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Determinants of Hyperemesis Gravidarum among Pregnant Women in Public Hospitals of Mekelle City, North Ethiopia, 2019: Unmatched Case-Control Study

Zenebe Tefera[1]*, Mandefro Assefaw[1], Mulugeta W/Selassie[2]

[1]Department of Midwifery, College of Medicine and Health Sciences, Wollo University, Dessie, Ethiopia
[2]Department of Pediatrics and Child Health Nursing, College of Medicine and Health Sciences, Wollo University, Dessie, Ethiopia

Abstract

Background: Globally, hyperemesis gravidarum affects 0.3 to 3.6% of pregnant women. The etiology of hyperemesis gravidarum is unclear. In Ethiopia, limited studies have been conducted on the determinants of hyperemesis gravidarum. Therefore this study is aim to identify the determinants of hyperemesis gravidarum among pregnant women in public hospitals of Mekelle city, North Ethiopia.

Methods: An unmatched case-control study was conducted from May to October 2019, with the ratio of 1:2(109 cases and 218 controls). Cases were women with hyperemesis gravidarum and controls were women who had no hyperemesis gravidarum. Cases were enrolled using consecutive sampling techniques and controls were selected by a systematic random sampling technique. Data were collected by interview value < structured questionnaire and analyzed using SPSS version 22. Statistical significance was considered at p- sing a str 0.05, and the strength of association was assessed by odds ratio and 95% confidence intervals.

Result: Being housewife (AOR=2.43; 95% CI; 1.27, 4.62), unplanned pregnancy (AOR=2.58; 95% CI; 1.27, 5.24), had family history of hyperemesis gravidarum (AOR=3.85; 95% CI; 1.69, 8.75). H. pylori infection (AOR=3.50; 95% CI; 1.92, 6.39), high perceived stress (AOR=7.01; 95% CI; 2.56, 19.18) and being in the first and second trimester (AOR=6.01; 95% CI; 1.87, 19.26), and (AOR=4.73; 95% CI; 1.59, 14.00) were determinant of hyperemesis gravidarum.

Conclusion and Recommendations: In this study; being a housewife, unplanned pregnancy, had a family history of hyperemesis gravidarum, H. pylori infection, high perceived stress, and being in the 1st and 2nd trimester of pregnancy were found to be the determinants of hyperemesis gravidarum. We recommend stress should be minimized through psychological support during follow up of pregnancy. Screening for H. Pylori should be taken as routine investigations for pregnant women who complain of nausea and vomiting.

Keywords: Hyperemesis Gravidarum; Determinants; Unmatched case-control study; Mekelle; Ethiopia

Introduction

Hyperemesis gravidarum (HG) is a severe type of vomiting of pregnancy which has got deleterious effect on the health of the mother and/or incapacitates her in day-to-day activities [1]. Its adverse effect includes dehydration, weight loss and starvation ketosis proved by positive ketone in urine at least once during pregnancy [1]. This may result in fluid and electrolyte imbalance and affecting the nutritional status and is potentially lethal if left untreated [2,3]. Hyperemesis gravidarum was considered for a long time to be a disorder caused by psychological distress, fear of childbirth, or resentment of the pregnant state [4,5]. Globally, the prevalence of HG was found to be between 0.3 and 3.6% with an average of 1.1% [6]. It's prevalence in Ethiopia also ranges from 4.4% to 8.2% [7–9].

Hyperemesis gravidarum is one of the health problems during pregnancy and it affects women's daily lives and was found to have adverse effects on daily life functioning. Clinical complications from nutritional deficiencies, psychological disorder, gastrointestinal trauma, and neurologic damage are the most common morbidities seen in women with HG [10,11]. It also contributes to the termination of wanted pregnancies that affects the couple family planning. Women with HG often require hospitalization, as a result, they lose time to both paid employment and housework with a significant economic burden [9,10,12]. Hyperemesis gravidarum also increases the risk for adverse pregnancy outcomes such as low birth weight, preterm birth, small-for-gestational-age infants, and low APGAR score [13]. It also hurts women's ability to care for their children, affects their relationship with partner and work capacity for most of the women [10].

