study (Table 3).

DISCUSSION

The main finding of this study was that women who reported a family history of hypertension were significantly associated with preeclampsia. Our observation of an association between family history of chronic hypertension and risk of preeclampsia is consistent with several previous reports.[20] Our results showed that diabetes mellitus was associated with the subsequent development of preeclampsia. The result of our study showing a relationship between preeclampsia and diabetes was also consistent with previous findings, diabetes mellitus was independently and significantly associated with an increased risk of preeclampsia.[21]

The result of this study is biologically plausible for several reasons. First, epidemiological and clinical data document a close association between insulin resistance, type 2 diabetes, and hypertension.[32] In addition hyperinsulinemia has been shown to stimulate the proliferation of vascular smooth muscle cells, enhance acute sympathetic nervous system activity and modify transmembrane cation transport, as well as renal sodium retention, release of the potent vasoconstrictor angiotensin II, and associated endothelial dysfunction. All of these alterations may contribute to blood pressure elevation and thus preeclampsia.[37]

Second, evidence from diverse settings suggests that family history of hypertension and diabetes are strongly and consistently related to biophysiological markers of vascular disorders. In women with a family history of hypertension, endothelial changes also appear to involve a relative deficiency in the production of nitric oxide, a vasodilator and inhibitor of platelet aggregation, along with increased production of endothelin-I, which is an extremely potent vasoconstrictor and activator of platelets. This shift in the production of locally acting vasoactive substances could enhance vasoconstriction in response to circulating pressor hormones. The net effect would be to cause widespread arteriolar constriction leading to hypoxic/ischemic damage in different vascular beds, systemic hypertension, and worsening placental ischemia.[38] These reports, when taken together with results from our study, suggest that women's family history of chronic hypertension and diabetes is an important risk factor for preeclampsia.

Table 3. Multiple logistic regression: only significant covariates included into the final model determinants of preeclampsia among pregnant women

Covariates	Cases	Controls	COR (95%CI)
Age			
< 20	14	43	1
20 – 24	32	67	1.45 (0.70-3.06)
25 – 29	50	109	1.40 (0.70-2.81)
30 – 34	27	49	1.69 (0.79-3.69)
35 & above	28	34	2.52 (1.16-5.54)
Residence			
Urban	82	195	1
Rural	69	107	1.53 (1.03-2.28)
Marital status			
Married	141	281	1
Single	10	21	0.94 (0.44-2.10)
Occupation			
Employed	33	72	1
Merchant	25	44	1.24 (0.65-2.35)
House wife	93	186	1.09 (0.67-1.77)
Education			
No formal education	71	122	1.54 (0.88-2.71)
Primary	15	39	1.02 (0.47-2.20)
Secondary	42	80	1.34 (0.76-2.56)
Higher education	23	61	1
Income in US$			
<$75**	88	170	1.09 (0.73-1.61)
≥$75	63	132	1
Alcohol intake			
Yes	80	122	1.66 (1.12-2.46)
No	71	180	1
Compliant to Folate use			
Yes	99	283	1
No	52	19	7.82 (4.11-13.88)
Exercise			
Yes	118	254	1
No	33	48	1.78 (0.90-2.42)
Partner change			
Yes	31	33	2.10 (1.23-3.60)
No	120	269	1
No of pregnancy			

The finding that women who acquired UTI in the current pregnancy were associated with significantly increased risk of preeclampsia is also consistent with a previous study.[23] The increased risk of preeclampsia suggests that acute maternal infection may play a role in the pathogenesis of preeclampsia.[39]

Various hypotheses have been proposed to explain the mechanism by which maternal infection may be associated with preeclampsia. A key feature of preeclampsia is the greater systemic inflammatory response of women who develop the syndrome compared to women who have normal pregnancies [40] which suggest that inflammation may play an important role in the pathogenesis. Acute infections such as UTI are an important source of inflammation. Thus, the underlying mechanism of infection may be indirect, by enhancing the maternal systemic inflammatory response. It may also include direct effects of infectious agents increasing the risk of acute uteroplacental atherosis, resulting in increased systemic inflammation and vascular endothelial dysfunction preceding the clinical onset of preeclampsia.[41] Although the exact mechanism of the association is uncertain, our study found an increased risk of preeclampsia associated with acute UTI.

