



Risk factor of the incidence of hyperemesis gravidarum: A population-based case-control study

Widya Nurfadillah A , Rafhani Rosyidah*, Evi Rinata, Yanik Purwanti

Departement of Midwifery ,Faculty Of Health Sciences, University of Muhammadiyah Sidoarjo
Jalan Mojopahit No.666 B, Sidowayah, Celep, Kec. Sidoarjo, Kabupaten Sidoarjo, Jawa Timur

*Corresponding author : rafhani.rosyida@umsida.ac.id

ABSTRAK

Latar Belakang: *Hyperemesis Gravidarum* adalah mual muntah yang parah dan berlebihan, dimulai pada usia kehamilan 4 dan 6 minggu dan puncaknya pada usia kehamilan 8-12 minggu dan biasanya mereda pada usia kehamilan 20 minggu. Akibat sering mual dan muntah yang berlebihan yaitu ibu hamil berisiko mengalami dehidrasi, kekurangan vitamin dan mineral, kehilangan 5% dari berat badan bahkan dapat terjadi membahayakan kesehatan janinnya.

Tujuan: Mengetahui faktor risiko kejadian hiperemesis gravidarum.

Metode: Jenis penelitian ini merupakan penelitian observasional analitik dengan rancangan penelitian metode Case Control dengan jumlah sampel 240 dan perbandingan kasus dan control pada penelitian yaitu sebanyak 1:1. Pengambilan data dilakukan di RSUD Sidoarjo dan RS Bhayangkara Porong pada bulan Oktober-Desember 2022. Penelitian ini menggunakan data sekunder, instrument yang digunakan berupa lembar pengumpul data dengan sumber data berasal dari rekam medis.

Hasil: Hasil penelitian menunjukkan bahwa faktor risiko memiliki hubungan dengan kejadian hiperemesis gravidarum yaitu pada usia ibu hamil ($p=0,014<0,05$, OR= 0,38, 95% CI: 0,184-0,7998). Paritas ($p=0,008$, OR=2,14, 95% CI: 1,253-2,656). Usia kehamilan ($p=0,000$, OR= 49,63, 95% CI: 18,730-131,51). Pendidikan ($p=0,188$, OR= 0,500, 95% CI: 0,204-1,228). Pekerjaan ibu hamil ($p=0,002$, OR= 2,34, 95% CI: 1,380-3,999). Jarak kehamilan ibu ($p=0,004$, OR=2,17, 95% CI: 1,298-3,642), anemia dalam kehamilan ($p=0,032<0,05$, OR= 0,422, 95% CI: 0,201-0,886) dan status ibu hamil ($p=0,004$, OR= 2,22, 95% CI: 1,315-3,74).

Kesimpulan: Hampir seluruh faktor risiko yang diteliti memiliki hubungan namun hanya pendidikan ibu yang didalam penelitian ini tidak memiliki hubungan. Dari usia ibu, paritas, usia kehamilan, pekerjaan ibu, jarak kehamilan, anemia, dan status BMI merupakan faktor risiko terjadinya kejadian *hyperemesis gravidarum*. Dengan mengetahui faktor risiko ini diharapkan tenaga kesehatan untuk dapat mendeteksi dini dan mengantisipasi untuk meminimalisirkan terjadinya keparahan saat ibu hamil terkena HEG.

KATA KUNCI: *hyperemesis gravidarum*; kehamilan; faktor risiko

ABSTRACT

Background: *Hyperemesis Gravidarum* is severe and excessive nausea and vomiting, starting at 4 and 6 weeks of gestation and peaking at 8-12 weeks of pregnancy, and usually subsiding by 20 weeks of gestation. As a result of excessive nausea and vomiting, pregnant women are at risk of dehydration, vitamin and mineral deficiencies, losing 5% of body weight, and can even endanger the fetus's health.

Objectives: to recognize the risk factors for the incidence of *hyperemesis gravidarum* to detect early and reduce the consequences of *hyperemesis gravidarum*.

Methods: This type of research is an analytical observational study with the research design of the Case Control method with a sample size of 240, and the ratio of cases and

controls in the study is 1: 1. Data were collected at Sidoarjo Regional Hospital and Bhayangkara Porong Hospital in October-December 2022. This study uses secondary data, the instrument used is a data collection sheet with data sources coming from medical records.

