Original Article

Effect of preeclampsia on the incidence rate of small-for-gestational-age of the fetuses among pregnant women in selected public hospitals in Tigray, Northern Ethiopia

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Abstract

Background: In low- and middle-income countries, including Ethiopia, small-for-gestational-age of the fetuses is a risk factor for fetal and neonatal mortality and morbidity that is linked to immediate perinatal adverse events and also to adult pathologic conditions in later life. In Ethiopia, particularly in Tigray, there is a paucity of information on the incidence rate and predictors of small-for-gestational-age of the fetuses among pregnant women.

Objective: To determine the incidence rate and predictors of small-for-gestational-age of fetuses among pregnant women in selected public hospitals in Tigray, Ethiopia.

Methods: A retrospective cohort study was conducted among preeclampsia (n = 239) and normotensive (n = 476) women who were in antenatal care follow-up before 20 weeks in selected hospitals of Tigray, from January 01, 2014, to March 31, 2019, to measure weight for gestational age of the fetuses every two to four weeks. Systematic sampling was used to select preeclampsia and normotensive women from the list in antenatal care logbook by their medical record numbers, using every three and every 25 intervals, respectively. A pre-tested structured checklist was used to extract data, then entered and cleaned using Epi Data version 3.1 and exported to Stata version 14 for analysis. The incidence rate was calculated by dividing all small-for-gestational-age of the fetus cases by the person weeks of follow-up. The Cox proportional hazard model was performed to identify predictors of small for gestational age of the fetuses.

Results: The incidence rate of small-for-gestational-age of the fetuses was higher among women with preeclampsia than normotensive women (94.5 versus 24.9 per 1,000 person weeks, Z = 9.42, p < 0.000001). A higher risk of small-for-gestational-age of the fetuses was observed among women with preeclampsia/eclampsia (AHR = 3.92, 95% CI 2.55-6.01), women with a history of low birth weight (AHR = 0.41, 95% CI 0.17-0.94), and women with poor gestational weight gain (AHR = 1.89, 95% CI 1.15-3.1).

Conclusions and recommendations: There were significant differences in the incidence rates of small-for-gestational-age of fetuses among preeclampsia, and normotensive women. Preeclampsia, a history of low birth weight and poor weight gain were significant predictors for small-for-gestational-age of the fetuses. It is necessary to strengthen the screening of preeclampsia for optimal fetal growth and to provide counseling on nutrients for adequate gestational weight gain. Further studies would also be beneficial to confirm the predictors at the community level. [*Ethiop. J. Health Dev.* 2020; 34(3):181-190]

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

Introduction

'Small-for-gestational-age' (SGA) fetuses is defined as an estimated fetal weight <10 percentiles for that particular gestational age, based on the non-customized growth chart (1). The terms 'intrauterine growth restriction fetus' and 'small-for-gestational-age fetuses' are often used to describe the same phenomena.

In low- and middle-income countries, around 32.4 million SGA fetuses (27%) are born each year. Ethiopia contributes about 838,000 cases per annum (2). SGA fetuses is a multifactorial disease of pregnancy that markedly increases fetal and neonatal mortality and morbidity, and is linked to immediate perinatal adverse events (such as prematurity, cerebral palsy, intrauterine fetal death), and also to adult pathologic conditions such as non-communicable diseases, as well as emotional, behavioral and social problems in later life (3-5).

In a study conducted in Northwest Ethiopia, intrauterine growth restriction fetuses contributed to 4.4% of adverse perinatal outcome (still birth, intrauterine death, low birth weight, and respiratory distress) (6). In addition, a study conducted in Tigray shows that SGA of the fetuses was attributed for 35% of very low birth weight and 54% of low birth weight, therefore neonatal mortality was higher among low birth weight and have also economic and environmental stress to the community and in health facilities(7). Neonatal mortality due to SGA of the fetuses in Ethiopia is 29 per 1,000 live births, but neonatal mortality among preterm and term SGA fetus is 1.6 per 1000 live birth and 20.8 per 1,000 live births respectively(8).