The cause of HG is unclear, but it is widely agreed that it is a multifactorial condition with sociodemographic, obstetrics, medical, and physiological contributing determinants [12,14,15]. However, a conflict betweenstudieswas found. Limited studies have been conducted toidentify the determinants of hyperemesis gravidarum in Ethiopia moreover; no study is done in the Tigray region. Therefore, this study aimed to identify determinants of HG, which could reduce the adverse perinatal outcome, hospitalization; time lost from paid employment, physical, psychological, economic, and social burdens of HG on women's lives, through prevention andearlyinitiation of intervention.

Materials and Methods

Study area and period

The study was conducted in public hospitals of Mekelle city namely Ayder, Mekelle, and Quiha hospital from May 1 to October 30, 2019.

***Corresponding author:** Zenebe Tefera, Wollo University, Dessie, Ethiopia; E-mail: zenebe7834@gmail.com

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Mekelle is the capital city of Tigray regional state located 780 km from Addis Ababa the capital city of Ethiopia. These public hospitals are serving a population of 9 million from Tigray, Afar, and southeast Amhara. According to 2018, the hospital's health management information system reports; 5322 pregnant women had their first antenatal care follow up.

Study design

Afacility-based unmatched case-control studydesign was employed.

Population

Source population: The source population was all pregnant women who visited the maternity center of the study hospitals during the studyperiod.

Study population: All pregnant women who were admitted to the hospitals with the diagnosis of hyperemesis gravidarum during the study period were study population for cases, whereas all pregnant women who visited the hospitals for antenatal care service during the studyperiod were studypopulation for controls.

Inclusion and exclusion Criteria

Inclusion Criteria: Pregnant women who were hospitalized due to HG diagnosed bythe clinicians were included as cases and pregnant women who were visiting antenatal care services at the same time but not have symptoms of HG were included as controls.

Exclusion Criteria: Pregnant women with severe nausea and vomiting, but diagnosed to have a concurrent medical and surgical illness (pyelonephritis, dyspepsia, and acute abdomen) were excluded.

Sample size determination and sampling technique

Sample size determination: The sample size was calculated with the assumption of a double population proportion formula for an unmatched case-control study using Epi Info software version 7.0. The following parameters were considered: 95% confidence interval, power was 80%; control to case ratio was 2:1 and different sample sizes were produced from previously identified determinants of HG and the maximum and manageable sample size was obtained by taking perceived stress as a determinant factor from a previous study done in south Ethiopia; where the proportion of exposure among cases to be 17.7% and among controls 6.1% with an odds ratio of 3.3 [16]. This yields a maximum sample size of 296 (99 cases and 198 controls). By adding 10% non-response rate, the final sample size required for the studywas 327 (109 cases and 218 controls).

Sampling technique

Cases were selected by a consecutive sampling technique with daily monitoring of all new admissions until the sample size was fulfilled. For each case, two controls were selected and this procedure was continued until the required sample size was attained. A systematic sampling technique was employed to select controls.

Study variables

Dependent variable: Hyperemesis gravidarum

Independent variables:

Sociodemographic variables

Age,

Residence,

Ethnicity,

Marital status,

Religion,

Educational status and

Occupational status

Obstetrics and gynecology related variables:

Primigravida

Nulliparous

Molar pregnancy

Multiple pregnancy

Gestational age

Unplanned pregnancy

History of dysmenorrhea

History of abortion and

History of neonatal death

Themedical and psychological related variable:

Helicobacter pylori infection

History of diabetic Mellitus

History of hyperemesis gravidarum

Family history of hyperemesis gravidarum

History of pre-pregnancy motion sickness

History of depression

Perceived stress status

Data collection procedure

Data were collected through face-to-face interviews and chart reviews using structured and pretested questionnaires adapted from existing literature [14-16]. The questionnaire includes four sections; socio-demographic, obstetric and gynecologic characteristics, medical and psychological characteristics, and questions that measured perceived stress status. The data were collected by five BSc midwives usingthe Tigrigna version questionnaire.

Data quality control

The questionnaire was prepared originally in English and was translated to Tigrigna (local language) and back to English by two independent persons to keep the consistency of the questionnaires. Data collectors and supervisors were trained. Close supervision was done by the principal investigator and supervisor during data collection. Completeness of the data was checked at the field level.