Results: The results showed that risk factors have an association with the incidence of hyperemesis gravidarum, namely the age of pregnant women ($p = 0.014 < 0.05$, OR = 0.38, 95% CI: 0.184-0.7998). Parity ($p=0.008$, OR=2.14, 95% CI: 1.253-2.656). Gestational age ($p=0.000$, OR= 49.63, 95% CI: 18.730-131.51). Education ($p=0.188$, OR= 0.500, 95% CI: 0.204-1.228). Maternal occupation ($p=0.002$, OR= 2.34, 95% CI: 1.380-3.999). Maternal pregnancy spacing ($p=0.004$, OR=2.17, 95% CI: 1.298-3.642), anemia in pregnancy ($p=0.032 < 0.05$, OR= 0.422, 95% CI: 0.201-0.886) and maternal status ($p=0.004$, OR= 2.22, 95% CI: 1.315-3.74).

Conclusions: Almost all risk factors studied had a relationship, but only maternal education in this study did not have a relationship. Maternal age, parity, gestational age, maternal employment, pregnancy distance, anemia, and BMI status are risk factors for hyperemesis gravidarum. By knowing these risk factors, it is hoped that health workers can detect early and anticipate to minimize the severity when pregnant women are exposed to HEG.

KEYWORD: hyperemesis gravidarum; pregnancy; risk factor

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INTRODUCTION

Hyperemesis gravidarum is a condition in pregnant women who experience severe nausea and excessive vomiting that often occurs more than ten times in 24 hours to interfere with the daily activities of pregnant women and the general condition of pregnant women, begins to deteriorate, and dehydration may occur(1).

Hyperemesis gravidarum is persistent vomiting in pregnancy, leading to weight loss (more than 5% of body mass) and ketosis. In severe cases, hyperemesis can lead to Wernicke's encephalopathy, central pontinemyelinolysis, and maternal death if untreated inappropriately. Infants of mothers with Hyperemesis gravidarum have a higher incidence of growth restriction. Hyperemesis gravidarum is defined as persistent vomiting in

pregnancy, leading to weight loss (more than 5% of body mass) and ketosis. In severe cases, hyperemesis can lead to Wernicke's encephalopathy, central pontinemyelinolysis, and maternal death if untreated inappropriately. Infants of mothers with Hyperemesis gravidarum have a higher incidence of growth restriction intrauterine and are significantly smaller at birth(2).

Hyperemesis gravidarum is most often characterized by severe nausea and vomiting that interferes with nutrient intake and metabolism, causes fluid and electrolyte imbalances, and generally requires hospital management. Hyperemesis gravidarum is a more powerful and potentially deadly condition if left untreated. Severe hyperemesis gravidarum can lead to maternal

complications such as nutritional deficiencies, psychological impact, electrolyte, and metabolic imbalances, fetal disorders such as behavioral and psychiatric disorders, abnormal placentation, and risk of malignancy (2).

Hyperemesis gravidarum begins before the end of the 22nd week of pregnancy. Hyperemesis gravidarum is divided into mild and severe, associated with metabolic disorders such as carbohydrate depletion, dehydration, and electrolyte imbalance (3). The etiology of hyperemesis gravidarum remains unclear. However, the etiology of hyperemesis gravidarum is associated with high body weight, age, multiple pregnancies, history of previous pregnancies, and nulliparity (4).

Based on a review of 1,301 cases of hyperemesis gravidarum in Canada, it is known that hyperemesis gravidarum is a potentially life-threatening condition that occurs between 0.8-3.2% including medical complications of hyperthyroidism, psychiatric disease, previous molar disease, gastrointestinal disorders, history of asthma, pregestational diabetes are significant independent risk factors for hyperemesis gravidarum while. At the same time, multiple fetal pregnancies have an increased risk and decreased risk for maternal age over 30 and smoking mothers (4).

The incidence of HEG is 0.5 - 10 per 1000 pregnancies. The likelihood of the disease is high in whites (16/1000 births) and low in blacks (7/1000 births). Based on data from WHO in 2013, of the total number of pregnancies world worldwide, HEG was found to be 12.5% of pregnant women who experienced hyperemesis gravidarum.

