ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF MEDICINE

DEPARTMENT OF EMERGENCY MEDICINE

DETERMINANTS OF EARLY AND LATE ONSET PREECLAMPSIA AMONG WOMEN DELIVERED AT GHANDI MEMORIAL HOSPITAL,2023: A CASE CONTROL STUDY.

PRINCIPAL INVESTIGATOR: AWOL SEID (BSC)

A RESEARCH SUBMITTED TO ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE, AND DEPARTMENT OF EMERGENCY MEDICINE FOR THE PARTIAL FULFILLMENT OF REQUIREMENTS OF DEGREE OF MASTERS SCIENCE IN EMERGENCY MEDICINE AND CRITICAL CARE NURSING .

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I, the undersigned MSc student, declare that I have submitted my original work on a title "**Determinants of early and late onset preeclampsia among women delivered at Ghandi memorial hospital,2023: a case control study"** for the examination.

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This thesis work has been submitted for examination with my approval as an advisor.

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APPROVAL BY THE BOARD OF EXAMINATION

This thesis by **Awol Seid** is accepted in its present form by the board of examiners as satisfying thesis requirement for the degree of masters in emergency medicine and critical care nursing.

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STATEMENT OF DECLARATION

I, undersigned, declare and affirm that this is my original work. All sources of materials that are included in the study have been given recognition through citation. Every effort has been made to avoid plagiarism in the preparation of this study. I solemnly declare that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma or certificate.

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ABBREVIATIONS AND ACRONYMS

ACS-	Acute Coronary Syndrome
ANC-	Antenatal Care
ARR-	Adjusted Relative Risk
AOR-	Adjusted Odds Ratio
BMI-	Body Mass Index
CI-	Confidence Interval
DM-	Diabetes Mellitus
EDHS-	Ethiopian Demographic and Health Survey
ETB-	Ethiopian Birr
EOPE-	Early Onset Preeclampsia
HELLP-	Hemolysis Elevated Liver Enzyme Low Platelet Count
LOPE-	Late Onset Preeclampsia
OR-	Odds Ratio
PE-	Preeclampsia
PI-	Principal Investigator
RR-	Relative risk
UTI-	Urinary Tract Infection

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Abstract

Background: preeclampsia is pregnancy induced hypertensive disorder characterized by elevated blood pressure and proteinuria. It can be classified into early onset preeclampsia (EOPE) and late onset preeclampsia (LOPE) based on gestational age. LOPE shares ~80 to 95%of all preeclampsia cases worldwide and its incidence were 0.3 and 2.7%, EOPE, LOPE respectively.

Objective: The primary purpose of this study was to identify determinants of early and late onset preeclampsia among women delivered at Ghandi memorial hospital from January,2021-2022.

Method: Hospital based unmatched case control study was conducted on 174 cases and 348 controls among women delivered at Ghadi memorial hospital from March 20, 2023 to April 20,2023. Women with confirmed preeclampsia and atypical preeclampsia were considered as cases and normotensive women will be considered as controls. Data was collected by using kobo collect application and exported into SPSS version 26 for analysis. Logistic regression was done. Finally, a p-value of less than 0.05 was declared as significant.

Result: Hypertension history in her family and history of high blood pressure in the previous pregnancy were significantly associated with early onset preeclampsia with (AOR=6.8, CI=1.64-28.6) and (AOR=9.8, CI=1.69-56.8) respectively. Advanced maternal age when first time pregnancy, history of UTI during pregnancy, history of contraceptive use, and lack of ANC visits with respective (AOR=14.55, CI=1.28-165), (AOR=8.36, CI=2.05-34.11), (AOR=4.34, CI=1.31-14.41) and (AOR=3.29, CI=1.47-7.35) respectively.

Conclusion: Generally, family history of hypertension, history of gestational hypertension and ANC visit were associated with increased risk of both early and late onset preeclampsia in this study. Nevertheless, history of UTI during pregnancy, advanced maternal age at first time pregnancy, lack of ANC visit and history of contraceptive use were found to be the risk factor for late onset preeclampsia. It is better to recruit specialty trained professionals and work together with primary health facilities to create a conducive environment so that patients with preeclampsia and other associated illnesses can be treated, educated and can have regular follow up.

Keywords: Early onset, late onset, preeclampsia, case control ,determinant

1. INTRODUCTION

1.1. Background

Preeclampsia (PE) is a hypertensive disorder of pregnancy distinguished by blood pressure of ≥140/90 mmHg in two or more successive measures of at least four hours apart or a diastolic blood pressure of greater than 110 mmHg on any one occurrence, with proteinuria of 300 mg and greater per 24 h or ≥+2 on a urine dipstick after the 20th week of gestation and normally resolves within 12 weeks postpartum (1,2).

Preeclampsia is classified into two; early onset preeclampsia (EOPE) diagnosed less than 33 weeks and late onset preeclampsia (LOPE) at 34 or more weeks of gestation based on gestational age. Among the two LOPE shares ~80 to 95%of all preeclampsia cases worldwide and its incidence were 0.3 and 2.7%, EOPE, LOPE respectively. Even though less common occurrence, EOPE is associated with nearly ten times increased risk of perinatal and maternal death and two times higher risk of perinatal death and threefold increased risks of maternal death in women with late onset disease were identified, weighted with normal pregnancy (3,4).

Some etiological features of early and late onset preeclampsia are similar. But there are several different risk factors which result in different outcomes. The two entities should be treated as different conditions from a causative and prognostic perspective(5)

Family history of diabetes mellitus, high pre-pregnancy body mass index ≥ 25 kg/m2 and weight gain ≥ 0.5 kg per week, older maternal age, smoking, unmarried status, and male fetus are the common risk/protective factors both EOPE and LOPE .Younger maternal age, nulliparity, history of chronic hypertension in the family and DM were more strongly associated LOPE whereas chronic hypertension and birth defect were the risk factor to early onset preeclampsia. A high risk of fetal death, perinatal death or severe neonatal morbidity is associated with EOPE (5,6).

Preeclampsia leads to several adverse outcomes for both the mother and the baby, including maternal and perinatal death. Of all pregnancies 5–10% are affected by preeclampsia worldwide. Nonetheless, in low-income countries, the incidence is close to 16.7% and causes 10% – 18% of maternal deaths globally (7). The World Health Organization (WHO) reveals that the incidence of preeclampsia is 7 times greater in low-income countries (2.8% of live

births) as compared to high income countries (0.4%) (1,7). Its prevalence ranges from 1.8% to 16.7% in developing countries (8).

