ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

EFFECT PREECLAMPSIA/ECLAMPSIA ON INCIDENCE RATE OF SMALL FOR GESTATIONAL AGE AMONG PREGNANT WOMEN IN MEKELLE GENERAL HOSPITAL AND AYDER COMPREHENSIVE SPECIALIZED HOSPITAL, TIGRAY, NORTHERN ETHIOPIA

BY

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A THESIS TO BE SUBMITTED TO SCHOOL OF PUBLIC HEALTH, COLLEGE OF HEALTH SCIENCES, ADDIS ABABA UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN EPIDEMIOLOGY AND BIOSTATISTICS.

OCTOBER, 2019

ADDIS ABABA, ETHIOPIA

Advisor's Approval Sheet

I, the under signed, declare that this thesis is my original work, has not been presented for a degree in any other university and that all resources of material used for this thesis have been fully acknowledged.

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Approval of the primary advisor and examining board

This thesis work has been submitted with our approval as university advisor and examining board.

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ACKNOWLEDGMENTS

I would like to express my deepest gratitude to Dr. Girma Taye and Yimer Seid who always accepted me with open arms and for their constructive comments from the beginning of research area selection and write up of my thesis report.

My gratitude goes also to Tigray Regional Health Bureau, Ayder Comprehensive Specialized Hospital and Mekelle General Hospital staff in general and my deepest appreciation goes to those people who give me valuable comments and suggestions. Last but not least many thanks to Health Management Information System staff of Ayder Comprehensive Specialized Hospital and Mekelle General Hospital for their dedicated support on providing the necessary information and also for data collectors.

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ACRONYMS AND ABBREVIATIONS

ACOG	American College of Obstetrics and Gynecology
ACSH	Ayder Comprehensive Specialized Hospital
AHR	Adjusted Hazard Ratio
ANC	Antenatal Care
BP	Blood Pressure
C/GHTN	Chronic/Gestational Hypertension
CHR	Crude Hazard Ratio
CI	Confidence Interval
CTG	Cardiotocography
EFW	Estimated Fetal Weight
GA	Gestational Age
GUI	Genitourinary Tract Infection
HELLP	Hemolysis, Elevated Liver Enzymes, Low Platelet Count
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HSTP	Health Sector Transformation Plan
IUGR	Intrauterine Growth Restriction
LMIC	Low and Middle-Income Countries
MGH	Mekelle General Hospital
MPH	Master of Public Health
MSc	Master of Science
PIH	Pregnancy Induced Hypertension
SGA	Small for Gestational Age
STATA	Statistical Analysis Software
USA	United State American
UTI	Urinary Tract Infection
VDRL	Venereal Disease Research Laboratory
WHO	World Health Organization

ABSTRACT

Background: In low and middle-income countries including Ethiopia, small for gestational age is a serious health problem, due to an increase in fetal and neonatal mortality and morbidity. In Ethiopia and particularly in Tigray there is a paucity of information on incidence rate and predictors of small for gestational age among pregnant women. Therefore the aim of this study is to determine the effect of preeclampsia on the incidence of small for gestational age among pregnant women in Mekelle General Hospital and Ayder Comprehensive Specialized Hospital, Tigray, Northern Ethiopia, 2019.

Methods: A retrospective cohort study was employed to compare the small for gestational age between the exposed; preeclampsia (n=239) and non exposed; normotensive (n=476) women who were antenatal care follow-up in Mekelle General Hospital and Ayder Comprehensive Specialized Hospital from January 01, 2014 to March 31,2019. Systematic sampling was used to select the study participants. A pre-tested structured data abstraction checklist was used to extract data. Collected data were entered and cleaned using Epi Data version 3.1 and exported to STATA version 14 for analysis. The incidence rate was calculated dividing all small for gestational age cases in the cohort for the person-weeks of follow-up. The data analysis was performed by Cox proportional hazard model.

Results: The incidence rate of small for gestational age was higher among preeclampsia than normotensive women (94.5 versus 24.9 per 1000 person weeks, Z=9.42, p<0.000001).The hazard of small for gestational age was four times higher in preeclampsia women than normotensive pregnant women, (AHR=3.92, 95% CI 2.55-6.01), history of low birth weight (AHR=0.41, 95%CI 0.17-0.94), poor gestational weight gain (AHR=1.89, 95% CI 1.15-3.1) were significant predictors.

Conclusion and recommendation: There is a significant difference between preeclampsia and normotensive pregnant women in terms of the incidence rate of small for gestational age. Preeclampsia, a history of low birth weight and weight gain had significant predictors for small for gestational age. It is needed to strengthen the screening of preeclampsia for optimal fetal growth, and counseling on nutrients for adequate gestational weight gain. Further study will be also important to confirm the predictors at the community level.

Keywords: Small for gestational age, preeclampsia/eclampsia, Tigray

1. INTRODUCTION

1.1 Background

Small for gestational age is defined as an estimated fetal weight less than 10 percentiles for that particular gestational age based on the non-customized growth chart(1). The terms intrauterine growth restriction and SGA often use to describe the same problem, although there are subtle differences between the two-term. IUGR is a clinical definition and applied to neonates with clinical evidence of malnutrition. IUGR means a fetus fails to reach its expected growth potential in uterine life. SGA is a multifactorial disease of pregnancy that markedly increases perinatal mortality and morbidity(2).

SGA is increasingly seen as a fetal gradual process due to the compromised intrauterine environment, which may assist the fetus to survive. Small size may be constitutional and reflect a normal physiological difference; however, the reduced growth rate may be secondary to maternal, placental, and/or fetal factors(2). According to the time of adverse intrauterine environment, the IUGR fetus may be classified as symmetric, and asymmetric. Symmetric growth restriction (20-30%) indicates a fetus whose entire body is proportionally small due to the adverse environment in early gestation and the growth impairment may be due to genetic factors, congenital infections or syndromes, or toxic effects. The second one is asymmetric growth restriction (70-80%), which indicates that an undernourished fetus means normal length but small weight. This type of growth restriction is usually occurring as the result of placental insufficiency (2).

SGA occurs alone or associated with pregnancy-induced hypertensive disorders: preeclampsia, gestational hypertension, and chronic hypertension. IUGR was associated with preeclampsia which shares a common placental phenotype described as placental insufficiency that originates in early gestation when the trophoblastic invades the deciduas. This process requires high availability of energy for cell growth, proliferation and metabolic activity(3).

For all SGA births, the highest prevalence was recorded in South Asia (44.5%), followed by Sub-Saharan Africa (25.5%) and Southeast Asia (24.3%), and also the prevalence of SGA in Ethiopia was 32.1%, which is one of the top ten countries with the highest numbers of SGA infants born based on the 2010 global survey(4). SGA infants were a higher risk of death during the newborn and infant periods. Neonates affected by SGA are usually undernourished and undersized(4).

1.2 Statement of the problem

In low and middle-income countries around 32.4 million infants (27%) are born small for gestational age annually. Ethiopia also contributes about 838 thousand cases which is a serious public health problem(4). SGA is associated with increased fetal and neonatal mortality and morbidity, being linked to immediate perinatal adverse events (prematurity, cerebral palsy, intrauterine fetal death, etc.) and also to adult pathologic conditions like obesity, hypertension, type-2 diabetes, cardiovascular diseases as well as emotional, behavioral and social problems in later life(5, 6). It is clear that growth-restricted fetuses remain a high-risk group for many adverse outcomes, but the potential contribution to the burden of global prenatal mortality was under-recognized(7).

Preeclampsia is often associated with SGA due to chronic placental hypo-perfusion compared to normal pregnancies(3). Most of the adverse prenatal outcomes(SGA) were significantly more common in those with preeclampsia/eclampsia compared to the other hypertensive disorders, but not clear compared to normotensive women (8). A study conducted in South Africa shows that 22.9% of SGA babies had deaths due to hypertensive disorders during pregnancy(9). A study conducted in Sub-Saharan countries(10)also documented that babies born to preeclampsia have an increased risk of being born prematurely, low birth weight and SGA compared to normotensive mothers. Currently, some studies recommended Low-dose aspirin for women at increased risk of preeclampsia and SGA, and cigarette smoking cessation for those smoker women(11).

Based on Child Health Epidemiology Reference Group Analysis, an estimated 21.9% of neonatal deaths in LMIC were attributable to being born SGA in 2012. In total, 67.7% were among term SGA infants, about 82% of term SGA weighing <2500 grams and an estimated 32.3% of neonatal deaths were among preterm SGA infants(12). Neonatal mortality due to SGA in Ethiopia was 29 per 1000 live birth in general, but among preterm SGA was 1.6 per 1000 live births and 20.8per 1000 live births due to term SGA. Neonatal deaths due to SGA were also 25.5%at population level(12).

The risk of SGA in developing countries was about six times higher than in developed countries(13). A multi-country analysis of mortality risk for SGA births in LMICs determined that the relative risk for neonatal mortality was 2.44 for term-SGA births, and15.4 for preterm-SGA births compared to babies born term-AGA(14). A study conducted in North West Ethiopia, the risk of neonatal death was 2.4 times higher among SGA than appropriate for gestational age neonate due to morbidity from meconium aspiration syndrome, hypoglycemia, hyaline membrane disease, and early-onset neonatal sepsis and intra-partum asphyxia(15). A study conducted in Tigray shows that low birth weight for gestational age was attributed for 35% of very low birth weight and 54% of low birth weight, therefore neonatal mortality was higher among low birth weight than normal birth weight and have also economic and environmental stress to the community and health facility(16).

1.3 Rational of the study

Small for gestational age is a serious health problem in low and middle-income countries ; especially sub-Saharan Africa where Ethiopia is no exception due to not only during the fetal, neonatal and infancy period, but also later in life affect by non-communicable diseases, such as, neurological, metabolic, respiratory and cardiovascular morbidities(6). So far, there is lack of study which clearly shows incidence rate of SGA among preeclampsia/eclampsia and normotensive pregnant women and other independent predictors of SGA among pregnant women, both in the study areas in Mekelle General Hospital and Ayder Comprehensive Hospital, Tigray and in Ethiopia generally, so there is a knowledge gap in the area of SGA research in our context. Therefore, this study will attempt to provide information about SGA among pregnant women.

1.4 Significance of the study

The results of the study will provide valuable information for the Ethiopian Federal Ministry of Health and Regional Health Bureau to give focus for the intrauterine growth fetus among the high-risk mothers for timely diagnosis and monitoring for better health outcomes of the fetus. This study will also help policymakers in designing context-specific appropriate strategies for addressing the modifiable risk factors of SGA by early screening, detection, treatment and control of the risk factors.

The results of this study will also be used for health professionals and communities to minimize the preventable predisposing factor that leads to SGA and will be used as a baseline for other researchers. It will also contribute to achieving the HSTP target for 2025 and 2035, preventable deaths of newborns and children under 5 years of age, to reduce neonatal mortality to at least as low as 15per 1000 live births and under 5 mortality to at least as low as 31per 1000live births, and 10per 1000 live births and 20per 1000 live births respectively(17).

2. LITERATURE REVIEW

2.1 Small for gestational age and Preeclampsia /eclampsia

Impaired utero-placental perfusion leads to intrauterine growth restriction and preterm birth. Utero-placental flow may be diminished by faulty development, acquired obstruction, or disruption of the utero-placental vasculature. Maternal medical conditions (chronic hypertension, renal insufficiency, cardiac disease, malaria) and obstetrical complications (pre-eclampsia, eclampsia) associated with vasculopathy and/or reduced maternal blood volume or blood pressure leads to diminished utero-placental perfusion (18).

Small for gestational age has been estimated to be 27 % of all live births in low and middle-income countries annually (more than 32.4 million infants) in 2010, with the prevalence of SGA babies ranging from 5.3 % in China to 41.5 % in Pakistan, the variability in SGA rates reflects not only socio-environmental factors and population differences, but also the application of different standards across studies(4). The most common abnormalities are poor growth due to inadequate blood supply through the placenta that is not functioning properly, and the problems of prematurity mostly associated with delivery before the term to protect the health of the mother or the fetus(19).

Based on secondary data analysis from WHO antenatal care trial the incidence of IUGR among preeclampsia women was 22.2%, and among women with gestational hypertension was 12.9% versus 13.1 % of IUGR was among normotensive women secondary to smoking, undernutrition and unexplained factor(20). The prevalence of SGA less than 10 percentile among mild and severe preeclampsia was 23% and 30.5% respectively but among normotensive was 13.2% and also among those who are less than 5 percentiles in the mild and severe cases were 13% and 16.4% respectively, but 4.2% in normotensive mothers(21). developing of SGA among preeclampsia and normotensive mothers were 17.1% and 6.6% respectively(22). A cross-sectional study done in the Tigray region shows that SGA was20.2% among preeclampsia/eclampsia, but not clear among the normotensive pregnant mothers(8).