In our study, preeclampsia was defined as systolic ≥ 140 or diastolic blood pressure ≥ 90 mm Hg on two separate readings taken at least four hours apart, and a proteinuria ≥ 3gms per 24-hour urine collection 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 (9). A study

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done in Tigray region shows that SGA fetuses was 20.2% among preeclampsia/eclampsia, but due to a lack of data for normotensive pregnant women, no comparison was possible (10). The effect of preeclampsia/eclampsia and other predictors on SGA fetus is unclear in previous studies(11-18). To the best of our knowledge, there is no study which clearly shows the incidence rate and predictors of SGA fetuses among pregnant women, both in Tigray and in Ethiopia generally. Therefore, there is a knowledge gap in the area of SGA fetuses research in our context. Accordingly, this study attempts to provide information about SGA fetuses among pregnant women in Tigray region.

Methods and materials

Study design, period and setting: An institutional-based, retrospective cohort study was conducted in Ayder Comprehensive Specialized Hospital (ACSH).

Study 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. and Mekelle General Hospital (MGH) in Mekelle, the capital city of Tigray, from January 1, 2014, to March 31, 2019. Mekelle is located in the north of Ethiopia, 783km from Addis Ababa. There were 7,200 ANC follow-ups in the last five years, with an annual average of 1,446 women in ACSH. ANC follow-up for high-risk and low-risk pregnancy was done in a separate examination room. The assessment was done by residents and midwiferies. For both low risk and high risk pregnancy, an ultrasound investigation was done. Those with high-risk pregnancies were passing through the Doppler ultrasound examination. The same to MGH, where there is a 5,200 ANC follow-up in the last five years with an annual average of 1,040 pregnant women(19).

Inclusion criteria: Exposure groups were pregnant women who attended ANC in either of the two hospitals and who were diagnosed with preeclampsia/eclampsia, including superimposed preeclampsia. Non-exposed groups were women who attended the ANC in either of the two hospitals and were not diagnosed with preeclampsia/eclampsia throughout the follow-up period.

Data collection procedures and follow-up time: The data collection tool was prepared in English, and the data abstraction form was populated with the most relevant variables in relation to SGA of the fetus. Data was extracted from ANC follow-up documents, medical records, which contain socio-demographic characteristics, obstetric and medical history, current pregnancy status, and pregnancy progressive follow-up metrics (fetal weight, the weight of mother during each visit, fundal height).

Follow up study subjects were started from the date of diagnosis of one preeclampsia and matched by time for two control groups, while ‘exit date’ means when the outcome developed or end of the study. ‘Event’ means the occurrence of SGA fetus per pregnant women

Exclusion criteria: Women who had chronic and gestational hypertension without proteinuria throughout their pregnancy, multiple pregnancies, pregnant women with renal diseases, and pregnant women with no ANC follow-up documents were excluded.

Sample size calculation: The sample size was determined, considering the two objectives, using the two-population proportion technique. Epi Info version 7.2.0.1 was used to calculate the sample size. To calculate the sample size, the level of significance taken at 95% confidence interval and 80% power, and unexposed: exposed (2:1) are used to increase the power of the study (20). SGA fetuses among gestational weight gain <28 pounds (23.8%) and SGA fetus among gestational weight gain between 28 and 40 pounds (14.2%) were given the maximum sample size by adding 10% for lost follow up compared to other variables (n = 229 versus n = 458) (21). The final sample size was taken based on feasibility and the maximum sample size was 715 participants during sampling which fulfills the criteria.

Sampling procedures and participant recruitment: MGH and ACSH were selected purposively because they are the largest public hospitals with maternal health services in Tigray region. A systematic sampling approach has used to select preeclampsia and normotensive women from the list in ANC logbooks by their medical record number, using every three and every 25 intervals in the same hospitals, respectively, with the first participant selected randomly for preeclampsia/eclampsia and normotensive, and the rest recruited according to a predetermined pattern. The sample size was split between the two hospitals proportionally to their ANC follow-up caseload. The average annual ANC follow-up from 2014 to 2018 in ACSH was 1,440, including 80 cases of preeclampsia; over the same period, the average annual ANC follow-up in MGH was 1,040, including 70 cases of preeclampsia/eclampsia. Therefore, based on the population proportion to size, a total of 715 (239 versus 476) study subjects were distributed across both hospitals. However, it was not feasible to include all the pregnant women who met the criteria.