Data analysis

The collected data were checked for completeness and entered into Epi-data version 3.1. Then the data were exported to SPSS version 22 and cleaned, coded, and collapsed before subsequent analysis. Summary statistics such as median, mean, interquartile range, and standard deviation were computed for cases and control groups. The independent variables were cross-tabulated among cases and controls. Then bivariate analysis was carried out to assess the crude association

between the independent and outcome variable. The variables with p-value <0.05 in bivariate analysis were entered into a multivariable logistic regression to assess the net effect by controlling confounders. The variables with $p < 0.05$ in multivariable logistic regressions were considered as statistically significant determinants for HG. The adjusted odds ratio (AOR) with 95% confidence interval (CI) was used to assess the strength of association. As a result, the model usedwas good as indicated by the Omnibus model goodness of fit test ($p \leq 0.001$ with the cut point <0.05) and Hosmer & Lemeshow model goodness of fit test (p=0.618 with cut point >0.05). Multicollinearity test was done and all determinants had a variance inflation factor less than 10 indicating that there was no high correlation between the independent variable.

Operational definition

Cases: Pregnant women who were hospitalized due to hyperemesis gravidarum diagnosed by the clinicians based on the clinical and laboratory finding.

Controls: Pregnant women who visited antenatal care services in the studyfacilities, but didnot have symptoms of hyperemesis gravidarum.

Perceived stress: It was measured with the perceived stress scale (PSS). PSS is a 10-item multiple-choice self-report psychological instrument for measuring the perception of stress. Each answer was scored 0 (never) to 4 (very often). Individual scores on the PSS can range from 0 to 40 with higher scores indicating higher perceived stress. Scores rangingfrom 0-13 would be considered **lowstress**. Scores ranging from 14-26 would be considered **moderate stress**. Scores ranging from 27-40 would be considered high perceived stress [17].

Ethical consideration

Thestudy protocol wasapproved by Mekelle University, College of Health Sciences institutional review board (IRB 1444/2018). A letter of cooperation was obtained from Tigray regional health bureau. Written consent was obtained from individual respondents. The participants' confidentiality was secured throughout the study and information regarding the identification of the patient was recorded anonymously. Information on the study was explainedtothe participants, includingthe objective, procedure, and benefit of the study. The respondents wereinformed thattheyhave the right to refuse or declineparticipation inthestudyatanytime.

Result

Maternal sociodemographic characteristics

In this study, a total of 105 cases and 210 controls were successfully interviewed with a response rate of 96.3%. The same proportion of cases (88.6%) and controls (88.6%) were in the age group of 20-34 years. The median age of case and control was 27 (IQR =5) and 28 (IQR = 6) respectively. The majority of cases (86.7%) and controls (93.8%) were living in urban. The majority (81.9%) of cases and (79.0%) of controls were Orthodox. Eighty-six percent of cases and 95.2% of controls were married. About forty-six percent of cases and 25.2% of controls were housewives. Table 1.

Table 1: Sociodemographic characteristics of respondents in public hospitals of Mekelle City, North Ethiopia, 2019.

Characteristics	Hyperemesis Gravidarum		Total (n=315) N (%)
	Cases(n= 105) N (%)	**Controls(n=210) N (%)**	
Age of the mother(in years)(n=315)			
<20	3(2.9)	2(1.0)	5(1.6)
20-34	93(88.6)	186(88.6)	279(88.6)
35-49	9(8.6)	22(10.5)	31(9.8)
Residence(n=315)			
Urban	91(86.7)	197(93.8)	288(91.4)
Rural	14(13.3)	13(6.2)	27(8.6)
Ethnicity(n=315)			
Tigryan	103(98.1)	203(96.7)	306(97.1)
Afar	2(1.9)	7(3.3)	9(2.9)
Religion (n=315)			
Orthodox	86(81.9)	166(79.0)	252(80.0)
Muslim	15(14.3)	37(17.6)	52(16.5)
Catholic	1(0.9)	2(1.0)	3(1.0)
Protestant	3(2.9)	5(2.4)	8(2.5)
Marital status(n=315)			
Married	90(85.7)	200(95.2)	290(92.1)
Single	15(14.3)	10(4.8)	25(7.9)
Educational level(n=315)			
Illiterate	6(5.7)	14(6.7)	20(6.3)
< 8 grade	14(13.3)	30(14.3)	44(14.0)
9-12grade	46(43.8)	82(39.0)	128(40.6)
Diploma and above	39(37.1)	84(40.0)	123(39.0)
Occupational status of the mother(n= 315)			
Employed	36(34.3)	116(55.2)	152(48.3)
Housewife	48(45.7)	53(25.2)	101(32.1)
Merchant	12(11.4)	27(12.9)	39(12.4)
Other [b]	9(8.6)	14(6.7)	23(7.3)

b = Farmer and student

Obstetrics and gynecological characteristics of respondents

The proportion of multigravida among cases and controls was 69.5% and 81 % respectively. Similarly, 63.8% of cases were para one and above. The median gestational age of the women for the case and control was 16 (IQR = 8) and 18 (IQR =11) respectively. About 62.9 and 57.1 percent of cases and control were admitted during the second trimester respectively. About thirty-four percent of cases and 12.9% of controls reported that the current pregnancy was unplanned. Most of the pregnancy (96.2%) among cases and 98.1% among controls were single tones. Table 2