The effect of preeclampsia/eclampsia for SGA have different strength from one study to other studies, a cohort study conducted in the USA shows that women with pre-eclampsia were 2.1 to 3.41 times more likely to develop SGA as compared with normotensive women after adjusting for maternal age, race, smoking, medical status, and gestational age(23). A study conducted in China shows that an increased risk of being born SGA infants to women with mild, moderate and severe pregnancy-induced hypertension, 1.17, 1.69 and 3.5 times respectively, compared to fetus with normotensive during pregnancy, but a study conducted in North Carolina shows that no significant association between hypertensive disorders during pregnancy and SGA compared to normotensive mothers(24, 25).

A cross-sectional and cohort study conducted in Indonesia shows that the result contraindicated on the association between preeclampsia/eclampsia and SGA(26, 27). A cohort study conducted in Canada shows that preeclampsia was 3 times riskier to developing SGA than normotensive mothers(22). In other studies, the risk of SGA was four times higher in infants born after pre-eclampsia than in the control groups. Among primiparas, pre-eclampsia was associated with a nearly threefold higher risk of SGA(28).

2.2Patho- physiology of small for gestational age and preeclampsia

The Patho-physiology of preeclampsia and SGA are incompletely understood, but endothelial dysfunction may play a role in both conditions. Oxidative stress, caused by increased production of free radicals and insufficient antioxidant defenses, is a known cause of endothelial dysfunction, and this will be causally related to preeclampsia and SGA(3).

In preeclampsia, fetal growth restriction results from the poor remodeling of the spiral arteries and formation of the utero-placental blood supply during placentation, starting to the reduced transfer of oxygen and nutrients for developing fetus during the 18 to 20 weeks of pregnancy. The hypoxic placenta, in turn, releases antiangiogenic factors into the maternal circulation which are hypothesized to invoke the maternal inflammatory response including endothelial dysfunction and lead to increased blood pressure. Thus, abnormal placentation may explain the relationship we have found between increases in maternal blood pressure and smaller birth size of the infant(29).

2.3 Management of small for gestational age and Preeclampsia/eclampsia

Based on the Royal College of Obstetrics and Gynecology recommendation management of SGA fetuses includes both monitoring and delivery methods. Women with SGA fetuses between 24 and 35+ 6weeksof gestation should receive a single course of antenatal corticosteroids when delivery is being considered. Doppler ultrasound for the Umbilical artery should be the primary surveillance tool for the SGA fetus, which is important to reduce perinatal morbidity and mortality in the high-risk population. But CTG and ultrasound assessment of amniotic fluid should not be used in the monitoring of SGA fetuses, because it is only used as a form of surveillance in SGA fetuses. Delivery of SGA will depend upon the gestational age of the fetus and the Doppler examination of umbilical artery results(2).

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In some studies, low-dose aspirin is recommended for women at increased risk of preeclampsia and small for gestational age as early as 16 weeks of pregnancy(11), and smoking cessation, bed rest and calcium supplementation. A meta-analysis study also determined that daily low-dose aspirin initiated before 16 weeks of gestation was associated with a significant decrease in the incidence of preeclampsia, severe preeclampsia, IUGR and preterm birth in women identified to be at risk(30). There is also some initiation based on the Federal Minister of Health if it has signs of severe IUGR among preeclampsia, admit to hospital for assessment and possible induction of labor or caesarian section(31).

2.4Predicting factors of small for gestational age

According to different studies, socio-demographic characteristics, obstetrics, behavioral and medical are factors found some of the predisposing factors of small for gestational age (27, 32, 33). The age of mothers less than 20 years was 21% increase risk has born SGA than those between 25 to 29 years old mothers(34). But some studies reflected that neither maternal age nor marital status had a significant effect on the SGA, but suggested that increased severity of outcome might be an important contributing factor (25).

Belongings to poor social strata were associated with more than two times higher risk of IUGR compared to a middle or high-income society(35). A study conducted in Ireland place of residence of a mother has no significant effect on SGA but employment status has a significant effect on fetal growth, mothers who have not worked were two times more risk to develop SGA than mothers in work(36).

Smoking and alcohol consumption during pregnancy has an effect on fetal growth based on some research but have a conflict of ideas between results (25, 37-40). Cigarette smoking in current pregnancy has two times more likely risk for SGA compared to nonsmoking mothers, but a study conducted in Indonesia(sample size=13,461) found that smoking was no statistically significant effect on SGA compared to nonsmoking(25, 27). A study conducted in North Carolina reported that alcohol consumption has no statistically significant effect on SGA(25), but a cross-sectional and case-control study conducted in Brazil(sample size=998) shows that alcohol consumption has a borderline effect on fetal growth retardation(38).

The inter-pregnancy interval has been stated to influence pregnancy outcome and birth: short inter-pregnancy intervals have been linked to increased risk for SGA, but there is a controversial issue related to the risk of birth interval on SGA in a different study. A study conducted in North Carolina with sample size of 1958 found that birth interval and SGA have not any statistically significant association(25), but a study conducted in Canada with cohort of 98,330 live birth found that inter-pregnancy intervals shorter than 6 months and greater than 60months, were significantly increased risks of SGA which modified by unmarried mothers in contrast to12 -23months interval(41).

A study conducted in Italy shows that pregnant mothers with diabetes mellitus have two times more likely to develop large for gestational age than those mothers who have no cases(32), but some studies show that diabetes mellitus has no statistically significant effect on SGA(25). A study conducted in Pakistan reported that the odds of developing fetuses with SGA among anemic pregnant mothers were 3 times higher compared to normal pregnant women(35). A study conducted in the USA shows that weight gain more than 40 pounds was protective for SGA, but weight gain less than 28 pounds increases the risk for SGA when compared to weight gain between 28-40 pounds for those underweight women(42). But a study conducted in North Carolina gestational weight gain was insignificant related to SGA(25).

In some studies pregnancy-induced hypertension and prim Para of the mothers had an interactive effect on the SGA birth compared to multipara mother with no clear pathological process(35), but a study conducted in Austria shows that being a first time mother was a significantly increased risk of SGA birth independently, however, the model did not have a good ability to predict an SGA birth(33). A case-control study conducted in Pakistan shows that, the probability of developing SGA fetus among mothers who have placenta previa was 3 times higher than those who have not placenta previa, and inter-villous hemorrhage has also significant effect on fetal growth, but pregnant mothers with abruption placenta and cardiac diseases have conflict of ideas toward the effect of SGA(27, 35, 38).

Mothers who have a previous obstetric history like the previous history of preeclampsia/eclampsia, SGA, stillbirth, history of low birth weight and prior miscarriage were increased risk for SGA (25, 32, 43). Pregnant women who have a previous history of preeclampsia were 2 times the risk of SGA birth compared to those normotensive nulliparous, women who experienced SGA in the previous pregnancy have at least eight-fold increased risk of recurrence(5).

The study conducted in Indonesia shows that being male sex was a 17% increase in the risk of SGA than the female fetus, but in other studies, male sex was a protective effect, on the other hands also sex has no effect on SGA (27, 44, 45). There was a risk tendency to SGA newborns in pregnant women with syphilis 2.6-fold more likely compared to VDRL negative women (38). A study done in southern Africa found that HIV positive women have 1.3 times the risk of SGA birth(46), genitourinary tract infection during the second trimester of pregnancy was risk for SGA, but maternal HIV infection and GUI during the 1st and 3rd trimester of the pregnancy were not statistically Significant association with SGA(47). Form the GUI, cervicitis, and UTI were a statistically significant risk for the SGA. Other intrauterine infections like syphilis may also lead to fetal growth restriction(48). A retrospective cross-sectional study conducted in Taiwan shows that women with tuberculosis have a high risk of SGA infants as compared to unaffected women, but a retrospective cohort study conducted in Washington State was no effect on SGA (44, 49).

2.5 Conceptual framework

The conceptual framework is organized based on the Baker hypothesis(2) and reviewed literature. Preeclampsia/eclampsia status with proximal effect to SGA; other predictors like socio-demographic factors, obstetrics factors, medical, behavioral factors affect SGA directly or through preeclampsia/eclampsia status. As it can be observed, SGA is at the end of the conceptual framework and all arrows from major factors are pointing towards the SGA to indicate the direct influences and indirect influence through preeclampsia/eclampsia status.

Socio-demographic factors which affect SGA include the age, residence, marital status, and education and occupation status. The majority of variables correlate with other variables such as obstetrics including preeclampsia/eclampsia, medical, and behavioral factors.

Obstetrics, medical and placental factors which were affected SGA directly or indirectly through preeclampsia. However behavior factors affect SGA through medical and placental factors. Fetal factor affect SGA due to intrauterine infection and sex of fetus. The broken arrows are used to indicate that the relationship is either indirect or week evidence. Like wises, obstetric and fetal factors.

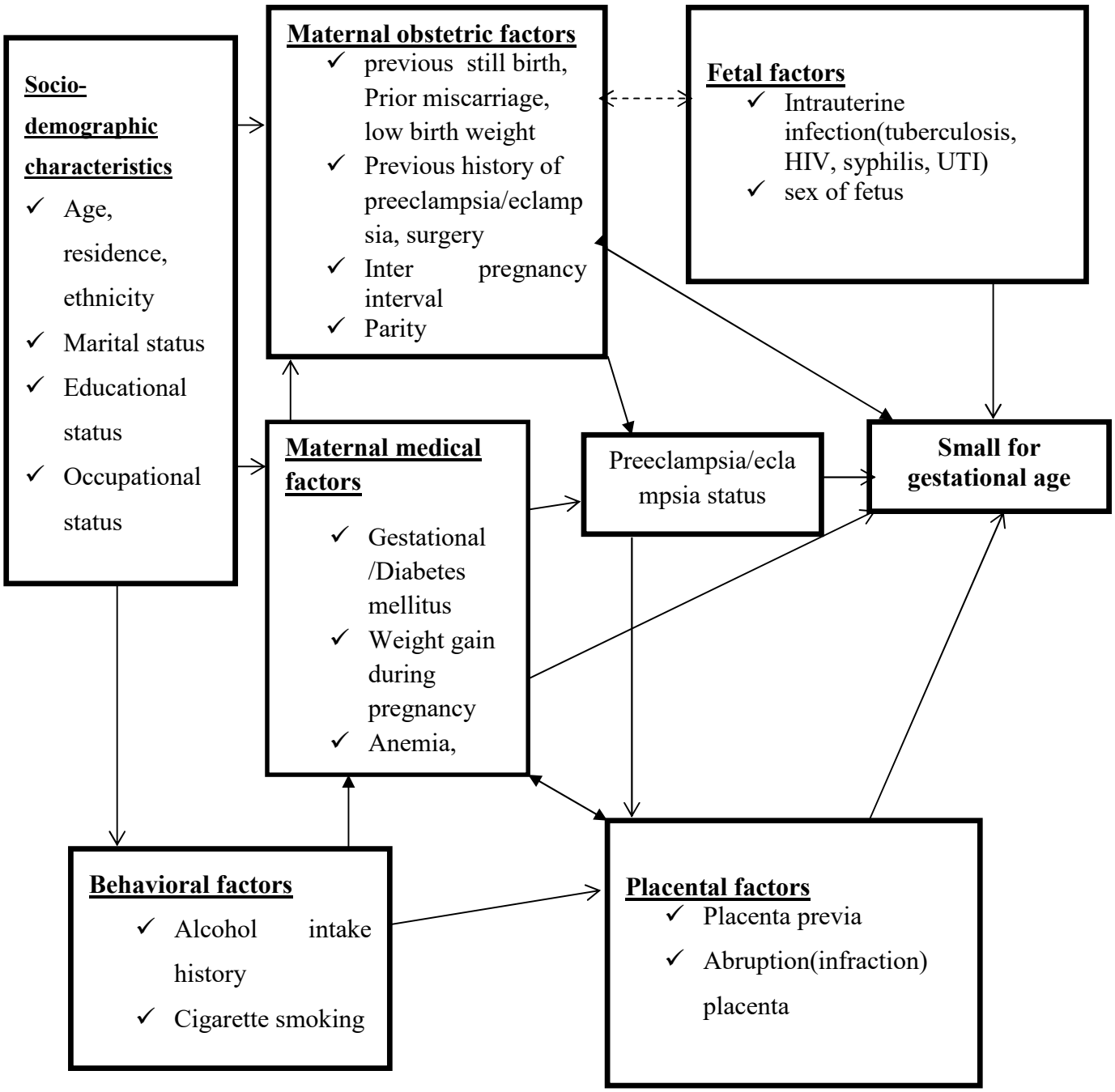

Figure 1: Adapted and modified conceptual framework for determining incidence rate and predictors of small for gestational age among pregnant mothers taken from Baker hypothesis (2) and different literature, 2019.

3. RESEARCH QUESTIONS

1. Is there any difference in terms of incidence rate of small for gestational age among preeclampsia/eclampsia and normotensive women?

4. HYPOTHESIS

There is a difference in the incidence rate of small for gestational age among preeclampsia/eclampsia and normotensive women.

5. OBJECTIVES

5.1 General Objective

To determine effects of preeclampsia on incidence rate of small for gestational age among pregnant women in MGH and ACSH, Tigray, Northern Ethiopia from 2014-2018.