weeks. ‘Survival’ means a lack of SGA fetus occurrence within the follow-up period. ‘Censored’ refers to pregnant women who were not developed SGA of the fetuses or end of the study, withdrawal of the study. Fetal growth follow-up (estimated fetal weight = EFW) was checked using clinical measures (symphysis fundal height) or ultrasound at two to four weeks for all women, so we took the EFW (1), then compared it against the growth standard chart to decide the outcome is SGA fetuses if EFW<10 percentiles or not SGA fetuses if EFW has >10 percentiles (but not include recurrent SGA of the fetuses and diagnosed before starting follow-up for both groups). Estimated fetal weight was calculated using ultrasound from the abdominal circumference, head circumference, and femoral length, or based on clinical measurement (EFW (gms) = 2,600+115 (symphysis fundal height -

30)) (22). Follow-up time was measured in weeks (20-40); the chart used extended to the 40th week (the average length of pregnancy).

The data was retrieved by two data collectors who hold degrees in midwifery and one supervisor with an MSC in clinical midwifery. Before the data collection period, the principal investigator provided all three with two days of training on how to abstract data. A pretest was conducted before the data collection in ACSH and MGH among 5% of the total sample size to check the time required to extract data, to add questions if necessary, and to ensure the logical sequence of the checklist.

Data management and analysis procedures: The collected data were entered and cleaned in Epi Data version 3.1, and exported to Stata version 14 for statistical analysis. Open Epi version 3.01 was used for power calculation. Variables missing value more than 10% had dropped to do complete case analysis(23). Variables missing values of more than 10%, such as education, occupational status, sex of the fetus, and birth interval, were dropped. Assumption of normal distribution had checked for the continuous variable by using the Shapiro–Wilk normality test ($p<0.05$), so normality had violated than reported the median and interquartile range (IQR), but for the categorical variable described by frequency and percentages. Baseline characteristics of exposed and unexposed participants were compared using Pearson's chi-square and Fisher's exact test for categorical data, and Mann–Whitney U test for continuous data.

The incidence rate was calculated by dividing all SGA of the fetuses' cases detected in the cohort by the person-weeks of follow-up and comparing the results of preeclampsia/eclampsia and normotensive women. Results were deemed significant if the Z-score test was $p<0.05$. The Kaplan–Meier curve was used to estimate the median duration of SGA fetuses' occurrence. The log-rank test was used to compare survival curves between preeclampsia and normotensive pregnant women. Cox proportional hazard model was used to determine the hazard ratio. During Cox regression analyses, all variables with clinical importance and with a p-value of ≤ 0.2 (24) on bivariate analysis were included in multivariable Cox regression to calculate AHR. We checked the interaction effect between independent variables. All variables were checked proportional hazard assumption by an observed and predicted graph, -log(-log(S(t)) plots, and global test. All confirmed the proportional hazard assumption, except ethnicity. The significance of the model used was checked using the Cox-Snell residuals and the omnibus test. Finally, the results were presented in tables, figures, and text.

Results

Socio-demographic characteristics of study participants: Among pregnant women registered for ANC from January 01, 2014, to March 31, 2019, the data of 239 preeclampsia/eclampsia and 476 normotensive women were retrieved from ANC logbooks. Of the total 239 exposed and 476 unexposed pregnant women included in this study, 187 (78.24%) exposed and 404 (84.87%) unexposed women were in the 20 to 34-year-old age group (see Table **1**).

Table 1: **Socio-demographic characteristics of pregnant women in MGH and ACSH, Northern Ethiopia, 2019**

Variables	Preeclampsia N (%)	Normotensive N (%)	p-value
Ethnicity			
Tigre	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; Other = Kunama, Erob; $p<0.05$ = significant

Maternal obstetric factors of study participants: Of the study participants, 36 (15.06%) women with preeclampsia/eclampsia and 38 (7.98%) normotensive women had a history of stillbirth. In addition, 211 (90.56%) exposed and 459 (96.6%) normotensive pregnant women had a history of low birth weight. Thus, there is a statistically significant association between history of low birth weight and preeclampsia (p<0.0001) (see Table 2).