In Ethiopia it is among the five leading causes of maternal death (hemorrhage, obstructed labor, preeclampsia/eclampsia, unsafe abortion, sepsis (2). From the 2016 Ethiopian Demographic and Health Survey (EDHS), nearly 412 mothers per 100,000 live births died due to gestation and related causes (9). Among pregnancy induced hypertension, preeclampsia and eclampsia have a significant impact on maternal and neonatal mortality and morbidity. Preeclampsia results in16% of maternal death in Sub-Saharan Africa and 16.9% of maternal death in Ethiopia. Developing countries like Ethiopia face unpleasant complications of the problem than developed ones (2,7,9).

It progresses to eclampsia and hemolysis elevated liver enzyme low platelet count (HEELP) syndrome unless prompt management is in place (8).

Regular ANC follow up during her pregnancy is a crucial preventive measurement which guarantees early diagnosis and permits prompt management as quickly as possible. In addition, Patient education regarding the physiological changes and challenges, preventing preeclampsia and other pregnancy related diseases during a pregnancy improves the woman's knowledge of detecting problems without delay, thus, allowing for quick medical intervention and the chance of interventional success significantly increases (8).

1.2. Statement of the problem

Preeclampsia is a progressive disease of pregnancy which results in different maternal and fetal complications including preeclampsia, acute renal failure, coagulopathy, placenta abruption, postpartum hemorrhage, intrauterine growth restriction, preterm birth, and maternal and fetal death (10). It accounts for around 22.1% of pregnancy induced hypertension in Africa, and 4.74 to 5.47 % in Ethiopia which contributes to the risk for maternal and perinatal mortality, preterm birth and low birth weight (11–14).

Preeclampsia develops in 20%of first pregnancies and results in at least 40% of premature birth (15). Each year there are around 50,000 maternal deaths worldwide from preeclampsia. Developing countries, including Ethiopia, shares most of these deaths (16). Recently nearly 98%maternal, fetal and neonatal deaths related to preeclampsia occur in low-income countries, with a large share of deaths in south Asia and sub-Saharan Africa (17). It also accounts for 15-20% of maternal mortality in developed countries (18).

Fetal growth restrictions (FGR) as well as short term and prolonged health consequences are important clinical differences for early and late onset preeclampsia in relation to maternal and fetal outcome. Abnormal placentation and FGR are related to EOPE and LOPE, whereas maternal factors were related to the LOPE, without a placental impact. In EOPE, the placental impairment is ‘extrinsic’ to the placenta, with partial spiral artery remodeling (an early pregnancy event). The source of LOPE is ‘intrinsic’ to the enlarging and fermenting placenta, restricting intervillous perfusion. Both pathways lead to secondary syncytiotrophoblast stress and release of proinflammatory factors into the maternal circulation. Maternal factors may increase the risk on many levels for the two stages of preeclampsia and contribute to the risk for both early and late onset forms (19).

Even though a number of clinical and biochemical investigations have been conducted for prediction or timely detection of preeclampsia, most of them are inapplicable for general use in most low-income countries. At present, in a large number of low-income countries there is not an exclusive, valid and practical screening test for preeclampsia (8).

The high load of maternal mortality in African societies is due to delayed health care seeking at the household level to obstetric emergencies often related to lack of information on when and where to get service (8).

The WHO recommends screening for pre-eclampsia during the third ANC visit at 32 weeks (20). In developing countries, obstetric and medical history and clinical examination of women are the main assessment for risk 2 strategies. Pregnant women should be evaluated at their first ANC visit for risk factors of preeclampsia, but screening should be done at every subsequent visit. Screening for pre-eclampsia using maternal history alone is accurate in detecting only 45.3% of cases(21).

Even though the risk factors for the two types of preeclampsia are different, no research has been conducted in Ethiopia on EO and LO preeclampsia specifically to identify their risk factors. Knowing these factors will help to identify the problem early and to start the management without delay. Therefore, this study will help as baseline information for EO and LO preeclampsia risk factor identification.

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1.3. Significance of the study

Nowadays pregnancy induced hypertension including preeclampsia is increasing in the world. It has many complications involving vital organs and leaves permanent disabilities up to death. To reduce and prevent these conditions and related consequences, clinicians have to understand the socio demographic, co morbid and clinical, reproductive and obstetric and behavioral determinants of preeclampsia.

Although preeclampsia is a life-threatening hypertensive condition during pregnancy, there are no sufficient research which indicates determinant risk factors of early and late onset preeclampsia in Ethiopia. Therefore, the result of this study will fill this gap and give some other evidence.

This study will identify determinants of early and late onset PE and will help for public education about the prevention of those modifiable factors. It will help health care workers to act on those factors to intervene in the impact and complication of preeclampsia on mother and fetus with respect to practice of antenatal care. Since limited studies done on determinant risk factors of early and late onset preeclampsia in Ethiopia, it will also be used as a baseline for future similar and related studies and probe researchers' interest for further studies.

The result of this study will also reveal the incidence of early and late onset preeclampsia and other predictors of preeclampsia for hospital managers and those who work on quality of care. Furthermore, the study will help for policy makers to prepare strategies and guidelines to improve quality of care with appropriate intervention to decrease maternal and fetal mortality. In addition, the aim of this study could be used to improve on the outcomes of preeclampsia by raising the quality of antenatal care offered to women by the health care personnel in the slums, especially by imparting knowledge about this condition so that they can recognize important symptoms and take appropriate and timely actions. This would in turn help prevent or reduce maternal mortality attributed to preeclampsia.

2. LITERATURE REVIEW

2.1. prevalence of preeclampsia

High blood pressure after 20 weeks of gestation plus proteinuria can be defined as preeclampsia. It affects 2-10% of pregnant women globally (22). Nevertheless, the overall prevalence of preeclampsia varies from 4.5-23% in some studies (15). About 4% of pregnancies in the United States, 2-16% in Nigeria and 6.1% in Kenya are affected by preeclampsia (21,23,24). Similarly, prevalence accounts 5%in Ethiopia (27).

Preeclampsia may have genetic factors but the actual etiology of this disorder is still not clear. It is a multifactorial and multicausal condition and vital to broadly carry out their various risk factors across different populations of countries.

Among the various risk factors of preeclampsia/early and late onset, this session reviewed different literature on sociodemographic, reproductive and obstetric, clinical and comorbid factors, and behavioral and family history related factors with the aim of identifying those associated with the problem in Ethiopia.

Generally, advanced or young maternal age, rural residency , history of gestational hypertension, maternal history of DM, history of preeclampsia and DM in the family were associated with PE. There are also variables which are associated with early and late onset preeclampsia. From these variables being age ≥35 and chronic hypertension are among the determinants of early onset preeclampsia and family history of hypertension, lack of ANC, nulliparity and primiparity are strongly associated with late onset preeclampsia.