5.2 Specific Objectives

1. To estimate the incidence rate of small for gestational age among preeclampsia/eclampsia and normotensive women.
2. To identify predictors of small for gestational age among pregnant women.

6. METHODS AND MATERIALS

6.1 Study setting

The study was conducted in Ayder Comprehensive Specialized Hospital and Mekelle General Hospital in Mekelle capital city Tigray, which is found 783kmsaway from Addis Ababa to the North. ACSH serves as a referral hospital for the Tigray region and adjacent districts of Afar and Amhara regions with a catchment population of about9 million and. The hospital provides a broad range of medical services to both in and outpatient of all age groups as linked. They also serve as a teaching hospital to several medical, dental medicine, nursing, midwifery, public health, pharmacy, anesthesia and medical laboratory students in both undergraduate and postgraduate programs. ACSH is the second-largest hospital in the nation, and it has 500 inpatient beds in the four major departments and other specialty units (ear, nose and throat, dermatology, and ophthalmology). ACSH has above 100 specialists in various areas of medical specialization. Mekelle General Hospital serves as a referral center for the surrounding district and population of the town for the catchment population of more than 700 thousand. It has 250 inpatient beds and 10 specialists, but those hospitals work in collaboration with each other(50).

There were 7200 ANC follow up in the last five years with an annual average of 1446 women in ACSH, and ANC follow-up for high risk and normal pregnancy was in a separate room by resident and midwifery. It has an equal opportunity of ultrasound for high risk and normal pregnant women. And also it has Doppler ultrasound for those high-risk pregnancies for their fetus. The same to MGH, where there is a 5200 ANC follow-up in the last five years with an annual average of 1041 women(50).

6.2 Study design and period

An Institutional based retrospective cohort study was conducted from January 1, 2014, to March 31, 2019, and the data extraction period was carried out from February 21, 2019, to March 31, 2019.

6.3 Populations

6.3.1Source Population

All pregnant women who attend antenatal care follow up in ACSH and MGH.

6.3.2Study population

All pregnant women who attended ANC follow up starting before 20 weeks of gestational age and whose preeclampsia/eclampsia status was determined, in ACSH and MGH over the study period.

6.4 Eligibility criteria

6.4.1 Inclusion criteria

Exposure groups were women who have preeclampsia/eclampsia, including superimposed preeclampsia. The population was selected after the physicians made a diagnosis as part of a routine case for the women. Control groups were women who attend the ANC from both hospitals and were not diagnosed as preeclampsia/eclampsia throughout the follow up time.

6.4.2 Exclusion criteria

Pregnant women who have known chronic and gestational hypertension without proteinuria throughout the pregnancy and renal diseases were excluded to know the effect of preeclampsia/eclampsia independent only, and twin pregnancy was also excluded from the study because of know effect to preeclampsia and SGA. Mothers who come to those hospitals by referral without ANC follow up documents were also excluded.

6.5 Sample size calculation and sampling procedures

6.5.1 Sample size calculation

The sample size of this study was determined considering the two objectives. For both objectives sample size was obtained using the two population proportion technique. Epi info version 7.2.2.6(United States center for disease prevention and control, Atlanta, GA) was used to calculate the sample size. To calculate sample size, (Z1-α/2= 95%, CI) and (Z1-β= 80%, power) with 10% lost to follow up, and 2 unexposed ratios to 1 exposed group are used(28). Details of the sample size calculation are provided in (Table 1).

Table 1: Sample size calculation for incidence rate and predictors of small for gestational age among pregnant women in MGH and ACSH, Tigray, Northern Ethiopia, 2018.

Specific objectives	Assumptions(proportions)		Sample size in each group	Total sample size with 10% lost follow up
1.	Percent of exposed (preeclampsia) with SGA(21)	23%	191	212
	Percent of unexposed (normotensive) with SGA(21)	13.2%	381	424
	Total			636
	Percent of exposed (severe preeclampsia) with SGA (21)	30.5%	72	80
	Percent of unexposed (normotensive) with SGA(21)	13.2	216	160
	Total			240
2	Syphilis(reactive)(48)	12.12%	98	109
	Syphilis(nonreactive)	2.7%	195	217
	Total			326
	Placenta preiva (yes)(35)	11.8%	150	167
	Placenta preiva (no)	4%	299	332
	Total			497
	Anemia(yes)(35)	23.1%	101	112
	Anemia(no)	10%	202	227
	Total			339
	Weight gain<28 pounds	23.8%	206	229
	Weight gain 28-40 pounds (42)	14.2%	412	458
	Total			687

The final sample size was taken based on feasibility and the maximum sample size from the list of variables for both objectives is 687, but the final cohort sample size was taken715.

6.5.2 Sampling Procedures and participant recruitment

Mekelle General Hospital and Ayder Comprehensive Specialized Hospital were selected purposely because those two Hospitals are the largest Public Hospitals with maternal health services in the Tigray region. Systematic sampling approach was used to select those with preeclampsia and normotensive women from ANC logbook by their medical record number using every three and twenty-five interval in the same hospitals respectively, and the first participant selects randomly for preeclampsia/eclampsia and normotensive, but the rest being selected according to a predetermined pattern. The sample size was split between the two hospitals proportionally to their ANC follow up the caseload. The actual average annual ANC follow up from 2014 to 2018in ACSH was 1440 including 80 of preeclampsia, while MGH has annual ANC follow up of 1040 including 70 of preeclampsia/eclampsia. Therefore based on the population proportion to size those 687(229 verses 458) study subjects were distributed to each hospital using the following formula.

nk= sample size for each hospital, Nm= total number ANC follow up in MGH (5200) and ACSH (7200). nk= Nm*n/N, nm= 5200*687/12400= 288(96 preeclampsia/eclampsia, 192 normotensive), nk=Nm*n/N, na=7200*687/12400=399(133 preeclampsia/eclampsia, 266 normotensive).

There are 12400 ANC follow up women in both hospitals, MGH (5200) and ACSH (7200) including 350 and 400 preeclampsia respectively in last five years. For MGH from 5200 is 4850 normotensive (minima sample size (n) =192) and 350 preeclampsia (n=96). However, during systematic sampling, we find 100 eligible for preeclampsia and 201 for normotensive. For ACSH from 7200 is 6800 normotensive (n=266) and 400 preeclampsia (n=133). However, during systematic sampling, we get 140 eligible for preeclampsia and 279 for normotensive. The final eligible sample size was taken (preeclampsia (n) =239, normotensive (n) =476).Detailed were seen in (Figure 2) below.

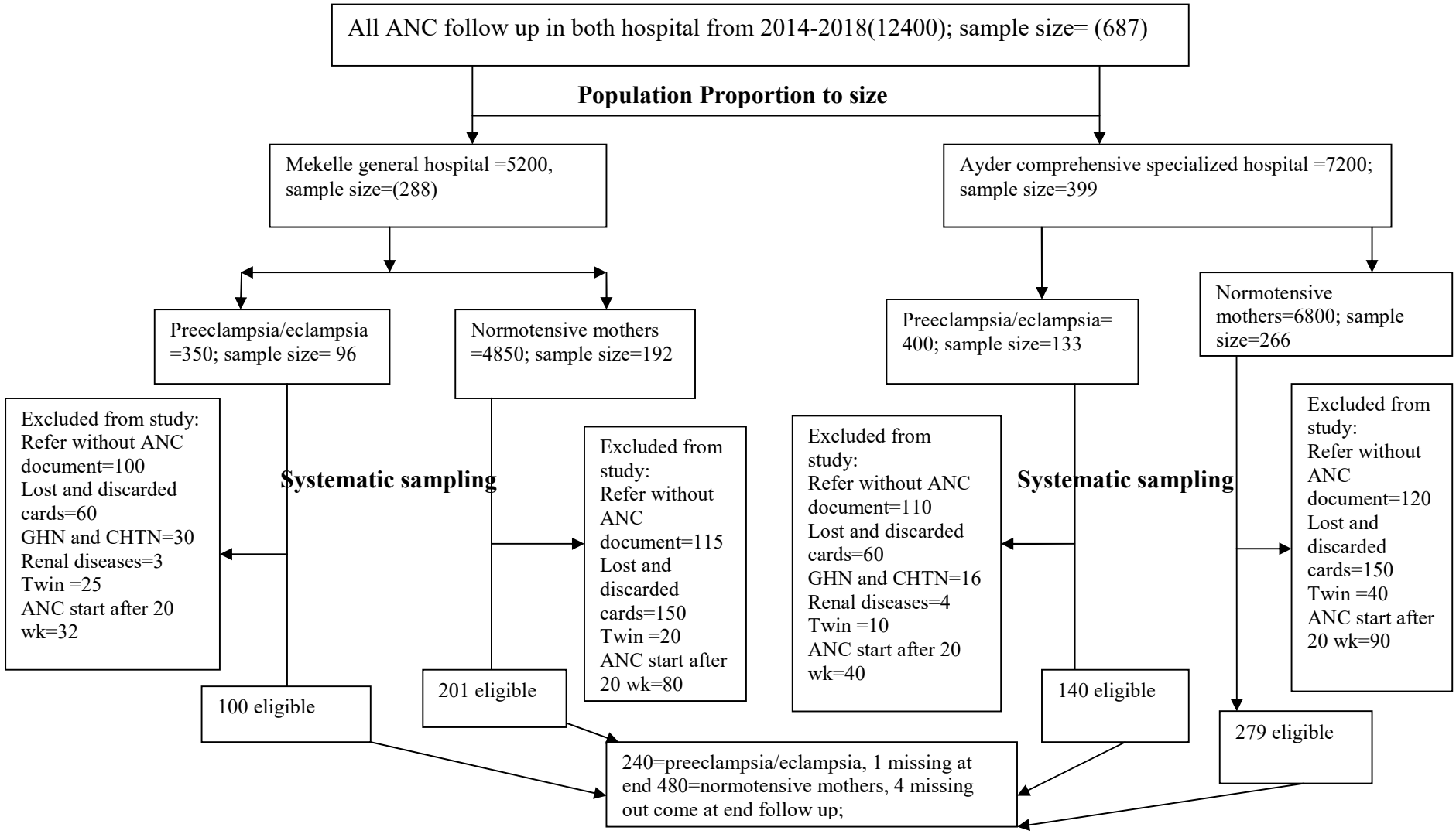

Figure 2: Schematic presentation of the sampling procedure for determining incidence rate and predictors of small for gestational age among pregnant women in MGH and ACSH, Tigray, Northern Ethiopia, 2019.

6.6 Data collection procedures and follow uptime

The data collection tool was prepared in English, the data abstraction form containing the most relevant variable in relation to SGA as explained in different literature. A date was extracted from pregnant women ANC follow up document, medical and obstetric detailed history which contain like, socio-demographic characteristics, obstetric and medical history, current pregnancy status, and pregnancy progressive follow up (fetal weight, weight of mother during each visit, fundal height).

Entry date was from the date of diagnosis of one preeclampsia and matched by time for two control groups, while Exit date means when outcome developed or end of the study. Event: occurrence of SGA per pregnant women weeks. Survival- means a lack of SGA occurrence within the follow-up period. Censored- pregnant women who were developed outcome or end of the study, withdrawal of the study. Fetal growth follow up (estimated fetal weight) was checked using clinical(symphysis fundal height) or ultrasound at most every fourth week for all women, so we take estimated fetal weight(1), then compare to growth standard chart to decide whether it is SGA if EFW<10 percentiles or not SGA if it has >10 percentiles (but not include recurrent SGA and diagnosed before starting to follow up time for both group). Estimated fetal weight is calculated using ultra sound from abdominal circumference, head circumference and femoral length or based on clinical (EFW (gms) = 2600+115(symphysis fundal height -30)(51) .Follow-up time was measured in weeks (20-40 weeks (average length of pregnancy)) and the chart we used also until the 40^{th} week.

The data was retrieved by two data collectors who have a degree in midwifery and work in ANC follow services after they were taken two days of training for the data collector and supervisor (MSC in clinical midwifery). Training was given for data collectors and supervisor on the contents of the data abstraction checklist and how to abstract data from pregnant women ANC follow up logbooks and medical records prior to the data collection period by the principal investigator. Details of the data abstraction procedures were provided in (ANNEX **IV**).

6.7 Operational definitions

Definition of exposure

Preeclampsia was defined as systolic blood pressure ≥ 140 or diastolic ≥ 90 mm Hg on two separate readings taken at least four hours apart or a single BP measurement of ≥ 160/110 mmHg and a proteinuria ≥ 300mg per 24-hour urine collection or dipstick reading of 1+ occurred after 20 weeks of gestation among previously normotensive women. Eclampsia means new-onset grand mal seizures in a woman with preeclampsia that cannot be attributed to other causes(52).

Superimposed preeclampsia occurred in women with hypertension history but have no proteinuria in early pregnancy before 20 weeks of gestation, which currently develops new-onset proteinuria. In addition, in women with hypertension and proteinuria before 20 weeks of gestation, may develop any of the following: (a) sudden increase in proteinuria and BP, and platelet counts of $<10^5$/micro liter in a woman, also include in the exposure group(52). Gestational age was estimated by the last normal menstrual period or using the first or second-trimester ultrasound by measuring the crown-rump length(53).