According to data from the World Health Organization (2019), the incidence of hyperemesis gravidarum reaches 3% of all pregnancies world worldwide. In Indonesia, the incidence rate of hyperemesis gravidarum in 2015 was 1.5-3% of all pregnant (Kemenkes RI, 2017). The incidence rate of hyperemesis gravidarum at Sidoarjo Regional Hospital in 2018 was 7.6%; in 2019 there was 10.8% and in 2020 the incidence rate of hyperemesis gravidarum decreased by 4.8%, this decrease in the incidence rate was due to restrictions on patient acceptance during the Covid-19 pandemic. However, the incidence rate of hyperemesis gravidarum at the Regional Hospital is still relatively high when compared to the data mentioned by WHO and Kemenkes RI.

Women with HEG will experience several complications such as vitamin k deficiency, if this is allowed to continue it will cause coagulopathy which can lead to increased blood loss, and vitamin B6 and B12 deficiency will cause anemia and neurological problems, which will complicate the delivery process and even cause maternal death. If complications are not treated immediately, it will allow pregnant women with HEG diagnoses to be at risk of giving birth to low birth weight babies. In addition, the complication that is likely to be experienced by the mother is Wernicke encephalopathy which will cause an overall pregnancy loss rate of both spontaneous and planned termination of pregnancy of 47.9% (5).

Electrolyte abnormalities associated with HEG have increased maternal mortality and life-threatening complications such as gastric failure, esophageal rupture, and intractable neurologic sequelae in some

cases. HEG can jeopardize pregnancy and perinatal and will even increase the risk of perinatal morbidity or mortality if not treated promptly (6). The maternal mortality rate in the Sidoarjo area in 2021 was 59.69 out of 100,000 and the infant mortality rate in Sidoarjo in 2021 was 3.01, of which the most common cause was low birth weight babies as much as 0.9%.

Hyperemesis gravidarum can affect the health of the mother and will also interfere with the development of the fetus she is carrying. If hyperemesis gravidarum cannot be recognized and treated quickly, it can have several impacts on the health of the mother and her fetuses such as nutritional deficiencies, prolonged pregnancy dehydration, malnutrition, ketonuria, and even more severe levels of Wernicke encephalopathy, central pontine myelinolysis, and maternal death. In addition, Norway shows that about 25% of women with HG consider terminating the pregnancy and 75% of them choose not to get pregnant again. Therefore, it is very important to know the risk factors that cause HEG because the impact is very influential on the process from pregnancy to childbirth. In Indonesia, there is still no research that examines the risk factors studied in the study with the incidence of HEG.

This study aims to determine the factors associated with the incidence of hyperemesis gravidarum. By knowing the risk factors of hyperemesis gravidarum, health workers, especially midwives, can anticipate and detect early to prevent severe complications from occurring both in pregnant women and fetuses which will endanger the condition of the mother and fetus.

MATERIALS AND METHODS

This type of research is an analytic observational study using the Case Control method, a design which uses a ratio of cases and controls in a study which is 1: 1. The case group included pregnant women aged 0-22 weeks with diagnosed HEG and the control group included pregnant women aged 0-22 weeks without diagnosed HEG or other pregnancy complications. Data collection will be conducted at Sidoarjo General Hospital and Bhayangkara Porong Hospital in October-December 2022.

This research has received ethical clearance from Sidoarjo Regional Hospital with number 893.3/057/438.5.2.1.1/2022. The samples of this study were pregnant women in January 2021-October 2022 who met the inclusion criteria, namely inclusion criteria, namely pregnant women with HEG diagnoses who have complete medical records that meet the variables, namely maternal age, parity, gestational age, maternal employment, maternal education, gestational distance, BMI status, and anemia and exclusion criteria, namely no maternal age, parity, gestational age, maternal employment, maternal education, gestational distance, BMI status and anemia in the mother's medical record.