2.2. Socio demographic determinants

A study done in Thailand, on risk factors of early and late onset of preeclampsia showed that: maternal age between 30 and 34 years (OR=2.40; 95% CI 1.19–4.83) and ages ≥35 years (OR=2.75; 95% CI 1.35–5.61) have an association with risk of preeclampsia. Late onset preeclampsia is more likely to occur between ages 30 and 34 years (OR=2.23; 95% CI 1.06-4.71) and ages ≥35 years (OR=2.69; 95% CI 1.27-5.70(26). Similar study done in Taiwan revealed that Women with Advanced maternal age > 35 years (RRR, 1.4; 95%CI, 1.3–1.5, $p < 0.01$) had higher risk to develop early onset preeclampsia (29).

Moreover, a study conducted on Determinants of Pre-eclampsia in south India showed that prepregnancy BMI of >25 (AOR = 7.56), were significantly associated with risk factors of pre-eclampsia (28).Another related study done in Nigeria and democratic republic of Congo shows that: Maternal age less than 30 years, lower educational status, maternal obesity was more likely increased risk of preeclampsia with Adjusted odds ratio (AOR) = 2.50, 9.08, 7.53) respectively and high BMI (OR = 2.82) (29,30).

Studies in northern parts of Ethiopia, Debre tabor and central Tigray had been conducted on determinants of preeclampsia revealed that being age between 10 and 15 years at menarche was approximately eight-fold increased risk of preeclampsia (AOR: 7.69; 95% CI: 3.10–25.29) with reference to age greater than 15 years. Having a new partner was four and two-fold at high risk of developing preeclampsia with odds of (AOR: 4.16; 95% CI: 3.49–17.03) (2). Moreover, an age range of 20–34 years [AOR = 0.071; 95% CI (0.015, 0.32)], being age group ≥35 years (AOR=4.00; 95% CI=1.25–12.80) and rural residence (AOR=3.30; 95% CI=1.50–7.26 were considered to be the high risk of developing preeclampsia (31).

2.3. Behavioral and family history determinants

The research done Thailand showed that; women having hypertension in her family had a 2-fold increased risk of late onset of preeclampsia (OR=2.12, 95%CI: 1.06, 4.22) and (95%CI: 1.04, 4.40) and early onset preeclampsia (OR=2.01, 95%CI: 0.66, 6.09)(26). Another Similar study done in Taiwan revealed that; chronic hypertension, DM, were considerably to develop preeclampsia (all p values< 0.01 as well chronic hypertension (RRR, 1.7; 95%CI, 1.6–1.9, $p < 0.01$) had higher risk to develop early-onset preeclampsia (32).

Furthermore, a study conducted on determinants of Preeclampsia in south India showed that history of chronic hypertension (AOR=6.69), history of diabetes (AOR=8.66), history of hypertension in her family (AOR = 5.48), were the significantly associated with risk factors of preeclampsia (28).

Prior history of preeclampsia had nearly 6 times increased risk to develop preeclampsia (OR:5.6; 95% CI:1.82, 9.28), and history of preeclampsia in her family, chronic hypertension was related with the risk of developing preeclampsia with odds ratio of (OR:1.68; 95% CI:1.26, 2.11), (OR: 2.52; 95% CI:1.29, 3.74) respectively with respect to the research done in sub-

Saharan Africa. There is also a relationship with nutrition and related factors, birth spacing with preeclampsia supported by few studies in the analysis (33).

Another related study done in Nigeria and democratic Republic of Congo shows that: previous history of pregnancy induced hypertension, diabetes, and history of preeclampsia in her family were more vulnerable to having preeclampsia (AOR) = 2.50, 7.53, and 3.57 respectively (29,30).

Studies in northern parts of Ethiopia, Debre tabor and central Tigray had been conducted on determinants of preeclampsia revealed that; Having a family history of preeclampsia were four-fold at high risk of developing preeclampsia with odds of (AOR: 4.16; 95% CI: 3.49–17.03). History of diabetes mellitus (AOR: 4.31; 95% CI: 1.66, 11.21), anemia (AOR: 3.23; 95% CI: 1.18, 8.86)(2) and prior history of PE (AOR: 5.55; 95% CI: 1.80, 17.10) were significantly associated with developing preeclampsia with respect to the study den in central Tigray (31).

Another study conducted in selected public hospitals of Addis Ababa illustrates that; prior history of PE (AOR: 4.28, 95% CI: 1.61, 11.43) had to be a strongly associated risk factor of preeclampsia(34). Moreover, a family history of DM in her family [AOR =0.28.2; 95% CI (0.081, 0.985)], history of hypertension in her family [AOR = 0.124; 95% CI (0.047,0.325)], [AOR = 3.355; 95% CI (1.112, 10.126)], and a maternal history of preeclampsia [AOR = 0.162; 95% CI (0.041, 0.640)] had significant association with preeclampsia (1).

2.4. **Obstetric and reproductive determinants**

According to the research done in Thailand, lack of ANC follow up had seven times increased risk of LOPE (OR=7.19; 95% CI 1.36--38.11) relative to those women who have regular ANC follow up during the first trimester (26). Similar study done in Taiwan revealed that Women, with nulliparity, chronic hypertension, primiparity (all p values< 0.01) was more strongly associated with late onset disease (27).

A study conducted on Determinants of Preeclampsia in south India showed that pregnancy above one fetus (AOR = 5.73) was at increased risk of PE (28).

According to the research done in sub-Saharan Africa shows that, prior history preeclampsia had nearly sixfold increased risk to develop preeclampsia (OR:5.6; 95% CI:1.82, 9.28), and lack of ANC visits has been associated with the risk of developing preeclampsia with odds ratio of (OR: 2.71; 95% CI:1.45, 3.96) (33).

Moreover, another related study done in Nigeria and democratic republic of Congo shows that: primigravity, previous history of pregnancy induced hypertension, polyhydramnios, were more likely increased risk of preeclampsia (AOR) = 20.25, 76.47,5.11, and 3.57 respectively and vitamin D deficiency (OR = 2.77) (29,30). In addition, a case control study conducted in Ghana on risk factors for the determinant on new onset and persistent postpartum preeclampsia demonstrated that: women who had history of contraceptive use were nearly nine times vulnerable for late onset preeclampsia compared to those who didn't use(AOR=8.74,CI=2.48-30.80) (35).

Studies in northern parts of Ethiopia, Debre tabor and central Tigray had been conducted on determinants of preeclampsia revealed women having a new partner was 4 times at high risk of developing preeclampsia with odds of (AOR: 4.16; 95% CI: 3.49–17.03)(2). Primigravida (AOR: 5.41; 95% CI: 2.85, 10.29), prior history of PE (AOR: 5.55; 95% CI: 1.80, 17.10) were significantly associated with developing preeclampsia with respect to the study done in central Tigray (31).