Definition of outcome

Estimated fetal weight measurement**:**

Incident of SGA, defined in this study, as an event, during follow-up time was ascertained retrospectively when EFW was<10 percentiles, classified as SGA based on the WHO growth standard chart, but not include those who have gross congenital anomaly, no SGA if it's EFW was >10 percentiles(1).

Definition of variables

Anemia: means hemoglobin level less than 11 grams per deciliter during pregnancy based on WHO criteria at ANC booking(54).

Cigarette smoking: if she smokes more than or equal to one cigarette per day the mother consider as a smoker(yes) and if not as nonsmoker(no)(28).

Alcohol drinking: based on self-report during ANC follow up "yes if she was taken during pregnancy and "no" if she was not taken during pregnancy.

Previous Stillbirth was defined as fetal death before birth, with gestational age ≥ 20 weeks and birth weight ≥ 500 grams in the previous pregnancy outcome(55).

Placenta preiva: the placenta is partially or totally attached to the lower uterine segment which conforms by the physician(56).

Abruptio placenta: is a Premature separation of the placenta from the site of uterine implantation before delivery of the fetus which confirms by an obstetrician(56).

Weight gain during pregnancy is calculated from last ANC visit minus to first ANC visit and categorized into poor weight gain(<=10 kg) and good weight gain(>10 kg)(45).

6.8 Variables

6.8.1 Dependent variable

Follow up time up to small for gestational age occurrence

6.8.2 Independent variable

Preeclampsia/eclampsia status

6.8.3 Covariate variables

1. **Socio-demographic characteristics**: Age of mothers, marital status, residence and ethnicity
2. **Behavioral factors**: Drinking alcohol and cigarette smoking history
3. **Maternal medical factors**: Weight gain during pregnancy, anemia at booking ANC, cardiac diseases, diabetes mellitus or gestational diabetes mellitus
4. **Maternal obstetric factors**: History of pregnancy induced hypertension, history of still birth, prior miscarriage, parity, history of low birth weight
5. **Fetal factors**: Intrauterine infection (tuberculosis, HIV, syphilis), UTI
6. **Placental factors:** Placenta previa, abruption placenta

6.9 Data management and analysis procedures

Collected data were entered, coded and cleaned in Epi Data version 3.1 and exported to STATA version 14(STATA Corp, College Station, Texas, USA) for statistical analysis and use Open Epi version 3.01 for power calculation. Assumption of normal distribution was checked for the continuous variable by using the Shapiro-Wilk normality test and histogram, so normality was violated, therefore we have reported the median and IQR (interquartile range), but for the categorical variable described by frequency and percentages. Baseline characteristics of exposed and unexposed participants are compared using Pearson's X^2 and fisher's exact test for categorical data and Mann-Whitney U test for continuous data.

The incidence rate was calculated dividing all SGA cases detected in the cohort by the person-weeks of follow-up(per 1000) and comparison between preeclampsia/eclampsia and normotensive women was significant if Z-score test p-value<0.05. The Kaplan-Meier curve (to describe free SGA of the study population) was used to estimate the median duration of SGA occurrence. The Log-rank test was used to compare survival curves between different categories of explanatory variables. Cox regression model was fitted to estimate HR with 95% CI and p-value <0.05, and also it is important to adjust for potentially confounding factors, including age of mothers, residence, ethnicity, marital status, weight gain, syphilis, tuberculosis, HIV, UTI, placenta previa, abruption placenta, previous stillbirth, history of PIH, abortion history, reproductive tract surgery, diabetes mellitus, cardiac diseases, anemia, smoking, alcohol drinking, and parity. In the bivariate Cox regression, there were eight variables that have a significant association with SGA (p<0.05) and also checked by the log-rank test. During regression analyses, all variables with clinical importance and P-value of ≤ 0.2(57) on bivariate analysis were included in multivariable Cox regression to calculate AHR. We checked the interaction effect between independent variables. All variables were checked on the observed and predicted graph and – ln –ln graph. Both graph confirmed that the proportional hazard assumption except ethnicity. Then the proportional hazard assumption was checked by using the global test (Schoenfield residuals) for both unadjusted and adjusted model. Significance of the model used was checked by the Cox Snell residual and Omnibus test. Finally, the result was presented in tables, figures, and text accordingly.

6.10 Data quality assurance

The data collection tool was prepared in English. A pretest was conducted on 34 (11 preeclampsia and 23 normotensive) women cards before the actual data collection in ACSH and MGH. Based on the pretest modification on a logical sequence, simplicity, and clarity of the checklist were done. Data collectors and supervisor were trained for 2 days on how to fill the checklist properly.

During the data collection process, the filled checklist was checked for their completeness and consistency by the principal investigator and one supervisor every day to correct any if it has faults. The investigator has entered the coded questionnaires in Epi data 3.1. Data cleanup was performed by running frequencies of each variable to check for clarity, completeness, and consistencies of data. On the other hand, when more than 10% of the cases had missing data, complete case analysis was used to dropping cases with missing scores(58). Variables missing value of more than 10% like educational status, occupational status, sex of fetus and birth interval were dropped based on the discussed above.

6.11 Ethical considerations

This study was carried out after getting ethical clearance from Addis Ababa University, school of public health, ethical clearance committee, and permission to conduct this study were secured in ACSH and MGH, Tigray. Further permission was obtained from the Medical Director of ACSH and MGH, the department head of the obstetric ward and HMIS focal person for the utilization of the cards. Since it is secondary data obtaining informed consent from the participants is not possible, but the confidentiality was maintained by making the data collectors aware not to record any identification information found on the card.

6.12 Dissemination of findings

The result of this study will be presented to Addis Ababa University as partial fulfillment of the master of public health in Epidemiology and Biostatistics. It will be submitted to Tigray Regional Health Bureau, ACSH and MGH and other concerned bodies. It will be also presented at seminars and an attempt will be made to publish in a reputable journal.

7. RESULTS

7.1 Socio-demographic characteristics of study participants

Among pregnant women registered for ANC from 01 January 2014 to 01 March 2019, the data of 239 preeclampsia/eclampsia and 476 normotensive women were retrieved from ANC logbook for the study. Out of the total 239 exposed and 476 unexposed pregnant women included in this study, 203 (84.94%) of exposed and 442 (92.86%) unexposed group were Tigrawi ethnic group. There is a significant association between ethnicity and preeclampsia/eclampsia (p=0.007).

One hundred fifty-four (64.44%) exposed and 415 (87.2%) unexposed mothers were living in urban areas. There is a significant association between residence and preeclampsia/eclampsia status (p<0.0001). One hundred eighty-seven (78.24%) exposed and 404 (84.87%) unexposed were in the age group of 20 to 34 years old. Two hundred three (84.94%) exposed and 432(90.76%) unexposed pregnant women were married. There is also a significant association between marital status and preeclampsia/eclampsia (p=0.04) (Table 2).

Table 2: Socio-demographic characteristics of pregnant women in MGH and ACSH, Tigray, Northern Ethiopia, 2019.

Variables	Preeclampsia N (%)	Normotensive N (%)	p-value
Ethnicity			
Tigrawi	203(84.94)	442(92.86)	**0.007**
Amhara/Afar	23(9.62)	24(5.04)	
Other	10(4.18)	8(1.68)	
Unrecorded	3(1.26)	2(0.42)	
Residence			
Urban	154(64.44)	415(87.2)	**0.0001**
Rural	82(34.31)	53(11.13)	
Unrecorded	3(1.26)	8(1.68)	
Age of mother			
15-19	9(3.77)	28(5.88)	**0.002**
20-34	187(78.24)	404(84.87)	
>35	43(17.99)	44(9.24)	
Marital status			
Married	203(84.94)	432(90.76)	**0.04**
unmarried	28(11.72)	30(6.3)	
Unrecorded	8(3.35)	14(2.94)	

Unmarried (never married, widowed, divorced), others (Kunama, Erob) p< 0.05=significant

7.2 Maternal obstetric factors of study participants

From 715 study participants, 36(15.06%) exposed and 38(7.98%) have a history of stillbirth or neonatal loss. There is a statistically significant association between those who have a history of stillbirth or neonatal loss and preeclampsia/eclampsia women (p=0.007). Sixty-six 66(27.5%) exposed and 107(22.5%) unexposed pregnant women had a history of abortion. Of study participant 211(90.56%) exposed and 459(96.6%), unexposed pregnant women have a previous history of low birth weight. History of low birth weight had a significant association between preeclampsia and normotensive women. But there is no statistically significant association among exposed and unexposed pregnant women by the history of abortion (p=0.275).

Of the study participant, 95 (39.75%) exposed and 195(40.97%) unexposed never had given birth before the current pregnancy. Parity had no significant association with preeclampsia/eclampsia (p=0.119). Two hundred four (85.36%) exposed pregnant women and 464(97.48%) unexposed pregnant women had no history of pregnancy-induced hypertension. There is a significant association between previous histories of pregnancy-induced hypertension and preeclampsia/eclampsia women (P<0001). Almost all pregnant mothers, 211(87.92%) exposed and 412(85.83%) had no history of reproductive tract surgery. However, there is no association between any history of reproductive tract surgery and preeclampsia/eclampsia (p=0.101) (Table3).

Two hundred thirty-two (97.07%) among exposed pregnant women and 465(97.69%) unexposed women had no placenta preiva. Of study participants, 16(6.69%) exposed pregnant women and 14(2.94%) unexposed pregnant women had abruption placenta. placenta previa had no association with exposure status (p=0.489), but abruption placenta had a significant association with preeclampsia/eclampsia status (p=0.028).

Table3: Maternal obstetric factors of pregnant women in MGH and ACSH, Tigray, Northern Ethiopia, 2019.

Variables	Preeclampsia/eclampsia (%)	N	Normotensive N (%)	p-value
History of stillbirth				
No	203(84.94)		436(91.6)	**0.007**
Yes	36(15.06)		38(7.98)	
Unrecorded	0		2(0.42)	
Prior miscarriage				
No	172(71.97)		368(77.31)	0.224
Yes	66(27.62)		107(22.48)	
Unrecorded	1(0.42)		1(0.21)	
Previous low birth weight				
No	211(90.56)		459(96.63)	**0.000**
Yes	22(9.44)		16(3.37)	
Unrecorded	6(2.51)		1(0.21)	
Parity				
Null Para	95(39.75)		195(40.97)	0.119
Primi-para	66(27.62)		158(33.19)	
Multipara	78(32.64)		123(25.84)	
History of PIH				
No	204(85.36)		464(97.48)	**0.0001**
Yes	35(14.64)		12(2.52)	
Surgery on the reproductive tract				
No	210(87.87)		408(85.71)	0.101
Yes	26(10.98)		67(14.08)	
Unrecorded	3(1.26)		1(.0.21)	
Abruption placenta				
No	222(92.89)		461(96.85)	**0.028**
Yes	16(6.69)		14(2.94)	
Unrecorded	1(0.42)		1(.21)	
Placenta Previa				
No	232(97.07)		465(97.69)	0.489
Yes	7(2.93)		9(1.89)	
Unrecorded	0		2(0.42)	

PIH: pregnancy induced hypertension, P<0.05=significant

7.3 Maternal medical factor and pregnancy status of study participants

We check the normality assumption for the first visit of gestational age by using the Shapiro Wilk test ($p<0.0001$) and histogram (left-skewed) (Figure 3) which violated normality assumption so we reported median with interquartile range. The median first visit of gestational age for preeclampsia/eclampsia women were 17.3 with interquartile range (15.9-18) and for those normotensive women 17 with interquartile range (14.6-18.7), no significant difference (Mann-Whitney U test, $Z=-1.147$, $p=0.251$).

Ten (4.17%) exposed and unexposed pregnant women 9(1.88%) had diabetes mellitus. Cardiac disease was more common in exposed 17(7.08%) than unexposed 9(1.88%) pregnant women. Anemia was highly experienced among exposed women 67(27.9%) than unexposed 26(5.42%) pregnant women. One hundred eighty-nine (78.75%) exposed and 332(69.2%) unexposed women were weight gain less than ten kilograms. All medical factors of pregnant women had a statistically significant association among an exposed and unexposed group ($p<0.05$).

Urinary tract infection was higher among unexposed pregnant women 107(22.48%) than exposed pregnant women 31 (12.97%). There is also a statistically significant association between UTI and preeclampsia/eclampsia women. Of those 715 study participants, 16(6.69%) exposed women and 22(4.62%) unexposed women had reactive to HIV ADIS. There is no association between HIV ADIS and preeclampsia/eclampsia women ($p=0.244$). Fourteen (5.86%) exposed pregnant women and 15(3.15%) unexposed pregnant women had reactive to tuberculosis. There is no significant association between tuberculosis and preeclampsia women ($p=0.173$). The majority of study participants; 234(97.91%) among exposed and 465(97.69) unexposed pregnant women had nonreactive to rapid syphilis test. there is no significant association between rapid syphilis and preeclampsia women ($p=0.852$).