Medical and psychological characteristics of respondents

Concerning medical characteristics, the proportion of history of diabetic mellitus among cases was 1.9% and that of controls was 1.0%. Twentypercent of the cases and 9% of controls were reporting a history of HG in their mothers and sisters. About forty-six percent of cases and 21.4% of controls were seropositive for Helicobacter pylori (H. pylori) infection. Pre-pregnancy motion sickness was reported by 13.3% of cases and 10% of controls. According to the perceived stress scale, it was observed that 19% of cases and 9% of controls had high perceived stress. Table 3

Determinants of hyperemesis gravidarum

The bivariate analyses revealed that marital status, residence, maternal occupation, gestational age, gravidity, parity, unplanned pregnancy, had a family history of HG, Helicobacter pylori infection, and perceived stress were found to have an association with the development of hyperemesis gravidarum.

After controlling for potential confounds on multiple logistic regression analysis; being a housewife, unplanned pregnancy, being in the first and second trimester of pregnancy, family history of HG, H. pylori infection and perceived stress were identified as determinants of hyperemesis gravidarum among pregnant women.

Accordingly, housewives pregnant women were 2.43 times more likely to develop HG as compared to employed pregnant women (AOR=2.43; 95% CI; 1.27, 4.62). In the same manner, women with unplanned pregnancy were 2.58 times more likely to develop HG as compared to women with planned pregnancy (AOR=2.58; 95% CI; 1.27, 5.24). Similarly, women in the first and second trimester of pregnancy were 6.01 and 4.73 times at increased risk of developing HG as compared to women in the third trimester(AOR=6.01; 95% CI; 1.87, 19.26) and (AOR=4.73; 95% CI; 1.59, 14.00) respectively.

Pregnant women who had a family history of hyperemesis gravidarum were 3.85 times more likely to develop HG as compared to those who had no family history of HG (AOR=3.85; 95% CI; 1.69, 8.75). Similarly, women who had H. pylori infection were significantly at increased risk of having HG compared to women who were not infected (AOR=3.50; 95% CI; 1.92, 6.39). In the same manner, pregnant women who had high perceived stress were 7.01 times more likely to develop HG as compared to women with low perceived stress (AOR=7.01; 95% CI; 2.56, 19.18) Table 4.

Table 2: Obstetrics and gynecological characteristics of respondents in public hospitals of Mekelle City, North Ethiopia, 2019.

Characteristics	Hyperemesis Gravidarum		Total (n=315) N (%)
	Cases (n= 105) N (%)	**Controls (n=210) N (%)**	
Gravidity (n=315)			
Primigravida	32(30.5)	40(19.0)	72(22.9)
Multigravida	73(69.5)	170(81.0	243(77.1)
Parity (n=315)			
Nulliparous	38(36.2)	47(22.4)	85(27.0)
Para one and above	67(63.8)	163(77.6)	230(73.0)
Unplanned pregnancy (n=315)			
Yes	36(34.3)	27(12.9)	63(20.0)
No	69(65.7)	183(87.1)	252(80.0)
Abortion history/pregnancy loss before 28 weeks (n=243)			
Yes	7(9.6)	11(6.5)	18(7.4)
No	66(90.4)	159(93.5)	225(92.6)
History of dysmenorrhea(n=315)			
Yes	12(11.4)	18(8.6)	30(9.5)
No	93(88.6)	192(91.4)	285(90.5)
History of previous neonatal death (n=230)			
Yes	4(6.0)	8(4.9)	12(5.2)
No	63(94.0)	155(95.1)	218(94.8)
Gestational age (n= 315)			
First trimester(0-12 week)	34(32.40)	48(22.9)	82(26.0)
Second trimester (13-27 week)	66(62.9)	120(57.1)	186(59.0)
Third trimester (28-40 week)	5 (4.8)	42 (20.)	47(14.9)
Number of embryo/fetus (n=315)			
Singleton	101(96.2)	206(98.1)	307(97.5)
Multiple	4(3.8)	4(1.9)	8(2.5)
History of molar pregnancy (n=315)			
Yes	2(1.9)	1(0.5)	3(1.3)
No	103(98.1)	209(99.5)	312(98.7)

Table 3: Medical and psychological characteristics of respondents in the public hospitals of Mekelle City, North Ethiopia, 2019.