In this study having periodontal disease or gingivitis is positively associated with preeclampsia. This report is also in line with previous findings.[25] There is a large body of evidence pointing to infection as a key factor in adverse pregnancy outcomes.[42] Thus, it appears that periodontal disease may play a nonspecific role in various adverse pregnancy outcomes.

This study revealed that periodontal disease is an independent risk factor for preeclampsia. This would be of great public health importance because periodontal disease is both preventable and curable.

Although the result of this study showed that alcohol intake during pregnancy was not significantly associated with development of preeclampsia, another study reported opposite results.[28] The possible explanation for this variation may be the difference in the type of alcohol being taken, the amount and the frequency of drinking, and possibly residual confounding, due to insufficient or unmeasured lifestyle habits. Lack of physical exercise during pregnancy posed a statistically significant relation with preeclampsia in our study. This result differred from the study conducted in Ghana.[29] However, exercise of low to moderate intensity is beneficial for general health reasons to maintain or improve circulation and physical fitness, and perhaps reducing the risk of preeclampsia.

It is well-established that the risk of preeclampsia is greater in twin rather than in singleton pregnancies [18] and we found a similar result in our study This may be due to the presence in twin pregnancies of circulating soluble fms-like tyrosine kinase 1 (sFlt1), which is a circulating antiangiogenic molecule of placental origin playing a central role in preeclampsia by antagonizing placental growth factor (PlGF) and vascular endothelial growth factor signaling in the maternal vasculature defect.[43] In twin pregnancies, circulating sFlt1 levels were twice as high as those in singleton pregnancies. The increased serum sFlt1 levels in twin pregnancies were correlated with increased placental weight. These findings suggest that the increased risk of preeclampsia in twin pregnancies may be due to increased placental mass that leads to increased circulating levels of sFlt1. Alternatively, relative placental hypoxia due to the increased size of the placenta is thought to play an important role for an increased secretion of sFlt1.[43]

Similar to previous studies [30,31,44] we found that folic acid supplementation during pregnancy was associated with a lower risk of preeclampsia. The observed beneficial effect of folic acid supplementation on preeclampsia may be related to several factors, of which the first is placental implantation and development. A well implanted and developed placenta is essential for the health and wellbeing of the mother and the fetus. Placental growth/development is a period of increased cell proliferation and differentiation. Therefore, higher folate intakes may be required

to support appropriate placental implantation and growth and development in early pregnancy. The second factor is the effect of folic acid in lowering blood homocysteine levels [45] as hyperhomocysteinemia is a risk factor for a number of pregnancy complications including preeclampsia.[46] The third factor is the effect of folate in improving systemic endothelial function and therefore reducing the risk of such complications as preeclampsia.[47]

There was a statistically significant relationship between advanced maternal age and preeclampsia in this study, which is in agreement with the results of previous studies.[15]

Sexual partner change did not confer an increased risk of preeclampsia in this study. Contrary to this, the study conducted in Gahanna reported opposite results.[29] This may be due to the low frequency of mothers who reported sexual partner change prior to the fourth month of the current pregnancy.

The present study reported a statistically significant relationship between anemia and preeclampsia; similarly other studies conducted in Sudan and India reported that severe anemia is significantly associated with preeclampsia.[26,27] The prevalence of anemia (<10.5mg/dL) in our study was 8.6% among cases and 2.3% among controls. In our study, the hemoglobin value was measured during the third trimester antenatal care booking, while the same result was found in the two abovementioned studies using hemoglobin values measured during the first trimester antenatal booking.

The findings of this study should be viewed in light of the following limitations. Any random and systematic measurement error in self-reported data might attenuate the associations observed in this study. Assessment of risk factors was made at diagnosis, hence recall bias is inevitable. Finally, the temporal sequence between exposure and disease may be difficult to establish (reverse causality). Further community-based matched case control studies are needed for further exploration of the potential determinants of preeclampsia.

CONCLUSIONS

A family history of hypertension was the most dominant risk factor of preeclampsia. It is concluded that these factors can be used as a screening tool for preeclampsia prediction and early diagnosis, allowing timely interventions to minimize deaths associated with severe preeclampsia/eclampsia.

CONFLICT OF INTEREST

The authors declare no competing interest.

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