Alcohol taking history and smoking was less than 5% in both exposed 7(2.93%) and unexposed 9 (1.9%) pregnant women, in both exposed 4(1.7%) and unexposed 8 (1.7%) pregnant women respectively (Table 4). There is no significant association between alcohol taking history and preeclampsia status ($p=0.463$), and smoking and preeclampsia ($p=0.535$).

Table 4: Medical factors and pregnancy status of study participants in MGH and ACSH, Tigray, Northern Ethiopia, 2019.

Variables	Preeclampsia N (%) or median (IQR)	Normotensive N (%) or median(IQR)	P
Firs visit of GA	17.3(15.9-18)	17(14.6-18.7)	0.251
Diabetes mellitus			
No	227(94.98)	468(98.32)	**0.017**
Yes	10(4.18)	8(1.68)	
Unrecorded	2(0.84)	0	
Cardiac disease			
No	219\8(91.21)	466(97.9)	**0.0001**
Yes	17(7.11)	9(1.89)	
Unrecorded	4(1.67)	1(0.21)	
Weight gain (kg)			
Poor	188(78.66)	330(69.33)	**0.005**
Good	40(16.74)	130(27.31)	
Unrecorded	11(4.67)	16(3.36)	
Anemia			
No	170(71.13)	445(93.49)	**0.0001**
Yes	67(28.03)	26(5.46)	
Unrecorded	2(0.84)	5(1.05)	
HIV status			
Reactive	16(6.69)	22(4.62)	0.244
Nonreactive	223(93.31)	454(95.38)	
Urinary tract infection			
Positive	31(12.97)	107(22.48)	**0.002**
Negative	208(87.03)	369(77.52)	
Rapid syphilis test			
Positive	5(2.09)	11(2.31)	0.852
Negative	234(97.91)	465(97.69)	
Tuberculosis status			
Reactive	14(5.86)	15(3.15)	0.173
Nonreactive	214(89.12)	442(92.86)	
Unrecorded	12(5.02)	19(3.99)	
Alcohol intake history			
No	227(94.98)	461(96.85)	0.463
Yes	7(2.93)	9(1.89)	
Unrecorded	5(2.09)	6(1.26)	
Cigarette smoking			
No	230(96.23)	463(97.27)	0.535
Yes	4(1.67)	8(1.68)	
Unrecorded	5(2.09)	5(1.05)	

Kg: kilograms, HIV: Human immune virus, P<0.05=significant, IQR: interquartile range

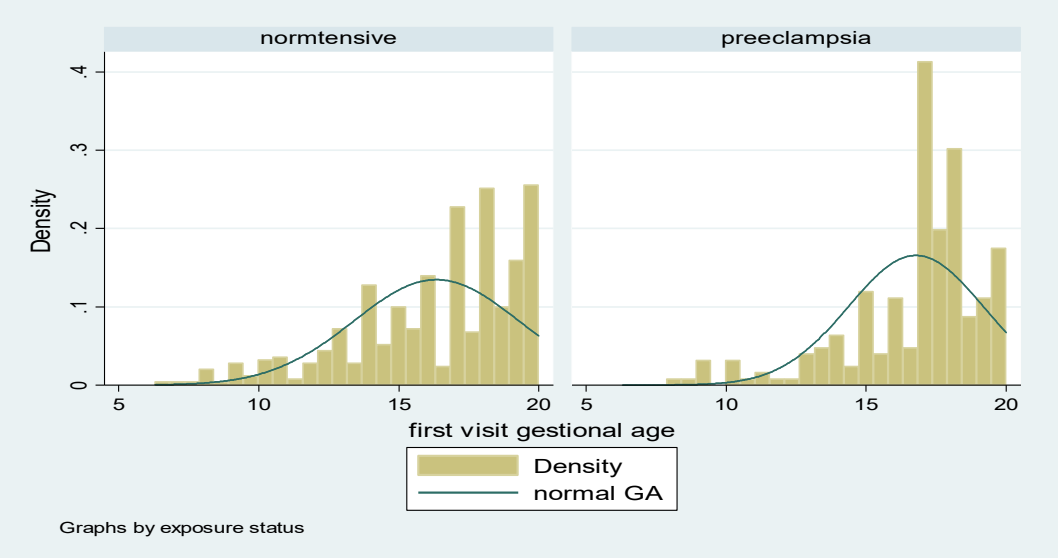

Figure 3: Normality test first visit of gestational age for the antenatal care of pregnant women in ACSH and MGH, Tigray, Ethiopia, 2019.

7.4 Incidence density for small for gestational age and outcome of the follow up of study participants

A total of 239 pregnant women with preeclampsia and 476 pregnant women with-out preeclampsia/eclampsia were followed for the maximum time of 20 weeks starting from 20 to 40 weeks. The incidence rate of SGA was 94.5(95% CI, 78-114.38) per 1000 person-weeks of follow-up among preeclampsia/eclampsia, and 24.9(95% CI, 19.78-31.29) per 1000 person-weeks of follow-up among normotensive women with the significant difference among the group which test by Z-score (Z=9.42, p<0.000001). The incidence rate of SGA for the age of women between 15-19, 20-34 and more than 35 was 41, 40 and 73 per 1000 pregnant women weeks follow up respectively.

Women who had a history of low birth weight was 52 SGA per 1000 pregnant women weeks follow up, whole for those who had no history of low birth weight was 41 per 1000 pregnant women weeks follow up. Women who had no birth, one birth in previous, multiparous had 47, 36 and 49 SGA per 1000 pregnant women weeks follow up respectively.

The incidence density of SGA among poor weight gain during pregnancy was 49 per 1000 pregnant women weeks follow up, but for those women who adequate weight gain was 26 SGA per 1000 pregnant women weeks follow up. Women who had anemic at ANC booking were 78 SGA per 1000 pregnant women weeks follow up, whereas women who had no anemia were 39 per 1000 pregnant women weeks follow up(Table 5).

Table 5: Incidence density of small for gestational age among pregnant mothers MGH and ACSH, Tigray, Northern Ethiopia, 2019.

Variables	Person- weeks	SGA	IR (95% CI) per 1000
Exposure status			
Normotensive	2933.9	73	24.9(19.8-31.2)
Preeclampsia	1111.4	105	94.5(78-114)
Age of mothers			
15-19	193.71	8	41(20-83)
20-34	3431.4	139	40(34-48)
>35	420.14	31	73(52-105)
Residence			
Urban	3311.4	127	38(32-46)
Rural	678.57	49	72(54-95)
Ethnicity			
Tigrawi	3653.1	155	42 (36-50)
Afar/Amhara	273.14	15	55(33-91)
Others	97.43	7	72(34-150)
Marital status			
Unmarried	270.43	20	74(48-115)
Married	3682.5	155	42(36-49)
History of Stillbirth			
No	3677.6	152	41(35- 48)
Yes	364.43	25	69(46- 101)
Prior miscarriage			
No	3039.3	135	44(37.5-53)
Yes	999.6	42	42(31-57)
History of low birth weight			
No	3791.6	163	43(37-50)
Yes	211.7	11	52(29-94)
Parity			
Nullipara	1523	72	47(37-59)
Primipara	1391.7	50	36(27-47)
Multipara	1130.6	56	49(38-64)
History of PIH			
No	3796.6	163	43(37-50)
Yes	248.71	15	60(36-100)

Previous surgery			
No	3588.7	156	43(37-51)
Yes	437.29	20	46(29-71)
Placenta preiva			
No	3935.9	175	44(38-51)
Yes	100.43	2	20 (5-79)
Abruption placenta			
No	3871	169	44(38-50)
Yes	163.2	9	55(29-106)
Diabetes mellitus			
No	3948.9	172	44(37-50)
Yes	92.86	5	54 (22-129)
Cardiac diseases			
No	3876.2	163	42(36-49)
Yes	136.43	12	88(50-154)
Weight gain (kg)			
Poor	2879.4	142	49(42-58)
Good	1002.7	26	26(18-38)
Anemia			
No	3498.4	137	39(33-46)
Yes	489.29	38	78(56-106)
HIV status			
Reactive	206.14	12	58(33-102)
Nonreactive	3839.1	166	43(37-50)
Urinary tract infection			
Positive	681.29	25	37(25-54)
Negative	3364	153	45(39-53)
Rapid syphilis test			
Reactive	80	4	50 (19-133)
Nonreactive	3965.3	174	44(38-50)
Tuberculosis			
Positive	152.14	10	66(35-122)
Negative	3726	160	43(37-50)
Alcohol taking			
No	3888.3	167	43(37-50)
Yes	95.14	5	53(22-126)
Cigarette smoking			
No	3891.3	169	43(37-50)
Yes	83.99	3	36(11-111)

PIH: pregnancy-induced hypertension, SGA: small for gestational age, IR: incidence rate

7.5 Kaplan Meier to estimate the probability of small for gestational age among pregnant women in the cohort

The minimum follow up time was 0.286 and 0.286 (in weeks) for pregnant women with preeclampsia/eclampsia and normotensive respectively, and the maximum follow up time was 18 and 19.6 weeks for both pregnant women with preeclampsia/eclampsia and normotensive respectively. Median follow up time for preeclampsia and normotensive was 6 and 18 weeks respectively. As the follow-up period increases number SGA free women decrease proportionally over time in both groups. Two hundred thirty nine preeclamptic and 476 normotensive pregnant women, who were at risk for SGA at the start of follow up which decreases to 309 (normotensive) and 126 (preeclampsia) at the 4th weeks of follow up and only152 (normotensive pregnant women) and 35 (preeclampsia) remained at the 8th weeks of follow up. SGA free survival was significantly lower among preeclampsia than normotensive pregnant women (log-rank test, X^2=102.91, df=1, p<0.0001) (Figure 4).

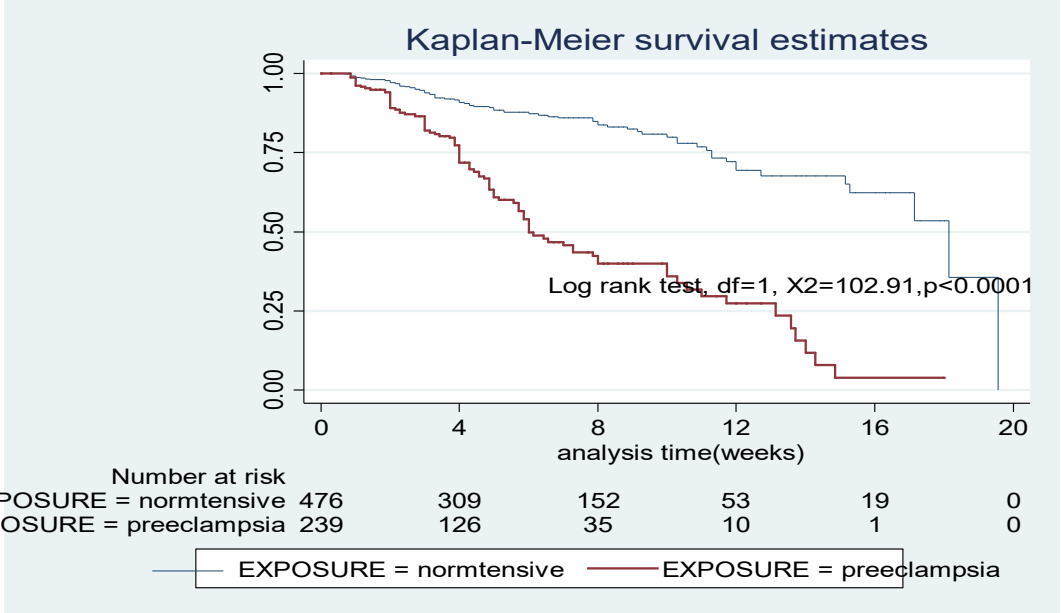

Figure 4: Survival curve of SGA among preeclampsia and normotensive pregnant women from 20 to 40 weeks in MGH and ACSH, Tigray, North Ethiopia, 2019.

7.6 Bivariate Cox regression analysis for predictors of small for gestational age among pregnant women

Bivariate Cox regression was done to assess impact preeclampsia/eclampsia on small for gestational age and other possible confounders. Socio-demographic characteristics such as the age of mothers, residence and marital status were statistically associated with SGA. Besides, the global test was done for the unadjusted model, so all variables satisfy the proportional hazard assumption except ethnicity (ANNEX II). The risk of SGA was two times higher among women whose age is greater than 35 years compared to those 20 to 34 years old, (CHR = 1.95, 95% CI 1.32-2.88). The risk of SGA was two times higher among women who live in rural areas than those who live in urban residents, (CHR = 1.97, 95% CI 1.41- 2.74). Those unmarried pregnant women were about two times more likely to develop SGA than those who married pregnant women, (CHR=1.86; 95% CI 1.16-2.96). The ethnic group was no statistically significant association with SGA (Table 6).

Table 6: Association between socio-demographic characteristics and small for gestational age among pregnant women in MGH and ACSH, Tigray, Northern Ethiopia, 2019.