Characteristics	Hyperemesis Gravidarum		Total(n=315) N (%)
	Cases(n= 105) N (%)	**Controls(n=210) N (%)**	
History of diabetic mellitus (n=315)			
Yes	2(1.9)	2(1.0)	4(1.3)
No	103(98.1)	208(99.0)	311(98.7)
History of hyperemesis gravidarum(n=243)			
Yes	16(21.9)	32(18.8)	48(19.8)
No	57(78.1)	138(81.2)	195(80.2)
Family history of hyperemesis gravidarum (n=315)			
Yes	21(20.0)	19(9.0)	40(12.7)
No	84(80.0)	191(91.0)	275(87.3)
H. pylori immunoglobulin test result(n=315)			
Positive	48(45.7)	45(21.4)	93(29.5)
Negative	57(54.3)	165(78.6)	222(70.5)
History of pre-pregnancy motion sickness (n=315)			
Yes	14(13.3)	21(10.0)	35(11.1)
No	91(86.7)	189(90.0)	280(88.9)
History of depression(n=315)			
Yes	3(2.9)	5(2.4)	8(2.5)
No	102(97.1)	205(97.6)	307(97.5)
Perceived stress status (n=315)			
Low stress	26(24.8)	111(52.9)	137(43.5)
Moderate stress	60(57.1)	90(42.9)	150(47.6)
High perceived stress	19(18.1)	9(4.3)	28(8.9)

Table 4: Determinants of hyperemesis gravidarum among pregnant women in public hospitals of Mekelle City, North Ethiopia, 2019.

Characteristics	Hyperemesis Gravidarum		COR (95%CI)	AOR (95% CI)
	Cases(n= 105) N (%)	**Controls(n=210) N (%)**		
Residence(n=315)				
Urban	91(86.7)	197(93.8)	0.43(0.19, 0.95)	.49(.18, 1.38)
Rural	14(13.3)	13(6.2)	1	1
Marital status(n=315)				
Married	90(85.7)	200(95.2)	1	1
Single	15(14.3)	10(4.8)	3.33(1.44, 7.71)	2.37(.79, 7.11)
Occupational status (n=315)				
Employed	36(34.3)	116(55.2)	1	1
Housewife	48(45.7)	53(25.2)	2.92(1.69, 5.01)	2.43(1.27, 4.62)*
Merchant	12(11.4)	27(12.9)	1.43(.66, 3.11)	.73(.27, 1.97)
Other[b]	9(8.6)	14(6.7)	2.07(.83, 5.18)	1.16(.37, 3.58)
Gravidity (n= 315)				
Primigravida	32(30.5)	40(19.0)	1.86(1.09, 3.19)	1.31(.32, 5.38)
Multigravida	73(69.5)	170(81.0)	1	1
Parity (n= 315)				
Nulliparous	38(36.2)	47(22.4)	1.97(1.18, 3.29)	1.09(.28, 4.19)
Para one and above	67(63.8)	163(77.6)	1	1
Unplanned pregnancy (n=315)				
Yes	36(34.3)	27(12.9)	3.54(1.99, 6.26)	2.58 (1.27, 5.24)*
No	69(65.7)	183(87.1)	1	1
Gestational age (n=315)				
First trimester	34(32.40)	48(22.9)	5.95(2.13, 16.60)	6.01(1.87, 19.26)*
Second trimester	66(62.9)	120(57.1)	4.62(1.74, 12.24)	4.73(1.59, 14.00)*
Third trimester	5 (4.8)	42 (20.)	1	1
Family history of hyperemesis gravidarum (n=315)				
Yes	21(20.0)	19(9.0)	2.51(1.28, 4.92)	3.85(1.69, 8.75)**
No	84(80.0)	191(91.0)	1	1