The independent variables in this study were maternal age, parity, gestational age, maternal employment, maternal education, gestational distance, BMI status, and anemia. While the dependent variable is hyperemesis gravidarum. The data analysis technique used was Univariate analysis to obtain a description of the frequency distribution and bivariate analysis using the chi-square test. The relationship between two variables is determined by the p-value

calculated with a significant $\alpha = 0.05$. The p-value is considered significant if $p < \alpha$ and the p-value are considered insignificant if $p \geq \alpha$. To determine the strength of the relationship between the dependent variable and the independent variable, the prevalence ratio, and odds ratio (OR), with a 95% confidence interval were used. The number of samples in this study was 240 with 120 in the case group and 120 in the control group. The sampling technique in this study used a quota sampling technique, namely determining each population stratum based on signs that have the greatest influence on the variables to be investigated. Quota means the determination of subjects based on the capacity in the study.

RESULTS AND DISCUSSION

RESULTS

This study was conducted at Sidarjo Hospital and Bhayangkara Puskas Sabhara Porong Hospital, both hospitals obtained a total sample of 240 pregnant women with, 120 pregnant women who experienced hyperemesis gravidarum included in the case group and 120 pregnant women who did not experience hyperemesis gravidarum included in the control group.

Demographic Characteristics of Mother

About fifty percent (50%) of cases of pregnant women who experience hyperemesis gravidarum and fifty percent (50%) of pregnant women who do not experience hyperemesis gravidarum are in the non-risk age group. Most of the age of pregnant women in this study were in a period not at risk, namely 20-35, as many as 201 (83.8%); most of the pregnant women were primigravida, pregnant women, as many as 89 (37.1%), almost all pregnant women's

education was in secondary and higher education as many as 217 (90.4%), most of the pregnant women's age is the second trimester and third trimester as many as 153 (63.8%), the average gestational age of pregnant women is $>$ two years and nulliparous as many as 123 (51.3%), almost all pregnant women have normal Hb as many as 203 (84.6%). The average pregnant woman has an ideal BMI of as many as 139 (57.9%).

Risk factors associated with hyperemesis gravidarum

Bivariable analysis was performed using the chi-square test to fulfill the strength of the relationship between the dependent variable and the independent variable, the prevalence ratio, and odds ratio (OR), with a 95% confidence interval (CI) were used.

The results of the chi-square analysis test show that the age of pregnant women has a relationship with the value ($p = 0.014 < 0.05$, OR = 0.38) so the age of pregnant women in the risk age category will be more at risk of hyperemesis gravidarum as much as 0.38 times. Parity has a relationship with the value ($p = 0.008 < 0.05$, OR = 2.14) so primigravida pregnant women are more at risk of 2.14 times experiencing hyperemesis gravidarum. Gestational age has a relationship with the value ($p = 0.000 < 0.05$, OR = 49.63) so pregnant women with 1st trimester gestational age are more at risk of 49.63 times experiencing hyperemesis gravidarum. Maternal education has no relationship with the incidence of hyperemesis gravidarum ($p = 0.188 > 0.05$, OR = 0.500). The occupation of pregnant women has a significant relationship with the value ($p = 0.002 < 0.05$, OR = 0.42) pregnant women who do not work are more at risk of 2.34 times

experiencing hyperemesis gravidarum. Pregnant women with a pregnancy interval of <2 years and nulliparous are more at risk of experiencing hyperemesis gravidarum 2.17 times ($p=0.004<0.05$, $OR=0.422$). Anemic pregnant women had a 0.422 times higher risk of hyperemesis gravidarum ($p=0.032<0.05$, $OR=2.36$), and pregnant women with non-ideal BMI had a 2.22 times higher risk of hyperemesis gravidarum ($p=0.004<0.05$, $OR=2.22$).

Table 1 shows the demographic characteristics of the respondents. Hyperemesis gravidarum was more common in multigravida and grandemultigravida, more common in the first trimester, more common in mothers with secondary and higher education, more common in mothers with a birth spacing of less than 2 years, and interestingly, more common in mothers who were not anemic.