Variables	Person time(in weeks)	SGA	CHR95% CI
Age of mothers			
15-19	193.71	8	1.06(0.52-2.16)
20-34	3431.4	139	1
>35	420.14	31	**1.95(1.32-2.88)***
Residence			
Urban	3311.4	127	1
Rural	678.57	49	**1.97(1.4- 2.74)***
Ethnicity			
Tigray	3653.1	155	1
Afar/Amhara	273.14	15	1.34(0.78 -2.27)
Others	97.43	7	1.68(0.78-3.58)
Marital status			
Unmarried	270.43	20	**1.86(1.2-2.97)**
Married	3682.5	155	1

CHR: crude hazard ratio, SGA: small for gestational age

Among the obstetric factors, having any history of stillbirth was found to have a statistically significant association with SGA. Any history of stillbirth or neonatal loss increased the risk of SGA by 72 %, (Crude HR=1.72; 95%CI 1.12-2.63). But obstetric history like prior miscarriage, history of PIH, previous surgery on the reproductive tract, parity, placenta previa, abruption placenta and history of low birth weight were not significant association with SGA. Preeclampsia/eclampsia was a statistically significant factor for SGA. Women with preeclampsia during pregnancy were four times more likely to have SGA than mothers without preeclampsia, (CHR = 4.32; 95% CI 3.17-5.87) (Table 7).

Table 7: Association between obstetric factors and small for gestational age among pregnant mothers in MGH and ACSH, Tigray, Northern Ethiopia, 2019.

Variables	Person time(in weeks)	SGA	CHR95% CI
Exposure status			
Normotensive	2933.9	73	1
Preeclampsia	1111.4	105	**4.3(3.17- 5.87)***
History of Stillbirth			
No	3677.6	152	1
Yes	364.43	25	**1.72(1.13-2.63)***
prior miscarriage			
No	3039.3	135	1
Yes	999.6	42	0.94(0.67-1.33)
History of low birth weight			
No	3791.6	167	1
Yes	211.7	11	1.23(0.66-2.26)
Parity			
Nullipara	1523	72	0.99(0.70-1.42)
Primipara	1391.7	50	0.72(0.49-1.06)
Multipara	1130.6	6	1
History of PIH			
No	3796.6	163	1
Yes	248.71	15	1.4(0.85-2.45)
Previous surgery			
No	3588.7	156	1
Yes	437.29	20	1.02(0.63-1.64)
Placenta priva			
No	3935.9	175	1
Yes	100.43	2	0.43(0.11-1.73)
Abruption placenta			
No	3871	169	1
Yes	163.2	9	1.29(0.66-2.53)

*: statistically significant ($p<0.05$), PIH: pregnancy-induced hypertension

Medical factors like; cardiac diseases, weight gain during pregnancy, and anemia at the booking of ANC were statically significant associated with SGA. The risk of SGA was two times higher among women with cardiac diseases than those without the diseases, (CHR=2.1; 95%CI1.18-3.81). The risk of SGA was two times higher among women with poor weight gain than those adequate weight gain during pregnancy, (CHR=1.93; 95%CI1.3-2.94). The risk of SGA was two times higher among anemic compared to non-anemic women, (CHR=2.09; 95%CI1.45-3.0). No statistically significant association was found between diabetes Mellitus and SGA. Infectious diseases and behavioral factors of women like; HIV, UTI, syphilis, tuberculosis, alcohol drinking, smoking had no significant association with SGA (Table 8).

Table 8: Bivariate Cox regression for the relationship between medical, current pregnancy status and small for gestational age in MGH and ACSH, Tigray, Northern Ethiopia, 2019.

Variables	Person time(in weeks)	SGA	CHR95% CI
Diabetes mellitus			
No	3948.9	172	1
Yes	92.86	5	1.25(0.5-3.04)
Cardiac diseases			
No	3876.2	163	1
Yes	136.43	12	**2.1(1.18-3.81)**
Weight gain (kg)			
Poor	2879.4	142	**1.93(1.3-2.94)**
Good	1002.7	26	1
Anemia (gm/dl)			
No	3498.4	137	1
Yes	489.29	38	**2.09(1.45-3.0)**
HIV status			
Reactive	206.14	12	1.39(0.77-2.5)
Nonreactive	3839.1	166	1
Urinary tract infection			
Positive	681.29	25	0.85(0.55-1.29)
Negative	3364	153	1
Rapid syphilis test			
Reactive	80	4	1.197(0.44-3.2)
Nonreactive	3965.3	174	1
Tuberculosis status			
Positive	152.14	10	1.55(0.82-2.94)

Negative	3726	160	1
Alcohol taking			
No	3888.3	167	1
Yes	95.14	5	1.2(0.5-2.95)
Cigarette smoking			
No	3891.3	169	1
Yes	83.99	3	0.77(0.25-2.4)

p<0.05=significant, HIV: human immune virus,

7.7 Multivariable Cox regression analysis for predictors of small for gestational age among pregnant women

Based on significance level (p-value≤0.2) in bivariate Cox regression possible confounders for preeclampsia/eclampsia which need to adjustment were age of mothers, residence, marital status, ethnicity, history of stillbirth, cardiac diseases, anemia at ANC booking, weight gain, parity, history of pregnancy-induced hypertension, and also diabetes mellitus and history of low birth weight included based on clinical significance to SGA. We checked the interaction effect between age, anemia and preeclampsia, anemia and cardiac diseases, but had no modifying effect among the variables; therefore it was not included in the final model.

Also, in addition, we checked the entire model with the global test (0.5526>0.1) for the assumption, which was found to fulfill the assumption of proportional hazard. After the adjustment for the effect of other variables, preeclampsia/eclampsia, a history of low birth weight and gestational weight gain found to have a statistically significant relationship with SGA. The remaining variables such as the age of mothers, residence, marital status, diabetes mellitus, cardiac diseases, and anemia was not statistically significant in the multivariable Cox regression. The significance of the model used was checked by the Omnibus test (x2 =85.74, p< 0.00001). The overall model was checked by Cox Snell residuals, so the configuration is very close to a 45° line, indicated that the proportional hazards model provides a reasonable fit to the data (Figure 5).

Pregnant women with preeclampsia/eclampsia were four times risky to develop fetuses with SGA as compared to women with no preeclampsia/eclampsia after controlling for socio-demographic factors, medical factors, obstetric factors, and infectious diseases, (AHR=3.92, 95% CI 2.55-6.01). The mother's previous history of low birth weight was a significant association with SGA. Women with a history of low birth weight were 41% risky of SGA as compared to no history of low birth weight, (AHR=0.41, 95%CI 0.17-0.94). Pregnant women's poor weight gain during pregnancy were two times risky to SGA as compared to adequate weight gain during pregnancy, (AHR=1.89, 95% CI 1.15-3.1)(Table 9).

Table 9: Multivariable Cox regression and test proportional hazard assumption for small for gestational age among pregnant women in MGH and ACSH Tigray, Northern Ethiopia, 2019.

Variables	CHR95% CI	AHR 95%CI	P(PH)
Exposure status			
Normotensive	**1**	**1**	
Preeclampsia	**4.32(3.17-5.87)**	**3.92(2.55-6.01)**	0.2002
Age of mothers			
15-19	1.06(0.52-2.16)	1.09(0.51-2.36)	0.2141
20-34	1	1	
>35	1.95(1.32-2.88)	1.32(0.82-2.13)	0.8703
Ethnicity			
Tigrawi	1	1	
Amhara/Afar	1.34(0.78 -2.27)	1.07(0.61-1.89)	0.1772
Others	1.68(0.78-3.58)	1.18(0.52- 2.73)	0.0455
Residence			
Urban	1	1	
Rural	**1.97(1.41-2.74)**	0.9(0.59-1.37)	0.7146
Marital status			
Unmarried	1.86(1.16-2.96)	1.20(0.71-2.03)	0.0766
Married	1	1	
History of stillbirth			
No	1	1	
Yes	**1.72(1.12-2.63)**	1.39(0.83-2.32)	0.8365
Previous low birth weight			
No	1	1	
Yes	1.23(0.66-2.26)	**0.41(0.17-0.94)***	0.6749
History of PIH			
No	1	1	
Yes	1.44(0.85-2.45)	0.65(0.35-1.23)	0.7263
Parity			

Nullipara	0.99(0.70-1.42)	0.94(0.60-1.48)	0.6900
Primipara	0.72(0.49-1.06)	0.78(0.5-1.21)	0.8543
Multipara	1	1	
Diabetes mellitus			
No	**1**	**1**	
Yes	1.25(0.5-3.04)	0.94(0.33-2.62)	0.4762
Cardiac disease			
No	1	1	
Yes	**2.1(1.18-3.81)**	1.76(0.88- 3.53)	0.4739
Tuberculosis			
Positive	1.55(.82-2.94)	1.12(0.52-2.39)	0.9645
Negative	1	1	
Weight gain d (kg)			
Poor	**1.93(1.3-2.94)**	**1.89(1.15 -3.1)***	0.5263
Good	1	1	
Anemia at booking(gm/dl)			
No	1	1	
Yes	**2.09(1.45-3.0)**	0.9(0.57-1.43)	0.8930
Global test			0.5526

AHR: adjusted hazard ratio, p<0.05=significant, P(PH): prob>X^2global test for proportional hazard assumption, *,p<0.05, PIH: pregnancy-induced hypertension

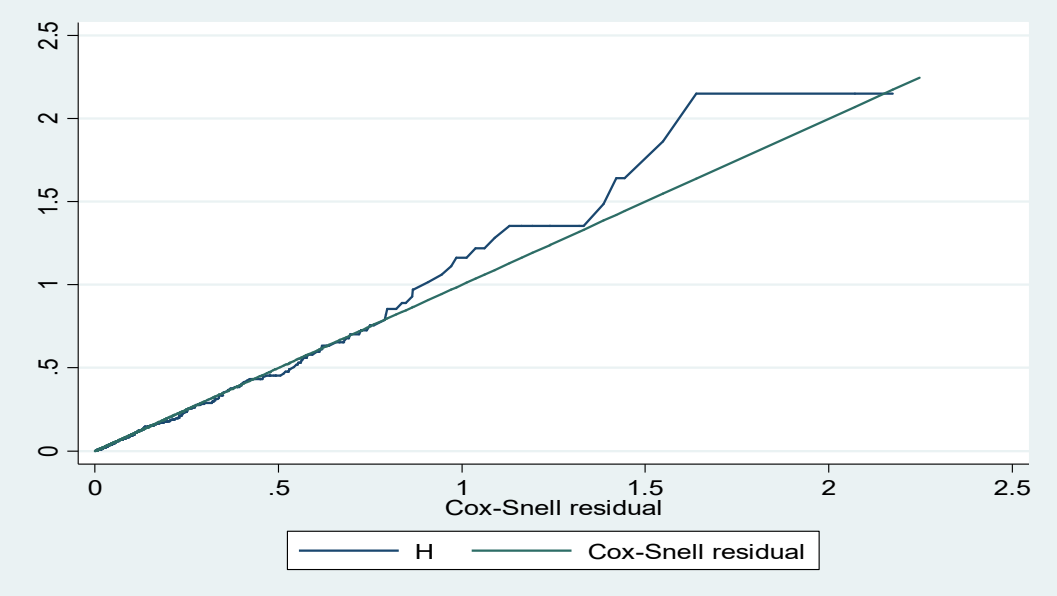

Figure 5: Overall model fit assessing by Cox–Snell residuals for small for gestational age among pregnant women in MGH and ACSH, Tigray, Northern Ethiopia, 2019.

8. DISCUSSION

In this hospital-based follow-up study, we observed a higher incidence rate of SGA among preeclampsia/eclampsia women than normotensive women. This finding was similar to studies done in China and Canada(22, 24). The similarity of the study might be because of the hospital-based setting, and study design. In contrast to our study, a cohort study conducted in Ghana found no statistically significant difference in the incidence of SGA among preeclampsia and normotensive women; variation of the sample size could be explained the disparity since that study was done among 16pregnant women unlike ours, and resident and marital status of study participant might also explain the variation due to significant difference between preeclampsia and normotensive pregnant women in our study, but not in Ghana (10). A study conducted in Nigeria had also no significant difference in the incidence of SGA between hypertensive disorders and normotensive women(59). This variation might be due to including all types of hypertensive disorders in the study, but in our study included only preeclampsia/eclampsia and superimposed preeclampsia. It might be also due to no clear follow-up time, marital status of study participant might also explain the variation due to significant difference between preeclampsia and normotensive pregnant women in our study. The exact comparison was not possible because of the scarcity of similar studies.

We indicated that also the number of SGA free decreases proportionally as the follow-up period increases in both preeclampsia and normotensive pregnant women but not at the same rate. The median SGA free time is lower in preeclampsia than normotensive pregnant women. Therefore the probability of SGA is higher in preeclampsia than normotensive pregnant women, which was supported by the log-rank test and regression analysis. This means when women took time with preeclampsia/eclampsia risk of SGA increases if not take immediate action(2). A retrospective cohort study conducted in the USA, preeclampsia increase the risk of developing SGA regardless of duration gestational age(23).