Another study conducted in selected public hospitals of Addis Ababa illustrates that; first time pregnancy (AOR: 2.68, 95% CI: 1.38, 5.22), prior history of PE (AOR: 4.28, 95% CI: 1.61, 11.43) and pregnancy more than one fetus (AOR: 8.22, 95% CI: 2.97, 22.78) had to be a strongly associated risk factors of preeclampsia (34).

2.5. Clinical and co morbid determinants

According to the study done in Taiwan; chronic hypertension, stroke, and hyperthyroidism has the risk of developing PE (all p values< 0.01)(27).

A case control study conducted on Determinants of Pre-eclampsia in south India also showed that history of renal disease (AOR=5.6) was the risk factor of PE (28).

According to the research done in sub-Saharan Africa; chronic hypertension, anemia during pregnancy were associated with the risk of developing preeclampsia with odds ratio of (OR: 2.52; 95% CI:1.29, 3.74), (OR: 3.22; 95% CI:2.70, 3.75) respectively (33).

Another related study done in Nigeria and democratic Republic of Congo shows that chronic hypertension and DM were more likely to have an increased risk of preeclampsia with Adjusted odds ratio (AOR) = 2.73, 10.78, respectively (29,30). Furthermore , a matched case control study done in Tanzania on UTI and preeclampsia among pregnant women revealed that : having a history of UTI during pregnancy were 8 times suffer from late onset preeclampsia(AOR=7.7,CI=2.71-14.4) (36).

Studies in northern parts of Ethiopia, central Tigray had been conducted on determinants of preeclampsia revealed that; history of DM 4 times and anemia during pregnancy 3 times associated preeclampsia (31).

2.3. Conceptual framework

The relationships between independent and dependent variables are illustrated in the conceptual framework below (figure1).

Socio demographic factors (maternal age) and behavioral and family history factors (obesity and family history of hypertension) are associated with the risk of both early and late onset preeclampsia (28,29).

Prior history of pregnancy induced hypertension and chronic hypertension has been associated with the risk of early onset preeclampsia (26,27). Whereas primiparity is independently associated with the risk of late onset preeclampsia (29).

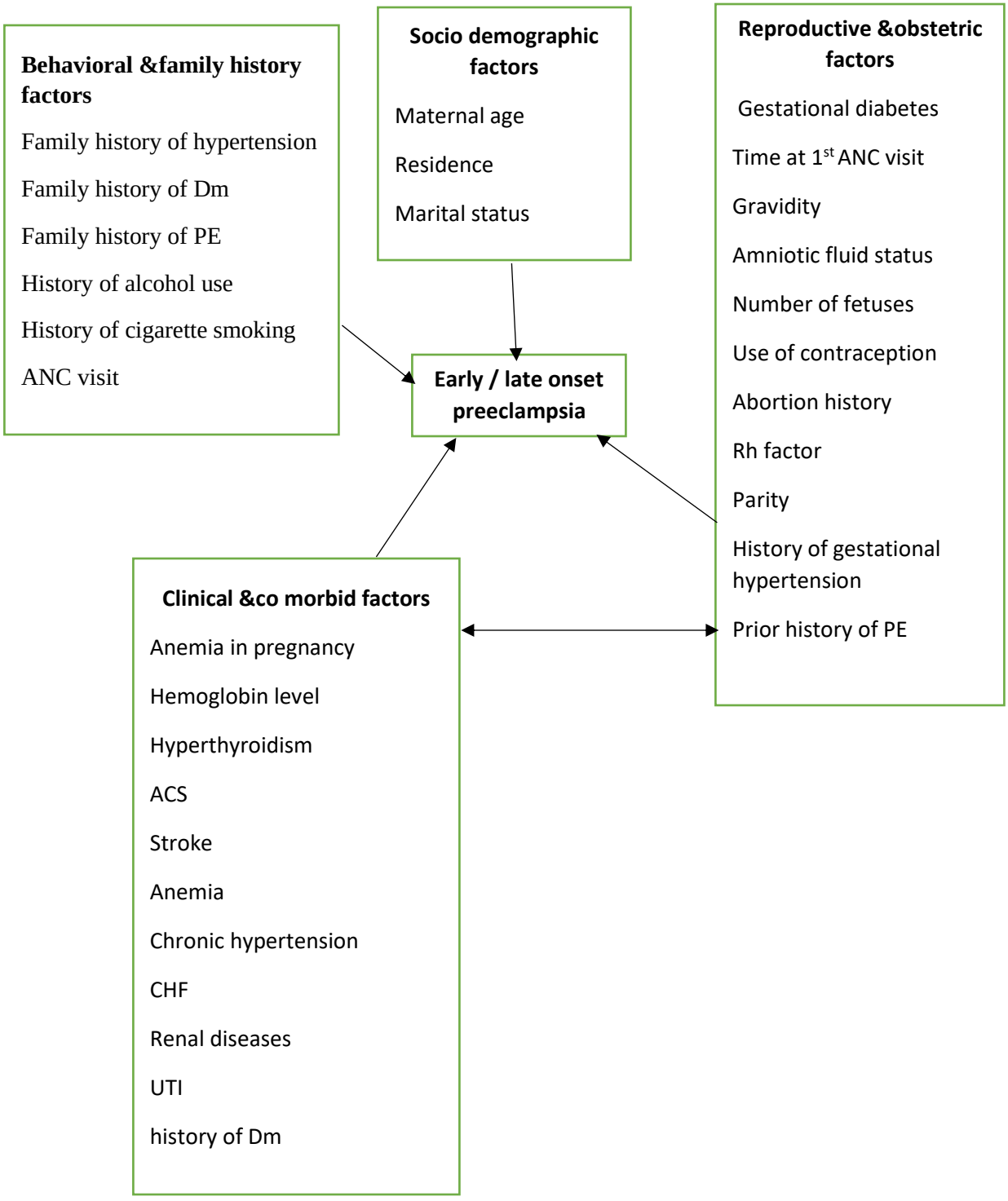

Figure 1: Conceptual framework shows risk factors of early and late onset preeclampsia at Ghandi memorial hospital, 2023 (37)**.**

3. STUDY OBJECTIVES

3.1. General objectives

The general objective of the study was to identify determinants of early and late onset preeclampsia among women delivered at Ghandi memorial hospital from January 2021 to January 2022.

3.2. Specific objectives

- To differentiate socio demographic factors associated with early and late onset preeclampsia among women delivered at Ghandi memorial hospital from January 2021 to January 2022.
- To identify factors associated with early and late onset preeclampsia among women delivered at Ghandi memorial hospital, from January 2021 to January 2022.