H. pylori immunoglobulin test result(n=315)				
Positive	48(45.7)	45(21.4)	3.09(1.86, 5.12)	3.50(1.92, 6.39)**
Negative	57(54.3)	165(78.6)	1	1
Perceived stress status(n=315)				
Low stress	26(24.8)	111(52.9)	1	1
Moderate stress	60(57.1)	90(42.9)	2.85(1.66, 4.87)	2.01(1.07, 3.79)*
High stress	19(18.1)	9(4.3)	9.01(3.66, 22.19)	7.01(2.56, 19.18)**

b = Farmers and student; * = p-value<0.05; ** = p-value <0.001; 1 = Reference; AOR = Adjusted Odd Ratio, CI = Confidence Interval, COR= crude odds ratio

Discussion

The current study investigates the determinates of hyperemesis gravidarum among pregnant women in public hospitals of Mekelle City and the finding shows that being a housewife was significantly associated with the development of hyperemesis gravidarum as compared to employed women. This finding is supported by a study conducted in the Bale zone, southern Ethiopia, and Netherland [15,18].

This study also shows that unplanned pregnancy was significantly associated with hyperemesis gravidarum as compared to a planned pregnancy. The possible explanation for the observed association could be that pregnant women may perceive the negative effect of unplanned pregnancy on their job, education, income, relationship with their partner and motivation to achieve their goal, which may expose them to anxiety and tension, which could lead them to be at the more severe end of nausea and vomiting. However, this finding contradicts a study done in southern Ethiopia in which no association was seen between HG and unplanned pregnancy [15]. The reason may be due to the difference in the study area and sample size. However, the finding is consistent with a study conducted in Turkey [19].

A family history of hyperemesis gravidarum was also found to have a significant association with HG. This finding contradicts a study conducted in Bale zone, south Ethiopia in which no association was seen between HG and family history of hyperemesis gravidarum [15]. The possible reason for the difference could be that the family history of hyperemesis gravidarum was based on self-report, which may lead to misclassification. However, this finding is consistent with a study conducted in Norway which shows that women with hyperemesis were at significantly higher risk of developing hyperemesis in their own pregnancy compared with daughters of women without hyperemesis [20]. This finding also consistent with a study conducted in the USA which shows that a significantly higher risk of hyperemesis in women whose sisters or mothers had the disorder [21]. The possible explanation for the observed association could be due to either shared environmental determinants among families or inheritance of some factors that can contribute to the development of hyperemesis gravidarum.

Women in the first and second trimester of pregnancy were significantly more likely to suffer from HG than those women who were in the third trimester of pregnancy. The finding is consistent with a study conducted in Jimma University Medical Center (southwest Ethiopia) and Bale zone (south Ethiopia) and the University of Michigan(United States) [7,15,22]. However, the finding contradicts a study conducted in Turkey, which shows that gestational age had no significant association with HG [23]. This may be due to the difference in sample size in which the sample size used in Turkey was half of the sample size of the current study.

Similarly, H. pylori infection was found to have a significant association with hyperemesis gravidarum. This finding is consistent with a study conducted in Addis Ababa (Ethiopia), Egypt, and China [24–26]. This maybe due to that H. pylori mayaggravate the hormone-induced changes in the chemoreceptor trigger zone in the brain stem including the vomiting center and electric functioning of the stomach, which could lead an infected pregnant woman to develop severe nausea and vomiting [27]. However, the finding is in contradicts a study conducted in Europe [28]. This might be explained by the difference in socioeconomic status between the two study areas in which the prevalence rate of H. Pylori-infection is much higher in women with low socioeconomic status [29]. Pregnant women with moderate and high perceived stress were found to have a statistically significant association with hyperemesis gravidarum as compared to women who have no low stress. This finding is consistent with a study done in south Ethiopia, Egypt, Turkey, and the USA [15,22,29,30].

Conclusion

This study concludes that being a housewife, being in the first and second trimester of pregnancy, unplanned pregnancy, had a family history of hyperemesis gravidarum, Helicobacter pylori infection, and high perceived stress were found to be the determinants of hyperemesis gravidarum among pregnant women. We recommend that health promotion messages are needed to focus to improve the utilization of contraceptives methods to prevent unplanned pregnancy and screening for H. Pylori should be taken as routine investigations for pregnant women who complain of nausea and vomiting. Healthcare providers should look for the emotional stress during pregnancy and should minimize the stresses through psychological support during follow up.

Data Availability

The datasets generated and analyzed during the study are available from the corresponding author upon request.

Conflict of interests

The authors declare that there are no conflicts of interest regarding the publication of this article.

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