In our study, a statistically significant association was found between preeclampsia/eclampsia and SGA with the power of 98.5%. This finding is supported by the studies conducted in Canada(22), and USA(23); which reported a significant relationship between preeclampsia and SGA. The similarity might be because of a similar study design and the study setting (hospital-based). Similarly, a nested case-control study conducted in Sri Lankan found a significant association between PIH and SGA(60), and retrospective cohort studies were done in South Carolina, Italy, and China showed that a statistically significant association between hypertensive disorders during pregnancy and SGA(24, 32, 47). An association between preeclampsia and fetal growth retardation was supported by the pathogenesis of a decrease in utero-placental perfusion in preeclampsia/eclampsia women which leads to SGA(3, 29).

A cohort study was done in Australia and North Carolina (25, 33)shows that no significant association between preeclampsia and SGA. The results may differ due to including any type of hypertension during pregnancy in the above study which dilutes the risk of preeclampsia for SGA, but in our study, we only included preeclampsia/eclampsia, superimposed preeclampsia. The other possible reason could be a higher sample size (n=1958, North Carolina but not Australia(n=713)), the chart used for outcome measure (latest Australian national birth weight percentiles standard for Australia study, but not clear for North Carolina study) and residence of the study participants. In our study, however, we use the WHO growth standard chart to measure SGA and the majority of study participants were urban residents (64.44%).On the other hand, preeclampsia has also protected effect for SGA, based on a study done in Indonesia (27), which might compensate for the effect of lower blood supply and nutrients for the reason of decrease in utero-placental perfusion.

In our study, the history of low birth weight was a protective effect for SGA. However, a study conducted in North Carolina was an increased risk of SGA(25); this variation might be in our study pregnant women more conscious about their current health of the fetuses due to the previous history of low birth weight. Variation of the sample size could be also explained the difference since that study was done among 1958pregnant women unlike ours.

Weight gain during pregnancy has a positive impact on fetal growth suggesting that energy balance is an important determinant of birth outcomes(61). In our study, poor weight gain during pregnancy was a significant predictor of SGA. This finding was consistent with a study conducted in Pakistan(45). This study is similar to our study both in the study setting (hospital-based), the measurement for the outcome and weight of mothers. However, this finding differed from a secondary analysis conducted in North Carolina(25). This variation might be due to the measurement we used for weight gain during pregnancy.

In this study anemia at booking was not a statistically significant association with SGA. This finding was similar to a prospective multicentre cohort study done in New Zealand, Australia, England and Ireland (62). This study is similar to our study because we use the same measurement for anemia classification of study participants and also might be due to design. But it differs from a study done in Pakistan(35). This variation could be occurring because of the large sample size in our study and the measurement we used. However, it is clinically significant because, Anemia, causing hypoxia which induces maternal and fetal stress, which stimulates the synthesis of corticotrophin-releasing hormone which important by increases fetal cortical production, which is likely to inhibit fetal growth(63).

This study has shown no association between diabetes mellitus and SGA, this finding is consistent with a study done in Pakistan and North Carolina(25, 35). But a cohort study was done in South Carolina diabetes mellitus had a protective effect for SGA as compared to no diabetes mellitus. This variation might be due to the genetic process, lifestyle and geography factors(47). Even if a conflict of idea between the result, is clinically significant for SGA, it means maternal diabetes mellitus increase risk possible due to micro-vascular changes that impaired the placenta, which might cause fetal growth restriction (2).

Cardiac diseases have a positive or negative effect on fetal growth due to decreases in perfusion of nutrients to the placenta that supply to the fetus (2). But in this study history of cardiac diseases had no significant effect on the developing of SGA. However, a cohort study conducted in the United Kingdom shows that heart diseases have increased the risk of developing SGA as compared to no history of heart diseases(64). This difference might be due to lifestyle, and socioeconomic status. On the other hand, a study done in Indonesia cardiac diseases has a protective effect for SGA as compared to no history of cardiac diseases, this might be due to the compensation effect of blood supply for the reason of decrease in utero-placental perfusion(27). The variation might also by chance (the proportion of SGA was high among no history of cardiac diseases).

In our study, the age of mothers had no statistically significant effect on SGA. This finding was consistent with the study done in North Carolina (25). But studies were done in Pakistan(n=270), and Tanzania(n=19269) age of the mothers had a significant effect on SGA; this variation might be because of the sample size difference from our study (n=715)(34, 45). But the age of mothers less than 19-year-old has clinical significant may be due to incomplete maternal physical growth, which is related to the mother's gynecological age, for this reason, the fetus also will have restricted growth(65).

Our result indicates that marital status had no significant relationship with SGA. This finding is similar to a study done in North Carolina and Chicago (25, 43). This might be due to a similar study setting (hospital-based) and by chance. But a retrospective cohort study was done in Canada; marital status association with SGA was modified by inter-pregnancy interval, means unmarried mothers and short and long inter-pregnancy interval at high risk develop SGA due to uncomfortable lifestyle, psychological stress, and cultural effect, but in our study we do not know the effect of inter-pregnancy interval, this might be the variation of the study(41). A retrospective study conducted in Taiwan also marital status was a protective effect for SGA, which is different from our study(44). This variation might be due to a higher sample size (n=4566) than our study, socio-cultural and study design differences.

9. STRENGTH AND LIMITATION OF STUDY

9.1 Strength of the study

- Retrospective cohort because we can see the temporal relationship between cause and effect
- Strong Power

9.2 Limitation of the study

- The narrow scope of the study setting and population so maybe affect the external validity
- Diagnosis of exposure was dependent on physician decision which may have individual variation in case diagnosis that leads to bias.
- Since weight gain was calculated from last visit and first but have-not equal length of time for the pregnancy period, so it may introduce measurement bias.
- The estimated fetal weight was taken from ultrasound results or clinical estimate (fundal height) for this study and some fetuses may have been misclassified into the wrong weight for the gestational age category, even gender information was not available so the estimated fetal weight may be over or underestimated.
- There is more than 10% missing value on occupational and educational status, sex fetus and birth interval.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1 Conclusions

In summary, this study showed that there is a significant difference between preeclampsia and normotensive pregnant women in terms of the incidence rate of small for gestational age. And also after adjusting for confounder preeclampsia/eclampsia has a significant association with small for gestational age. Previous bad obstetric history such as; a history of low birth weight had a protective effect for small for gestational age, but medical factors such as; poor weight gain during pregnancy had an increased risk of small for gestational age. However, the age of mothers, anemia, cardiac diseases, and diabetes mellitus had no statistically significant effect but it may have clinical implications.

10.2 Recommendations

To Ethiopian Federal Minister of Health and Regional Health Bureau:

- We recommend giving the focus of fetal growth among preeclampsia high-risk mothers for timely diagnosis, management and monitoring for better health outcomes.

To policymakers:

- To prepare strategies for addressing the modifiable factors for SGA like poor weight gain by early screening, detection, and control.

To health professionals:

- Repeated screening for pregnant women with a high risk of preeclampsia/eclampsia to minimize the risk of developing SGA.
- Advice and intervene nutrients could help in increasing maternal weight gain during pregnancy.

To researcher

- Further community based prospective cohort studies with large sample size, close follow up and repeated measurement of the outcome at important time points and detailed assessment of nutritional status of pregnant mothers with pre-pregnancy body mass index measurement needed to conduct.

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ANNEXES

ANNEX I: Frequency

Table 10: Descriptive status of study participants in MGH and ACSH, Tigray, Northern Ethiopia, 2019.

Variables	Frequency	Percent
Age of mothers		
15-19	37	5.17
20-34	591	82.66
>35	87	12.17
Ethnicity		
Tigrawi	645	90.21
Amhara/Afar	47	6.57
Others	18	2.52
Unrecorded	5	0.72
Residence		
Urban	569	79.58
Rural	135	18.88
Unrecorded	11	1.54
Marital status		
Unmarried	58	8.11
Married	635	88.81
Unrecorded	22	3.07
History of stillbirth		
Yes	74	10.35
No	639	87.37
Unrecorded	2	0.28
Prior miscarriage		
No	540	75.52
Yes	172	24.2
Unrecorded	2	0.28
History of low birth weight		
No	670	93.71
Yes	38	5.31
Unrecorded	7	0.98
Parity		
Nullipara	290	40.56
Primipara	224	31.33
Multipara	201	28.11
History of PIH		
No	668	93.43
Yes	47	6.57
Previous surgery		
No	618	86.43

Yes	93	13.01
Unrecorded	4	0.56
Abruption placenta		
No	683	95.52
Yes	30	4.2
Unrecorded	2	0.28
Placenta Previa		
No	697	97.48
Yes	16	2.24
Unrecorded	2	0.42
Diabetes mellitus		
No	695	97.2
Yes	18	2.52
Unrecorded	2	0.42
Cardiac diseases		
No	684	95.66
Yes	26	3.64
Unrecorded	5	0.7
Gestational weight gain		
Poor	520	72.73
Good	170	23.78
Unrecorded	25	3.5
Anemia		
No	615	86.01
Yes	93	13.01
Unrecorded	7	0.98
HIV status		
Positive	38	5.31
Negative	677	94.69
Urinary tract infection		
Positive	138	19.3
Negative	577	80.7
Rapid syphilis test		
Reactive	16	2.42
Nonreactive	699	97.76
Tuberculosis		
Positive	29	4.06
Negative	655	91.91
Unrecorded	31	4.34
Alcohol taking		
No	688	96.22
Yes	16	2.24
Unrecorded	11	1.54
Cigarette smoking		
No	693	96.92
Yes	12	1.68

Unrecorded	10	1.4

ANNEX II: Log-rank test and proportional hazard assumption

Table 11: Log-rank test for equality of survival function (small for gestational age)among pregnant women and proportional hazard assumption in MGH and ACSH, Northern Ethiopia, 2019.

Variables	**Observed SGA**	**Expected SGA**	X^2	**p-value**	**P(PH)**
Exposure status					
Normotensive	73	131.33	102.91	**0.0000**	0.2560
Preeclampsia	105	46.67			
Age of mothers					
15-19	8	8.31	11.68	**0.0029**	0.3274
20-34	139	152.15			
≥35	31	17.54			0.4186
Residence					
Urban	127	146.91	16.71	**0.000**	
Rural	49	29.09			0.4208
Ethnicity					
Tigrawi	155	160.99	2.84	0.2417	
Amhara/afar	15	11.68			0.1500
Others	7	4.34			0.0392
Marital status					
Unmarried	20	11.39	7.07	**0.0079**	0.5947
Married	155	163.61			
History of stillbirth					
No	152	161.54	6.55	**0.015**	
Yes	25	15.46			0.6204
Previous miscarriage					
No	135	133.08	0.11	0.7364	
Yes	42	43.92			0.4143
History of low birth weight					
No	163	164.92	0.43	0.5111	
Yes	11	9.08			0.1378
Parity					
Nullipara	72	65.12	3.84	0.1479	
Primipara	50	62.31			0.9576
Multipara	56	50.57			0.3479
History of PIH					
No	163	167.32	1.88	0.1700	
Yes	15	10.68			0.5675
Pervious reproductive surgery					
No	156	156.35	0.01	0.9307	

Yes	20	19.65			0.9060
Placenta priva					
No	175	172.40	1.53	0.2166	
Yes	2	4.60			0.6602
Abruption placenta					
No	169	170.93	0.56	0.4543	
Yes	9	7.07			0.7188
Diabetes mellitus					
No	172	172.97	0.24	0.6236	
Yes	5	4.03			0.7060
Cardiac diseases					
No	163	169.12	6.67	**0.0098**	
Yes	12	5.88			0.1256
Weight gain					
Poor	144	126.18	9.96	**0.0016**	0.9735
Adequate	26	43.82			
Anemia at booking					
No	38	20.63	16.86	**0.0000**	
Yes	137	154.37			0.2878
HIV status					
Positive	12	8.81	1.23	0.2667	0.9410
Negative	166	169.19			
Urinary tract infection					
Positive	25	28.76	0.6	0.4403	0.1606
Negative	153	149.24			
Rapid syphilis test					
Reactive	4	3.36	0.13	0.7208	0.4801
Nonreactive	174	174.64			
Tuberculosis					
Positive	10	6.58	1.87	0.1718	0.6885
Negative	160	163.42			
Alcohol taking history					
No	167	167.84	0.18	0.6735	
Yes	5	4.16			0.4005
Cigarette Smoking					
No	169	168.15	0.2	0.6582	
Yes	3	3.85			0.2886

P(PH): prob>X^2global test for proportional hazard assumption

ANNEX III: Data abstraction format

Instruction: Please read and review the checklist as well as a circle for given numbers or tick for the box to those closed-ended question and write the answer for the open-ended questions.