4. METHODS AND MATERIALS

4.1. Study Area and period

4.1.1. Study area

The study was conducted at Ghandi memorial hospital (GMH) in Addis Ababa, Ethiopia. GMH is one of the oldest public hospitals in Addis Ababa, located on the Ras Desta Damtew Street just next to the headquarter of the Commercial Bank of Ethiopia (CBE). The GMH, established in 1959 GC, is a pioneer in maternal & neonatal health services in Ethiopia. The hospital was named after the world-renowned Mahatma Gandhi, an Indian lawyer, politician, social activist, and writer who became the leader of the nationalist movement against the British rule of India. Recently, the hospital upgraded its hospital bed capacity to 350 with a total annual patient flow of 5984 patients. GMH is directly operated by the Ministry of Health, providing medical services, particularly focused on reproductive, maternal and neonatal health (38).

4.1.2. Study period

The study was conducted from March 20, 2023 to April 20, 2023 at Ghandi memorial hospital in Addis Ababa, Ethiopia.

4.2. Study design

Hospital based unmatched retrospective case control study was conducted to identify determinants of early and late onset preeclampsia.

4.3. Population

4.3.1 Source population

All women delivered from January 2021 to January 2022 at Ghandi memorial hospital were the source population.

4.3.2. Study population for cases and controls

4.3.2.1. Study population for cases

Preeclamptic women identified by systematic random sampling who delivered at Ghandi memorial hospital from January 2021 to January 2022 were the study population.

4.3.2.2 Study population for controls

Normotensive non proteinuria women identified by systematic random sampling that delivered at Ghandi memorial hospital.

4.3.3. Study unit

All selected cases and controls that delivered at Ghandi memorial hospital from January 2021 to January 2022 and fulfill the eligibility criteria.

4.4. Eligibility criteria for cases and controls

4.4.1. Inclusion criteria for cases

All selected women who delivered at Ghandi memorial hospital from January 2021 to January 2022 with confirmed preeclampsia as well atypical preeclampsia was included as cases.

4.4.2. Inclusion criteria for controls

All selected normotensive non proteinuria women who gave birth ≥37 weeks at Ghandi memorial hospital from January 2021 to January 2022 were included as controls.

4.4.2.1. Exclusion criteria for cases

Women with eclampsia and HEELP syndrome during the study time were excluded.

4.5. Sample size determination

Sample size was determined by using factors significantly associated with the dependent variable from the previous study, and the larger were taken. It was calculated by using Epi info version 7.2.5.0 and the double population proportion formula with the assumptions of 95% CI, 80% power, case to control ratio of 1: 2, and 10% margin of error. Sample size was calculated for both early and late onset preeclampsia using specific formula for case control study as follows:

For early onset $n_1 = \frac{(z_\alpha + z_\beta)^2 2pq}{p_2 - p_1}\left[\frac{r+1}{2r}\right]$ $\quad n_2 = rn_1$

For late onset $\underline{n}_1 = \frac{(\underline{z}_{a+}\underline{z}_\beta)^2}{\underline{p}_2 - \underline{p}_1}\left(\frac{\underline{r}+1}{2\underline{r}}\right)$ $\quad \underline{n}_2 = \underline{r}\underline{n}_1$

Where; n_1 =sample size for cases $\quad p_1$ = proportion for cases

n_2 = sample size for controls $\quad p_2$ =proportion for controls

r = ratio of control to case $\quad p = \frac{p_1 + p_2}{2}$

The final sample size was $N = (n_1 + n_2) + (\underline{n}_1 + \underline{n}_2)$

The percent of cases exposed among early onset preeclampsia of nulliparous women (P1) and the percent of controls exposed (P2) were taken as 60.86% and 39.3% respectively.

Moreover, the percent of cases exposed among late onset preeclampsia women with family history of hypertension (q1) and percent of controls exposed(q2) with respective percentages of 38.9%and 57.7 % from the previous study (26). To get the maximum sample size, P2 and q2 with the corresponding odds ratio were taken for early onset and late onset preeclampsia. Then the total calculated sample was 204 (68 cases and 136 controls) for early onset preeclampsia and 270 (90 cases and 180 controls) for late onset preeclampsia. For the possibility of non-respondents, 10% of the total sample size was added for both early and late onset preeclampsia and the total sample was the sum of the two which is 225 (75 cases & 150 controls) and 297 (99 cases and 198 controls) for early onset and late onset preeclampsia respectively. The final sample size was 522 (174 cases and 348 controls).

Table 1: Sample size calculation to determinants of early and late onset preeclampsia at Ghandi memorial hospital, Ethiopia 2023

Variables	Proportion control	Proportion case	OR	Level of confidence	Power	Ratio control to cases	sample size for cases	sample size for controls	Total sample size after adding 10%	Reference
Sample size for early onset preeclampsia										
Nulliparous	39.13 %	60.9 %	2.42	95%	80%	2	68	136	225(75 cases 150 controls)	(26)
Sample size for late onset preeclampsia										
Having family history of hypertension	38.9%	57.7 %	2.14	95%	80%	2	90	80	297(99 cases 198 controls)	(26)
Final sample size									522 (174 cases 348 controls)	

4.6. Sampling techniques and procedures

Based on the reports obtained from the delivery ward registry of the hospital among women delivered from January 2021, to January 2022, all controls per each case were selected by systematic random sampling from the registration book every 5^{th} value of their card number (1793/348) until the calculated sample size was reached. A total of 379 preeclampsia cases were identified from the registry book of delivery ward. Then the cases early and late onset preeclampsia were identified based on gestational age from the chart by their card number. Among 379 preeclampsia cases 154 were early onset preeclampsia and 225 were late onset preeclampsia. Then cases were selected every 2 value (154/75) and every 3^{rd} value (225/99) for early and late onset preeclampsia respectively. The first study participant was selected by lottery method from the sampling frame arranged in order, while the subsequent study participants were identified by successively adding a constant to the starting random number until the total sample size was reached.

4.7. Study variables

4.7.1. Dependent variable

Early and late onset preeclampsia

4.7.2. Independent variables

Socio demographic characteristic

- Maternal age
- Residence
- Marital status

Reproductive and obstetric factors

- Gravidity
- Parity
- Previous history of preeclampsia
- History of gestational hypertension
- Number of pregnancies (singleton or multiple)
- Amniotic fluid status
- History of abortion
- Use of contraception
- Rh factor

Clinical and co morbid factors

- Stroke
- Anemia
- Hemoglobin level
- Thyroid diseases
- UTI
- ACS
- CHF
- Renal disease
- Chronic hypertension

History of DM

Behavioral and family history related factors

Cigarette smoking

Family history of DM

History of alcohol use

ANC follow up

family history of preeclampsia

Family history of hypertension

4.8. Data collection tools

The data were collected by using structured questionnaires which were adopted and modified from previous Studies (28,29,36). The tool consists of socio demographic, reproductive and obstetric, clinical and co morbid, behavioral and family history variables.