Table 2: **Maternal obstetric factors of pregnant women in MGH and ACSH, 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			
Nullipara	95 (39.75)	195 (40.97)	0.119
Primipara	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)	
Abruption placenta			
No	222 (92.89)	461 (96.85)	**0.028**
Yes	16 (6.69)	14 (2.94)	
Unrecorded	1 (0.42)	1 (0.21)	
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

Maternal medical factors and pregnancy status of study participants: The median first visit of gestational age was 17.3 with IQR (15.9-18) for preeclampsia/eclampsia women, and 17 with IQR (14.6-18.7) for normotensive women. There was no significant difference between the two groups (Mann–Whitney U test, Z = -1.15, p = 0.25). One hundred and eighty-nine (78.8%) preeclampsia and 332 (69.2%) normotensive women had poor gestational weight gain. Accordingly, there is a significant association between weight gain and preeclampsia (p = 0.005) (see Table 3).

Table 3: **Medical factors and pregnancy status of study participants in MGH and ACSH, Northern Ethiopia, 2019**

Variables	Preeclampsia N (%) or median (IQR)	Normotensive N (%) or median (IQR)	p-value
First visit of gestational age	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	218 (91.21)	466 (97.9)	**0.0001**
Yes	17 (7.11)	9 (1.89)	
Unrecorded	4 (1.67)	1 (0.21)	
Weight gain			
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/ADIS 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)	

$p<0.05$ = significant; IQR = interquartile range

Incidence density of small-for-gestational-age of the fetuses among pregnant women: A total of 239 pregnant women with preeclampsia and 476 pregnant women with no preeclampsia/eclampsia were followed for 20 weeks starting from the 20th week of pregnancy. The incidence rate of SGA fetuses was 94.5 (95% CI 78-114.38) per 1,000 person weeks among women with preeclampsia/eclampsia, and 24.9 (95% CI, 19.78-31.29) per 1,000 person weeks of follow-up among normotensive women, with the significant difference among the preeclampsia/eclampsia and normotensive pregnant women which test by Z-score Z = 9.42, $p<0.000001$).

Kaplan–Meier to estimate the probability of small-for-gestational-age of the fetuses among pregnant women: The minimum follow-up time (in weeks) for both women with preeclampsia/eclampsia and normotensive women was 0.286, and the maximum follow-up time was 18 and 19.6 weeks for women with preeclampsia/eclampsia and normotensive women, respectively. The median follow-up time for preeclampsia and normotensive women was six and 18 weeks, respectively. Fetuses with SGA free was significantly lower among women with preeclampsia than normotensive women (log-rank test, $X^2 = 102.91$, df = 1, $p<0.0001$) (Figure 1).

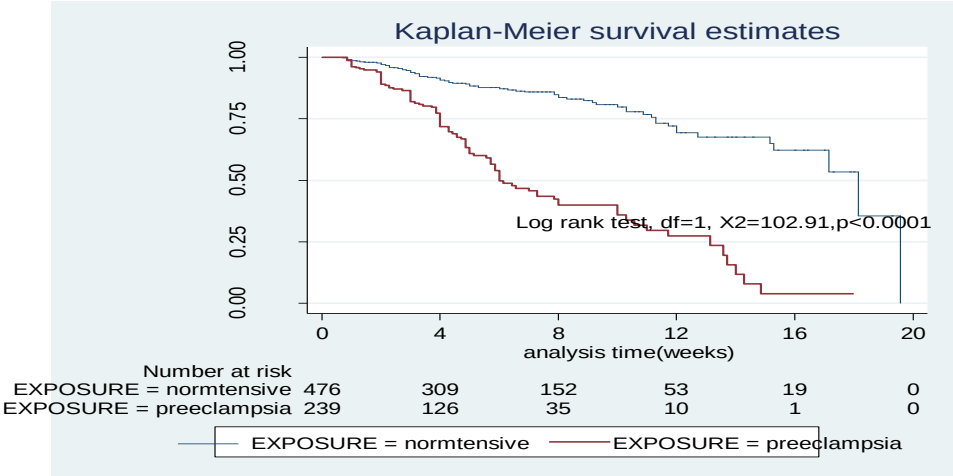

Figure 1: **Survival curve of SGA fetuses among preeclampsia and normotensive pregnant women from 20 to 40 weeks in MGH and ACSH, northern Ethiopia, 2019**

Multivariable Cox regression analysis for predictors of small-for-gestational-age of the fetuses among pregnant women: Based on significance level (p-value ≤ 0.2) in bivariate Cox regression, possible confounders for preeclampsia/eclampsia which needed adjustment were age of mothers, residence, marital status, ethnicity, history of stillbirth, cardiac diseases, anemia, weight gain, parity, and history of pregnancy-induced hypertension. Diabetes mellitus and history of low birth weight were included to multivariable cox-regression based on its clinical significance to SGA of the fetuses.