Date ……../……/……

Name of Data Abstractor_____/signature_____

Name of supervisor_____/signature _____

MRN----------

Preeclampsia/eclampsia ☐

Normotensive mother ☐

Part I: Socio demographic characteristics of Mother			
No.	Questions	Coding category	Skip
101	Age of the mother (in yrs.)	----------	
102	Residence	1. Urban 2. Rural	
103	Ethnicity	1. Tigray 2. Amhara 3. Afar7.Others	
104	Marital status	Single ☐ Married ☐ Divorced ☐ Widowed ☐ Unrecorded ☐	

Part II: maternal obstetric and medical history			
No	Question	Coding category	Skip
201	Does she have Previous stillbirth or neonatal loss?	1. Yes 2. No 9. Unrecorded	
202	Does she have a History of prior miscarriage?	1. Yes 2. No 9 Unrecorded	
203	Birth weight of last baby < 2500g	1. Yes 2. No 9. Unrecorded	
204	Does she have previous history of gestational hypertension or preeclampsia/ eclampsia	1. Yes 2. No 9. Unrecorded	
205	Previous surgery on the reproductive tract?	1. Yes 2. No 9. Unrecorded	
206	Does she have gestational or diabetes mellitus (DM)?	1. Yes 2. No 9. Unrecorded	
207	Does she have a history of Cardiac disease?	1. Yes 2. No 9. Unrecorded	
208	Does she have placenta preiva in the current pregnancy?	1. Yes 2. No 9 Unrecorded	
209	Does she have an abruption placenta?	1. Yes 2. No	

Part III- Current Pregnancy Status			
No	Question	Coding category	Skip
301	First visit of ANC	---------- DD/MM/YYYY	
302	Gestational age	_____in weeks	
303	Excepted date of delivery (in weeks)	---------- DD/MM/YYYY	
304	Gravidity	_____in number	
305	Parity	_____in number	
306	Platelet count	_____in cells/micro liters	
307	Hemoglobin status at booking	_____ in g/dl	
308	HIV/AIDS status	1. Reactive 2. Nonreactive	
309	Positive urine test for infection or UTI	1. Yes 2. No	
310	Proteinuria	1. Positive 2. Negative	
311	Abnormal body movement	1. Positive 2. Negative	
312	Tendon reflex	1. Positive 2. Negative	
313	Renal function test (creatinine level)	----------mg/dl	

314	Liver function test (aspartate aminotransferase)	---------- unit/liter	
315	Rapid syphilis test(VDRL)	1. Positive 2. Negative	
316	TB status	1. Reactive 3. Nonreactive 9. Unrecorded	
317	Does she take alcohol during pregnancy?	1. Yes 2. No 9 Unrecorded	
318	Does she have a smoking history?	1. Yes 2. No 9 Unrecorded	

Part VI- Pregnancy progress follow up

Date diagnosis of preeclampsia/eclampsia=----------/----------/----------DD/MM/YYYY

GA (wks)	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Weight of mothers(kg)																							
EFW (gm)																							
fundal height (cm)																							

ANNEX IV: Medical record data abstraction guide

Introduction

This data abstraction guide was used for training of data collectors, supervisor and as a reference when data collectors are abstracting data from the ANC logbooks and medical records of pregnant mothers on ANC follow up and who come by referral with ANC follow up the document in ACSH and MGH, Tigray, Northern Ethiopia.

Objective of the study: To determine effect of preeclampsia on incidence of small for gestational age among pregnant women in MGH and ACSH, Tigray, Northern Ethiopia, 2014-2018.

Type of record to review: Midwifery/residents/obstetric and gynecologist: ANC follows up the document (pregnancy progress note), ultrasound findings and interpretation, obstetric and medical detailed history should be reviewed to abstract relevant variables of interest. If two sources of documentations oppose each other review the record of the most senior clinician having the highest rank.

Place of variables: the majority of socio-demographic characteristics of pregnant women can be obtained from the cover page of the medical record and others are located inside the document.

Time needed to fill the checklist

On average, it is expected that 20-25 minutes was needed to read and review pregnant mothers' ANC follow up documents and medical records and fill out on the checklist.

Eligibility criteria

Inclusion criteria: All pregnant women who have preeclampsia/eclampsia, including superimposed preeclampsia, were selected after the physicians made a diagnosis as part of a routine case. Controls are women who attend the ANC from both hospitals and were not diagnosed as preeclampsia/eclampsia throughout the study.

Exclusion criteria: Pregnant women who have renal diseases, known chronic and gestational hypertension without proteinuria throughout pregnancy to know the effect of preeclampsia independent only and twin pregnancy are also excluding from the study because of know effect to preeclampsia and SGA. Mothers who came to this hospital by referral with no ANC follow up the document.

Acronyms and Abbreviations

ADIS	Acquired Immune Deficiency Syndrome
ANC	Antenatal Care
BP	Blood Pressure
DM	Diabetes Mellitus
EFW	Estimated Fetal Weight
GA	Gestational Age
IUGR	Intrauterine Growth Restriction
HIV	Human Immunodeficiency Virus
MRN	Medical Record Number
TB	Tuberculosis
UTI	Urinary Tract Infection
VDRL	Venereal Disease Research Laboratory
WHO	World Health Organization

Operational definitions

Definition of exposure

Preeclampsia was defined by new-onset hypertension with systolic blood pressure ≥140 mm Hg or diastolic≥90 mm Hg on two occasions at least4- 6 hours apart and proteinuria (≥0.3 g in 24 hours or1+ on a urine dipstick when 24-hour urine was not available) after 20 weeks of pregnancy. Severe preeclampsia was diagnosed if the patient had one or more of the following criteria in addition to mild preeclampsia: systolic blood pressure ≥160mm Hg or diastolic ≥110 mm Hg on two occasions at least 4- 6 hours apart, proteinuria (≥5 gin 24 hours or 3+ or greater protein on two random urine samples collected at least 4 hours apart when a 24 hour urine was not available), oliguria of <500 mL in 24 hours, renal impairment with creatinine ≥1, cerebral or visual disturbances, pulmonary edema, right upper quadrant pain, impaired liver function (aspartate aminotransferase >1.5 times normal), low platelets (<120,000). Eclampsia means new-onset grand mal seizures in a woman with preeclampsia that cannot be attributed to other causes. Superimposed preeclampsia was occurred in women with previous hypertension history but have no proteinuria in early pregnancy before 20 weeks of gestation, which currently develops new-onset proteinuria. In addition, in women

with hypertension and proteinuria before 20 weeks of gestation, may develop any of the following: (a) sudden increase in proteinuria and BP, and a platelet count of less than 10^5/micro liter in a woman whose hypertension was previously well controlled. Gestational age was estimated by the last normal menstrual period or using first or second-trimester ultrasound by measuring crown-rump length**.**

Definition of non-exposure group

A pregnant mother with normotensive (<140/90 mmHg) throughout the pregnancy period, but if a mother develops preeclampsia/eclampsia during the follow-up time we include in the exposure group.

Definition of outcome

Incident of Small for gestational age, which is defined in this study, as an event, during follow-up time was ascertained retrospectively when EFW was <10 percentiles, classified as SGA based on the WHO growth standard chart, but not include those who have gross congenital anomaly, no SGA if it's EFW was >10 percentiles.

Definition of variables

Severe anemia: means hemoglobin level less than 11 grams per deciliter during pregnancy.

Cigarette smoking: if she smokes more than or equal to one cigarette per day the mother consider as a smoker (yes) and if not as nonsmoker (no).

Alcohol drinking: based on self-report during ANC follow up "yes if she was taken during pregnancy and "no" if she was not taken during pregnancy.

Previous Stillbirth: was defined as fetal death before birth, with gestational age ≥ 20 weeks and birth weight ≥ 500 grams in the previous pregnancy outcome.

Placenta previa: the placenta is partially or totally attached to the lower uterine segment which conforms by the physician.

Abruption placenta: Premature separation of the placenta is defined as separation from the site of uterine implantation before delivery of the fetus which confirms by the obstetrician.

Weight gain during pregnancy: was calculated from the last visit of ANC to the first visit of ANC based on this less than10 kg as poor weight gain and greater than 10kg adequate weight gain.

ANNEX V: Curriculum Vitae (CV)

Personal profile

Name: EmbabaTekelayeWelesemayat

Sex: Female

Date of Birth: 24/04/1985 E.C

Age: 26 years

Place of birth: TahtayMachew

Marital Status: Single

Health status: Normal

Nationality: Ethiopian

Contact Address: Addis Ababa, Ethiopia

Tel mobile: +251914190455

Email Address:embebatek2013@gmail.com

Educational Background and qualification

Educational level	Place	Years (Ethiopian calendars)
Grade 1-8	Kewanti Elementary School	1993-2000
Grade 9-12	Kellmino Special High School	2001-2004
Degree in public health	Aksum university, college of health science	2005-2008

Educational qualification

BSc in public health from Aksum University College of health science (2013_2016 G.C) with CGPA of 3.89.

Language

Tigrigna, Amharic and English

Additional professional experience

I have one year teaching experience in Aksum University, College of health science as graduate assistant II.

Other interest and activity

I am interested in lessening the NWES program and reading different articles and books. And also, I am interested to help the community, because if I help the community it will create great satisfaction, willingness, and happiness.

CURRICULUM VITEA

Present Address

Private P.O.Box:16450, Addis Ababa, Ethiopia

Cell phone: 251911769926
Home : 25116462423
E-mail : girmataye2009@gmail.com

Personal data

Name : Girma Taye Aweke
Nationality : Ethiopian
Marital Status : Married (with children)

Education

- Ph.D. Biometry (Biostatistics): University of KwaZulu-Natal, South Africa, 2006

Employment:

Addis Ababa University, College of Health Sciences, School of Public Health,
Academic Rank: Associate Professor of Biostatistics,

Projects (on-going and recently completed):

1. Urban Vulnerability to Health: People and Places (recently completed)
2. Epidemiological synthesis of HIV for Addis Ababa City Administration (recently completed)
3. Capacity Building and Mentoring Project (CBMP) for HMIS (on-going)
4. MELA Project (Just starting)
5. DDCF support to Ethiopian health Information system.project

Awards

- In recognition of contribution as an ***external evaluator*** of under graduate program in Statistics at Addis Ababa University, 1999.
- In recognition of ***scientific contribution*** to Ethiopian Statistical Association, 2000
- In recognition of ***contribution to research development*** at Plant protection research centre of Ethiopia, 2002.
- In recognition of contribution to Ethiopian ***Research and training*** project of Ethiopia, 2002.
- In recognition of contribution to the ***teaching and practice of biostatistics in Africa*** (awarded by American Statistical association), 2006.

Few Recent (selected) Publications

Journal articles (Peer reviewed):

1. Tilahun Ferede, **Girma Taye** and Yohannes Yebabe (2012). Multilevel Modelling of Modern Contraceptive Use among Rural and Urban Population of Ethiopia. American Journal of Mathematics and Statistics, Vol. 3, No. 1.

2. **Girma Taye** and Dan Makumbi (2014). Studying GxE interaction under different management system and yield level using Linear-bilinear models: The case of CIMMYT Intermediate to Late Hybrids Trails in Eastern Africa. **Ethiop. J. Agric. Sci. 24:1, 1-27.**
3. Girma Taye eta l. (2016). Effect of climate change on burden of Malaria in Ethiopia. EJHD.
4. Mirgissa Kaba, Girma Taye, Muluken Gizaw & Israel Mitiku. (2016). Vulnerability to HIV infection: Places and Persons in Urban Settings of Ethiopia, EJHD, vol 30, N(1).
5. Diriba Tadesse and Girma Taye (2017). Application linear mixed model to Multi-location variety trial in the presence of missing plot, JESA, Vol 25, pp 1-11
6. Tarekegn Argaw, Girma Taye, Dechasa Bedada, Ashenafi Ayano (2018). Longitudinal Analysis of Arabica Coffee Bean Yield: Application of Linear Mixed Model for Clustered Longitudinal Data. Academic Research Journal of Agricultural Science and Research. Vol. 6(7), pp. 370-382. September 2018 DOI: 10.14662/ARJASR2018.049 ,
7. Anisa Mohamed, Girma Taye, Muluken Gizaw. 2019. Quality of life and associated factors among patients with breast cancer under chemotherapy at Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia, POLS ONE

Technical publication

- Lemma W, Moreira Dos Santos Elizabeth; Ali Jemal; **Taye Girma**, Kifle Yibeltal. Evaluation of Reproductive Health/Family Planning Project of Oromia Development Association (ODA): 2000--2008. David and Lucile Packard Foundation. May 2010.

Proceedings

- Several proceedings published in different professional association conferences

Books

- ***Girma Taye*** et.al. (2000), Design and Analysis of Experiments, EIAR, Addis Ababa
- ***Gima Taye*** (eds.) (2005). Proceeding of the 9th Sub-Saharan Africa Network of the International Biometric Society Conference.

Professional affiliations

- Member of International biometrics society (secretary of Ethiopian group, 1997-2002, 2006-upto date).
- Member of Ethiopian Statistical society. (Secretary, 1995-1997)
- Member of Ethiopian Public Health Association
- Associate Editor for the Journal of Ethiopian Statistical Association and Natural Resources, Ethiopian
- Reviewer of articles for several national and international journals.