4.9. Data collection procedures and techniques

Three nurses as a data collector, one nurse as a supervisor and one data clerk were recruited and trained on the objectives of the study, the nature of variables, and way of approach to study units, and other issues. The data were collected from charts using structured and pretested questionnaires. All the cases and controls for both early and late onset preeclampsia were selected by systematic random sampling from women who delivered at Ghandi memorial hospital during the study period and fulfilled the inclusion criteria until the calculated sample size was obtained.

4.10. Data quality assurance

The tool was checked for its coherence & completeness and pretested among 5% of the total sample size. Training was given for data collectors, the data clerk and the supervisor prior to the actual data collection started for one day. The collected data were checked for completeness and appropriateness. It is also cleaned, ordered, coded and categorized for analysis.

4.11. Data analysis and presentation

The data were collected by the kobo collect application then exported to SPSS version 26 for analysis. Descriptive statistics were done and presented using texts, frequency tables. Binary logistic regression was done for each variable and variables with p-value less than 0.25 were

eligible for the final model. multicollinearity was checked. Multiple logistic regression was done using adjusted odds ratios with the corresponding 95% confidence intervals. Hosmer-Lemeshow test result shows the model was fit. Finally, a p-value less than 0.05 was declared as statistically significant.

4.12. Operational definition

Early onset preeclampsia; is defined as preeclampsia that develops at ≤33 weeks of gestation(3).

late-onset preeclampsia; is described as preeclampsia that develops at or after 34 weeks of gestation(3).

Atypical preeclampsia; can be defined as non proteinuric gestational hypertension plus hemolysis or normotensive gestational proteinuria with the presence of hemolysis or the presence of preeclampsia after 48 h postpartum; and before 20 weeks of pregnancy(39).

Gravidity; defined as the sum of all pregnancies, including all live births and pregnancies that did not result in a live birth(38).

Parity; defined as pregnancies that resulted in the delivery at 6 months (4 weeks) gestation, of either a live birth or a stillbirth(40).

4.13. Ethical consideration

Letter of permission was obtained from Addis Ababa University, College of Health Sciences and department of Emergency Medicine to conduct the study. Then the letter was submitted to Ghandi memorial hospital and Addis Ababa City Administration Health Bureau (AACAHB). An ethical clearance or letter of cooperation was also obtained from these institutions after review of the proposal. Any personal identifiers like name were not to be used at the time of data collection.

4.14. Dissemination of plan

The result of this study will be disseminated to Addis Ababa University, College of Health Sciences, School of Medicine, Department of Emergency Medicine and the Library. It will also be submitted to AACAHB and Ghandi memorial hospital. The result will also be uploaded to Addis Ababa University's portal and published in journals.

5. RESULT

In this hospital based unmatched case control study, a total of 496 participants (174 cases and 322 controls) who delivered at Ghandi memorial hospital were involved with 5 lost and 21 incomplete cards.

5.1.Socio demographic characteristics of participants

Among participants, majority 78 (36.6%) of early onset and 113 (39.9%) late onset preeclamptic women were under the age group of 25-29 years. Addis Ababa residents were higher than residents who were outside Addis Ababa with the proportion of (70.9% & 56.2%) for early and late onset preeclampsia respectively. Regarding marital status of the participants, more proportion of early onset and late onset preeclamptic women were married 487 (98.2%).

Table 2: Socio demographic characteristics of women delivered at Ghandi memorial hospital in Addis Ababa, Ethiopia 2023.

Variables	Categories	Early onset (213)		Late onset (283)	
		Cases (n%)	Control (n%)	Cases (n%)	Control (n%)
Age in years	<24	26(12.2%)	44(20.7%)	24(8.5%)	54(19.1%)
	25-29	28(13.1%)	50(23.5%)	38(13.4%)	75(26.5%)
	30-34	13(6.1%)	31(14.6%)	24(8.5%)	41(14.5%)
	>35	8(3.8%)	13(6.1%)	13(4.6%)	14(4.9%)
Marital status	married	73(34.3%)	137(64.3%)	95(33.6%)	182(64.3%)
	Single	1(0.5%)	1(0.5%)	4(1.4%)	2(0.7%)
	divorced	1(0.5%)	0(0.0%)	-	-
Residence	Addis Ababa	47(22.1%)	104(48.8%)	48(17.0%)	111(39.2%)
	Outside Addis Ababa	28(13.1%)	34(16.0%)	51(18.0%)	73(25.8%)

5.2. Determinants of early onset preeclampsia

Initially different variables like residence, number of ANC visit, number of fetuses, anemia during pregnancy, hemoglobin level, history of UTI, preeclampsia, gestational hypertension, abortion, contraceptive use, and family history of hypertension were associated with early onset preeclampsia in the binary logistic regression analysis. All were p-value <0.25. These variables were taken and analyzed together using multiple logistic regression models.

After controlling the effects of potentially confounding factors using multivariable logistic regression model, having hypertension in her family 6.8 times and history of gestational hypertension 9.8 times associated with early onset preeclampsia (AOR=6.80,CI=1.64-28.6,p=0.008) and (AOR=9.8,CI=1.69-56.8,p=0.011) respectively. Women with complete ANC follow up were 98% less likely to develop early onset preeclampsia as compared to who had incomplete ANC follow up (AOR=0.02,CI=0.007-0.060,p=0.001). **(Table 3)**

Table 3. Factors associated with early onset preeclampsia among women delivered at Ghandi memorial hospital, Ethiopia 2023.

Variables with category	Early onset preeclampsia (213)				
	Cases (75)	Controls (138)	COR (95%CI)	AOR (95%CI)	P-value
Residence					
Addis Ababa	47	104	1	1	
Outside Addis Ababa	28	34	1.82(0.99-3.34)	1.55(0.57-4.2)	0.389
Hgb level					
<11	10	7	2.88(1.05-7.91)	4.5(0.58-35.4)	0.148
>11	65	131	1	1	
No of ANC visit					
complete ANC visit	8	118	0.02(0.008-0.048)	0.02(0.007-0.06)	0.001*
Incomplete ANC visit	67	20	1	1	
Contraceptive use					
Yes	10	11	1.78(0.72-4.40)	2.4(0.45-12.8)	0.302
No	65	127	1	1	
UTI during pregnancy					
Yes	13	4	7.02(2.20-22.4)	1.6(0.28-9.8)	0.584
No	62	134	1	1	
Anemia during pregnancy					
Yes	6	4	2.9(0.79-10.66)	0.14(0.01-1.9)	0.142
No	69	134	1	1	
History of gestational HTN					0.011*
Yes	12	4	6.38(1.98-20.6)	9.8(1.69-56.8)	
No	63	134	1	1	
Family history of HTN					
Yes	19	10	4.34(1.9-9.9)	6.8(1.64-28.6)	0.008*
No	56	128	1	1	
History of preeclampsia					
Yes	20	7	6.8(2.7-17.02)	1.8(0.56-5.98)	0.321
No	55	131	1	1	
History of abortion					
Yes	23	31	1.53(0.8-2.86)	0.58(0.21-1.6)	0.304
No	52	107		1	
Multiplicity of pregnancy					
singleton	69	134	1	1	0.135
twins	6	4	2.9(0.79-10.67)	4.55(0.6-33.2)	