In addition, we checked the entire model with the global test (0.5526>0.1) for the assumption, which satisfies the proportional hazard assumption. The significance of the model used was checked using 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, indicating that the proportional hazards model provides a reasonable fit to the data (Figure 2).

Pregnant women with preeclampsia/eclampsia were at a four times greater risk of developing fetuses with SGA compared to normotensive women, after controlling for socio-demographic factors, medical factors, obstetric factors, and infectious diseases (AHR = 3.92, 95% CI 2.55-6.01). Women with a history of low birth weight were at a 41% higher risk of SGA fetuses compared to women with no history of low birth weight (AHR = 0.41, 95% CI 0.17-0.94). Pregnant women with poor gestational weight gain were twice as likely to develop SGA of the fetuses compared to women with adequate gestational weight gain (AHR = 1.89, 95% CI 1.15-3.1) (see Table 4).

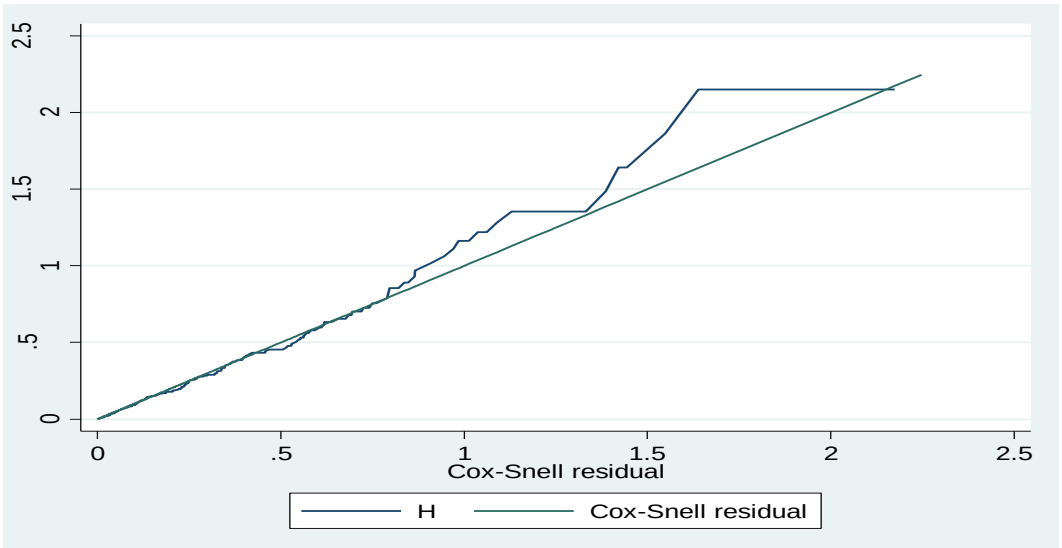

Figure 2: **Overall model fit assessing by Cox-Snell residuals for small-for-gestational-age of the fetuses among pregnant women in MGH and ACSH, northern Ethiopia, 2019**

Table 4: **Multivariable Cox regression and test proportional hazard assumption for small-for-gestational-age of the fetuses among pregnant women in MGH and ACSH, Northern Ethiopia, 2019**

Variables	CHR 95% CI	AHR 95% CI
Exposure status		
Normotensive	**1**	**1**
Preeclampsia	**4.32 (3.17-5.87)**	**3.92 (2.55-6.01)**
Age		
15-19	1.06 (0.52-2.16)	1.09 (0.51-2.36)
20-34	1	1
≥35	1.95 (1.32-2.88)	1.32 (0.82-2.13)
Ethnicity		
Tigre	1	1
Amhara/Afar	1.34 (0.78 -2.27)	1.07 (0.61-1.89)
Other	1.68 (0.78-3.58)	1.18 (0.52- 2.73)
Residence		
Urban	1	1
Rural	**1.97 (1.41-2.74)**	0.9 (0.59-1.37)
Marital status		
Unmarried	1.86 (1.16-2.96)	1.20 (0.71-2.03)
Married	1	1
History of stillbirth		
No	1	1
Yes	**1.72 (1.12-2.63)**	1.39 (0.83-2.32)
Previous low birth weight		
No	1	1
Yes	1.23 (0.66-2.26)	**0.41 (0.17-0.94)***
History of PIH		
No	1	1
Yes	1.44 (0.85-2.45)	0.65 (0.35-1.23)
Parity		
Nullipara	0.99 (0.70-1.42)	0.94 (0.60-1.48)
Primipara	0.72 (0.49-1.06)	0.78 (0.5-1.21)
Multipara	1	1
Diabetes mellitus		
No	**1**	**1**
Yes	1.25 (0.5-3.04)	0.94 (0.33-2.62)
Cardiac disease		
No	1	1
Yes	**2.1 (1.18-3.81)**	1.76 (0.88- 3.53)
Tuberculosis		
Positive	1.55 (0.82-2.94)	1.12 (0.52-2.39)
Negative	1	1
Weight gain		
Poor	**1.93 (1.3-2.94)**	**1.89 (1.15 -3.1)***
Good	1	1
Anemia at booking (gm/dl)		
No	1	1
Yes	**2.09 (1.45-3.0)**	0.9 (0.57-1.43)
Global test		**0.5526**

C/AHR: Crude/adjusted hazard ratio; PIH: pregnancy-induced hypertension; p<0.05 = significant, * = p<0.05

Discussion

In this hospital-based follow-up study, we observed a higher incidence rate of SGA of the fetuses among preeclampsia/eclampsia women than normotensive women. This finding is similar to studies conducted in China and Canada (12, 13). A multicenter retrospective study in China shows that preeclampsia interacts with age, in that those less than 25 years had an increased risk for SGA of the fetuses (25). The similarity of this finding 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 of fetuses among preeclampsia and normotensive women; variation of the sample size could be explain the disparity, and resident and marital status of study participants might also explain the variation because of significant differences between preeclampsia and normotensive pregnant women in our study, which were absent in the study conducted in Ghana (18). A study conducted in Nigeria also had no significant difference in the incidence of SGA of fetuses between hypertensive women and normotensive women (26). This variation might be because of the inclusion of all types of hypertensive disorders in the study, whereas our study included only preeclampsia/eclampsia and superimposed preeclampsia.

The median SGA of fetus free time is lower in preeclampsia than normotensive pregnant women. Therefore, the probability of a fetuses with SGA is higher in preeclampsia than normotensive pregnant women, which was supported by the log-rank test and regression analysis. This means when women stay a long time with preeclampsia/eclampsia, the risk of SGA fetuses increases if no immediate action was taken (5). In a retrospective cohort study conducted in the USA, preeclampsia increased the risk of developing SGA of the fetuses, regardless of gestational age (11).

In our study, a statistically significant association was found between preeclampsia and SGA of the fetuses with the power of 98.5%. This finding is supported by a study conducted in Canada (12), which reported a significant relationship between preeclampsia and SGA of the fetuses. The similarity might be because of similar study design and study setting. Similarly, retrospective cohort studies done in South Carolina (USA), Italy, and China showed a statistically significant association between hypertensive disorders during pregnancy and SGA of the fetuses (13, 17, 27). An association between preeclampsia and fetal growth retardation is supported by the pathogenesis of a decrease in utero-placental perfusion in preeclampsia/eclampsia women, which leads to SGA of the fetuses (28, 29).

Cohort studies conducted in Australia and North Carolina (USA) (14, 30) showed no significant association between preeclampsia and SGA of the fetuses. The results may differ because that study included any type of hypertension, which dilutes the risk of preeclampsia for SGA fetuses, whereas in our study, we only included preeclampsia/eclampsia and superimposed preeclampsia. The other possible reason could be the different charts used for outcome measures for Australia and to our study. In our study, we used the WHO growth standard chart to measure weight for gestational age of the fetus. On the other hand, a study conducted in Indonesia (15), preeclampsia had a protective effect for SGA of the fetuses, which might be because of the compensation effect for lower blood supply and nutrients due to the preeclampsia /eclampsia effects.

In our study, the history of low birth weight was a protective effect for SGA of fetuses. However, a study conducted in North Carolina showed an increased risk of SGA of fetuses (14); variation of the sample size could also explain the difference since that study was done among 1,958 pregnant women.