NOTE: * p-value <0.05) or significantly associated

1=reference

5.3. Determinants of late onset preeclampsia

In the binary logistic regression analysis, factors found to be associated with late onset preeclampsia with p-value of <0.25 were residency, marital status, amniotic fluid status, history of abortion, history of preeclampsia, history of gestational hypertension, RH factor, time of ANC follow up started, anemia during pregnancy, UTI during pregnancy, contraceptive use, family history of DM, hemoglobin level, maternal age, age at first pregnancy, number of ANC visit and parity. To control the effect of confounding variables, those variables were entered into multiple logistic regression.

On multiple logistic regression, maternal age >35 , age at first pregnancy between 25-29 and >35 years, history of gestational hypertension, history of contraceptive use, history of UTI during pregnancy, family history of hypertension and number of ANC visit were found to be statistically significant determinants of late onset preeclampsia. Thus, those aged between 25-29 were 65% less likely to develop late onset preeclampsia as compared to age less than 24 (AOR=0.35,CI=0.13-0.95, p=0.038). Advanced maternal age >35 and being age between 25-29 years at first pregnancy were 14 times and 4 times increased risk of late onset preeclampsia as compared age <24 (AOR=14.55, CI=1.28-165) and (AOR=4.18, CI=1.82-9.61) respectively.

Mothers who had incomplete ANC follow were three times more likely to suffer from late onset preeclampsia as compared to those who had complete ANC follow up (AOR=3.29, CI=1.47-7.35, P=0.004). History of gestational hypertension and contraceptive use nearly four times, family history of hypertension six times and history of UTI during pregnancy eight times increased risk of late onset preeclampsia (AOR=3.87, CI=1.25-11.45, P=0.019), (AOR=4.34, CI=1.31-14.41, P=0.016), (AOR=5.98, CI=2.07-17.31, P=0.001) respectively. (**Table 4**)

Table 4. Factors associated with late onset preeclampsia among women delivered at Ghandi memorial hospital, Ethiopia 2023.

Variables with category	Late onset preeclampsia (283)				
	Cases (99)	Control (184)	COR (95% CI)	AOR (95%CI)	P-value
History of gestational HTN					
Yes	19	9	0.22(0.09-0.50)	3.78(1.25-11.45)	0.019*
No	80	175	1	1	
UTI during pregnancy					
Yes	19	3	14.33(4.12-49.8)	8.36(2.05-34.11)	0.003*
No	80	181	1	1	
Contraceptive use					
Yes	19	7	6.0(2.43-14.86)	4.34(1.31-14.41)	0.016*
No	80	177	1	1	
Family history of HTN					
Yes	24	11	5.03(2.35-10.79)	5.98(2.07-17.31)	0.001*
No	75	173	1	1	
Maternal age					
<24	24	54	1	1	
25-29	38	75	1.14(0.61-2.12)	0.35(0.13-0.95)	0.038*
30-34	24	41	1.32(0.66-2.64)	0.65(0.24-1.81)	0.412
>35	13	14	2.09(0.85-5.11)	0.65(0.16-2.73)	0.560
Age at first pregnancy					
<24	49	126	1	1	
25-29	40	46	2.24(1.31-3.83)	4.18(1.82-9.61)	0.001*
30-34	7	10	1.8(0.65-4.99)	2.77(0.66-11.64)	0.163
>35	3	2	3.86(0.63-23.79)	14.55(1.28-165)	0.031*
No of ANC visit					
complete ANC visit	58	150	1	1	0.004*
Incomplete ANC visit	41	34	3.12(1.81-5.39)	3.29(1.47-7.35)	

NOTE: * p-value <0.05 or significantly associated

6. Discussion

Some literature had shown that there was no risk factor linked to only early onset preeclampsia. This study also in line with those literatures. With regard to magnitude of association, early onset preeclampsia appears to be linked mainly to history of gestational hypertension and family history of hypertension. Late onset preeclampsia was independently associated with history of UTI during pregnancy, advanced maternal age at first time pregnancy and history of contraceptive use as well as history of gestational hypertension and family history of hypertension.

In this study women who had a history of hypertension in her family were approximately 7 times increased risk of early onset preeclampsia compared to those without the condition. This result was supported by a case control study conducted in Thailand which revealed nearly 2 times higher than those without the condition (26). This consistency might be due to similarity in study design and the higher degree of association for this research could be the larger sample size used for this study. The exact means of family history of hypertension to cause early onset preeclampsia is not clear. Since it is caused by both placental and maternal factors, genetic predisposition of the mother, and sharing of similar environment and other exposures with the family is thought to be the main reason for the development of this condition.

The odds of early onset preeclampsia for women having history of hypertension during the past pregnancy were 10 times higher as compared to those without the condition. This result was supported by the study done in Nigeria and Democratic republic of Congo on determinants of preeclampsia which revealed 7.53 times higher for cases than normotensive controls(29,30). It contradicts with different studies done in Thailand, Taiwan and Kenya(26,32,37).The possible explanation for this result could be women having history of gestational hypertension doubles the risk of developing coronary heart disease in the future which causes narrowing of maternal cardiovascular system that results in high maternal blood pressure.

This study also indicated that women who had complete ANC follow up were 98% less likely to develop early onset preeclampsia compared to those who had incomplete ANC visit. The possible explanation for this result could be, women who have regular ANC follow up might have a screening for the possible risk factors of the disease and early identify and take preventive measures.

According to this study's finding, those with a maternal age between 25 and 29 were 65% less likely to develop late onset preeclampsia with reference to those whose age <24 years. This result was supported by the study done in central Tigray, Ethiopia (31).

In this study being maternal age >35 years when first time pregnancy were 14 times suffer from late onset preeclampsia compared to those <24 years. It was in line with the study done in Thailand on risk factors of early and late onset preeclampsia (26). This result was not supported by different literatures done in Taiwan, India and Kenya (3,6,37). The possible reason for this result is that; since late onset preeclampsia is mainly associated with maternal factors like age and comorbidity, when the age increases the cardiovascular system becomes narrowed and incompetent. As a result , the mother experiences high blood pressure when getting pregnant during advanced age.