In our study, poor weight gain during pregnancy was a significant predictor of SGA of fetuses. This finding is consistent with a study conducted in Pakistan (31). This study is similar to our study both in terms of the study setting, the measurement for the outcome, and the weight of mothers. However, this finding differed from a secondary analysis conducted in North Carolina (14). This variation might be because of the measurement we used for weight gain during pregnancy.

In this study, anemia had no statistically significant association with SGA of the fetuses. This finding is similar to a prospective cohort study done in New Zealand, Australia, England, and Ireland (32). This study is similar to our study because of the same measurement for anemia classification. But it differs from a study done in Pakistan (33). This variation might be because of the large sample size in our study, and the measurement for anemia classification. However, anemia has a clinical effect, because hypoxia may induce fetal stress, which synthesizes corticotrophin-releasing hormone, increases fetal cortical production, and may inhibit fetal growth (34).

Our study showed no association between diabetes mellitus and SGA of the fetuses. This finding is consistent with a study done in North Carolina (14). However, the findings from a cohort study conducted in South Carolina indicate that diabetes mellitus has a protective effect for SGA of the fetuses compared to no diabetes mellitus. This variation might be because of a different lifestyle and sample size (27). However, diabetes mellitus has a clinical significance for SGA of the fetuses, which means maternal diabetes mellitus increase risk because of micro-vascular changes that impair the placenta, which might cause fetal growth restriction (5).

Cardiac diseases have a positive or negative effect on fetal growth because of decreases in the perfusion of nutrients to the placenta that supply the fetuses (5). But in this study, the history of cardiac diseases had no significant effect on the development of SGA of the fetuses. However, a cohort study conducted in the UK shows that heart diseases increase the risk of

developing SGA of the fetuses, compared to no heart diseases (35). This difference might be because of lifestyle and socio-economic status. On the other hand, in a study done in Indonesia, cardiac diseases had a protective effect for SGA of the fetuses compared to no cardiac diseases. This variation might be because of the compensation effect (15).

Limitations of this study

The narrow scope of the study setting and population may have affected the external validity. Diagnosis of exposure was dependent on physician decision, which may have depended on physician knowledge in case diagnosis, leading to bias. Since weight gain was calculated from the last visit of ANC and first of ANC, but have-not equal length of time for the pregnancy period, so it may have introduced measurement bias. Estimated fetal weight was taken from ultrasound results or clinical estimate, so 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 have been being over- or under-estimated. Variable's more than 10% missing value on occupational and educational status, sex of the fetuses, and birth interval were dropped. We cannot assess the income, detail the nutritional status of pregnant women.

Conclusions and recommendations

In summary, this study showed that there is a significant difference between preeclampsia and normotensive pregnant women in terms of the SGA of fetuses' incidence rate. Also, after adjusting for confounders, preeclampsia/eclampsia had a significant association with SGA. Bad obstetric history, such as a history of low birth weight, had a protective effect for SGA of the fetuses, but medical factors such as poor gestational weight gain had an increased risk of SGA of the fetuses. However, anemia, cardiac diseases, and diabetes mellitus had no statistically significant effect, but it may have clinical implications. Therefore, it is necessary to strengthen the screening of preeclampsia for optimal fetal growth, and counseling on nutrients for adequate gestational weight gain. Further studies are needed to confirm the predictors at the community level.

Abbreviations

ACSH = Ayder Comprehensive Specialized Hospital; ANC = antenatal care; C/AHR = crude/adjusted hazard ratio; EFW = estimated fetal weight; HMIS= health management information system; MGH = Mekelle General Hospital; SGA = small-for-gestational-age

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Availability of data and materials

The data sets used during the current study are available from the principal author on reasonable request.

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Author contributions:

ET: carried out the conception of the research, design, statistical analysis, interprets, writing the draft manuscript and critically revised manuscript. GT & YS: carried out the design, statistical analysis and revising the draft manuscript. FG: Analysis and editing tasks of the draft manuscript. ZH: conducted the proofreading, statistical analysis, revising the draft manuscript. All authors approved the final version of the manuscript.

Ethical approval

This study was carried out after securing clearance from the ethical clearance committee at the School of Public Health, Addis Ababa University, and after permission was granted to conduct the study in ACSH and MGH, Tigray. Further permission was obtained from the Medical Directors of ACSH and MGH, the department head of the obstetric ward, and HMIS focal person for the utilization of the medical cards. The code number given to the study was ERC/0015/2019.

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