This result also indicated that lack of ANC follow up was significantly associated with late onset preeclampsia compared to women who had regular follow up. This was consistent with the study done in Thailand which showed lack of ANC was 7 times increased risk of late onset preeclampsia (26). This might be the missing information and screening test due to lack of ANC which could increase the risk of different factors to playing a vital role to cause late onset preeclampsia.

The odds of late onset preeclampsia for mothers who had a history of hypertension in her family were 6 times higher with reference to those without the condition. This result was comparable with the research done in south India and Thailand (26,28).

A strong association was observed in this study between UTI and late onset preeclampsia which were nearly 8 times . This result was in line with a case control study conducted in Tanzania which showed the odds of mothers who had UTI during her pregnancy was 7.7 higher as compared to those without the condition (36). Despite the exact etiology of late onset preeclampsia not clear, it is thought to be; UTI during pregnancy causes widespread systemic inflammatory response. As a result, the mother may experience high blood pressure.

With respect to this research, women who had a history of contraceptive use were approximately 4 times higher in increased risk of late onset preeclampsia. It was supported by the study done in Ghana which revealed use of contraceptive results in 8.74 times increased

risk of late onset preeclampsia (35). Different studies didn't support this result and it needs further research.

This study also revealed that women having gestational hypertension during her previous pregnancy were 4 times more likely to suffer from late onset preeclampsia compared to those who had no history of this condition. This result was supported by the study done in Nigeria and Democratic republic of Congo (29,30). In contrast, it is not supported by literature done in Taiwan, Thailand and India (10,26,28,34). This discrepancy might be the difference in the environmental factor and study design.

7. Strength and limitation of the study

7.1. Strength of the study

This study design was quite appropriate to assess the relationship between dependent and independent variables compared to cross sectional, case report and case series studies.

The study is new in its kind that no other published similar study, which identified determinants of early and late onset preeclampsia has been done in the Country yet.

7.2. Limitation

Since this study was a retrospective chart review it had been faced with poor documentation of patient history. The first limitation might be lack of documentation on history of alcohol use, history of cigarette smoking, and documentation of height and weight to calculate BMI. Due to this the study didn't demonstrate those variables.

The other limitation of this study was, since it had been conducted in a single center and might cause a decrease in its representativeness.

Since this study is new and very few studies conducted, it was very difficult to discuss with other's work.

8. Conclusion and Recommendations

8.1. Conclusion

In this study, maternal history of contraceptive use, history of UTI during current pregnancy, maternal age between 25-29 for current pregnancy and advanced maternal age (>35) when first time pregnancy was independently associated with late onset preeclampsia. In addition, lack of ANC follows up, having hypertension during the previous pregnancy and hypertension history in the family was significantly associated with late onset preeclampsia. Generally, family history of hypertension, history of gestational hypertension and ANC visit were associated with both early and late onset preeclampsia. With regard to magnitude of association, history of gestational hypertension and family history of hypertension were more strongly associated with early onset preeclampsia.

8.2. Recommendations

Based on the findings of this study, some points of improvement were recommended by the researcher.

Hospitals: They are recommended to incorporate preventive and screening modalities of preeclampsia and other chronic illnesses in their plan. It is better to recruit specialty trained professionals and create a conducive environment so that patients with preeclampsia and other associated illnesses can be treated, educated and can have regular follow up. They should also work together with primary health facilities which are close to the community.

Health care providers: They should identify and treat factors associated with the two subgroups of preeclampsia early, schedule for follow-up care and educate about the preventive modalities of the conditions.

Researchers: There is greater scarcity of research on determinants of early and late onset preeclampsia in Ethiopia or outside Ethiopia. Therefore, further studies are very important in the area. Large prospective and multi centered studies should be carried out to have a better picture for identification of determinants of the condition and help for better management.

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ANNEX I: QUESTIONNAIRES

Table 4 Tools of determinants of Sociodemographic characteristics of early and late onset preeclampsia at Ghandi memorial hospital, 2023

S. N	Item question	Response
101	How old was the mother when giving birth?	---
102	Where was her Residency?	1.urban 2.rural
103	What was her marital status?	1.Married 2.Single 3. divorced 4.widowed

Table 5 Tools of determinants of reproductive and obstetric factors at Ghandi memorial hospital,2023.

S. N	Item question	Response
201	Has she been pregnant before this pregnancy? (Include all pregnancies that ended in life births, spontaneous or induced abortions, ectopic pregnancy and stillbirth as well)	Yes no
203	If yes, how many times has she been pregnant? (Including the current pregnancy)	___times
204	Has she ever given birth before?	Yes No

205	If yes, how many times?	---times
206	What is the multiplicity of mothers for the current pregnancy?	Singleton Twins…….
207	Amniotic fluid status	Oligohydramnios Polyhydramnios Normal
208	Does she ever have a history of spontaneous abortion?	Yes No
209	If yes, how many times?	--times
211	How old was she at her first pregnancy(years)?	---years
212	At what gestational week did she give birth?	---wks.
213	Was she using modern contraceptives in the last 12 months before this pregnancy?	Yes No
214	If yes, what type?	1.Pill 2. Injectable 3.Implant 4. Condom 5.Iced
215	Has she ever been diagnosed with preeclampsia?	Yes No
216	Has she ever had Gestational diabetes during previous pregnancy?	Yes No
217	Has she ever had high blood pressure during previous pregnancy?	Yes No
218	RH factor	Positive

		Negative

Table 6 tools of determinants of behavioral and family history factors at Ghandi memorial hospital ,2023.

SN	Item question	Response
301	Was she smoking a cigarette during the pregnancy?	Yes No
302	Was she drinking alcohol during the pregnancy?	Yes No
303	When was her first ANC visit?	1.At 1st trimester 2.After 1st trimester 3.No ANC visit
304	How many visits did she have?	……. times
305	Has her family ever had or have hypertension? (Check all that apply for first degree relatives only)	Yes No
306	If yes, who?	1. Father 2. Mother 3. Sister 4. Brother
307	Family history of preeclampsia?	Yes No
308	Has her family ever had DM?	Yes No

Table 7 tools of determinants of clinical and comorbid factors Ghandi memorial hospital ,2023

SN	Item question	Response
401	Was she ever diagnosed with Hyperthyroidism /hypothyroidism?	Yes No
402	Was she ever diagnosed with a stroke?	Yes No
403	What was the hemoglobin level of the mother in mg/dl?	--mg/dl
404	Was she diagnosed with anemia during pregnancy?	Yes No
405	Has she ever had a DM?	Yes No
406	Did she have Chronic hypertension?	Yes No
407	Has she ever had CHF?	Yes No
408	Has she ever had a history of ACS?	Yes No
409	Has she ever had Chronic renal disease?	Yes No
410	Has she ever had UTI during pregnancy?	Yes No