Table 1. Demographic characteristics of pregnant women with and without HEG

Characteristics	Category	Case		Control	
		N	%	N	%
Age of the Pregnant Mother	Age at risk (<20 years and >35 years)	12	10	27	22.5
	Non-risk age (20-35 years)	108	90	93	77.5
	Total	120	100	120	100
Parity	Primigravida	55	45.8	34	28.3
	Multigravida dan Grandemultigravida	65	54.2	86	71.7
	Total	120	100	120	100
Gestational Age	1st Trimester	82	68.3	5	4.2
	Trimester 2 and Trimester 3	28	31.7	115	95.8
	Total	120	100	120	100
Mother's Education	Primary education	8	6.7	15	12.5
	Secondary and Higher Education	112	93.3	105	87.5
	Total	120	100	120	100
Mother's job	Working	59	49.2	35	29.2
	Not Working	61	50.8	85	70.8
	Total	120	100	120	100
Pregnancy Distance	<2 years and Nulliparous	73	60.8	50	41.7
	>2 years	47	39.2	70	58.3
	Total	120	100	120	100
Anemia	Normal	108	90	95	79.2
	Abnormal	12	10	25	20.8
	Total	120	100	120	100
BMI Status	Not Ideal	62	51.7	39	32.5
	Ideal	58	48.3	81	67.5
	Total	120	100	120	100

Table 2 shows that the factors associated with the incidence of hyperemesis gravidarum are parity, gestational age, occupation, gestational distance, and BMI status.

DISCUSSION

This study was conducted to identify factors associated with the incidence of hyperemesis gravidarum in the Sidoarjo area. From several characteristics of pregnant

Table 2. Hyperemesis Gravidarum risk factors in pregnant women

Characteristics	Category	Case	Control	P-value	OR	(95% CI)
Age of the Pregnant Mother	Age at risk (<20 years and >35 years)	12	27	0.014	0.38	0.184-0.798
	Non-risk age (20-35 years)	108	93			
Parity	Primigravida	55	34	0.008	2.14	1.253-3.656
	Multigravida dan Grandegravida	65	86			
Gestational Age	1st Trimester	82	5	0.000	49.63	18.730-131.51
	Trimester 2 and Trimester 3	28	115			
Mother's Education	Primary education	8	15	0.188	0.500	0.204-1.228
	Secondary and Higher Education	112	105			
Mother's job	Working	59	35	0.002	0.42	0.250-0.725
	Not Working	61	85			
Pregnancy Distance	<2 years and Nulliparous	73	50	0.004	2.17	1.298-3.642
	>2 years	47	70			
Anemia	Anemia	108	95	108	95	0.032
	Not anemia	12	25			
BMI Status	Not Ideal	62	39	0.004	2.22	1.315-3.748
	Ideal	58	81			

women that have been analyzed, it was found that several factors are associated with hyperemesis gravidarum, including maternal age, parity, gestational age, occupation, pregnancy distance, anemia, and BMI status by knowing the factors associated with hyperemesis gravidarum can detect early to anticipate and reduce the consequences of hyperemesis gravidarum and can also maintain the development and growth of the fetus running well and generally during pregnancy.

The results showed that the age of pregnant women suffering from hyperemesis gravidarum was found to be more at risk, namely 35 years compared to the non-risk age of 20-35 years. This study is in line with research conducted by Nithiyasri et al 2020 and Fiaschi et al 2016 HEG is found more at a

younger age, namely at the age of 18-25 years. This is due to mothers who reject and accept their pregnancy and also due to physical maturity and organs. Mothers who have sufficient age are said to reduce the risk of developing hyperemesis gravidarum because it is considered that their reproductive organs are mature and have emotions and are stable and ready to face pregnancy. However, even mothers who have a mature age do not rule out the possibility of experiencing HEG because psychological factors also allow mothers to experience HEG (2),(7).

Meanwhile, research conducted in Poland found that women of younger ages had a lower risk of HEG compared to those aged 26-30 years. At the age after 31 years of age, the risk of HEG increases almost 2 times in

women with age > 35 years and if women have a history of being susceptible to HEG, the risk of developing HEG is much increased with age (8).

In this study, primigravida pregnant women were more at risk as much as 2.14 times compared to multigravida and grandmultigravida pregnant women. This is following research conducted previously where in their study, primigravida women were more likely to experience hyperemesis gravidarum because the pregnancy was not as optimal as women who had experienced previous pregnancies. Primigravida women usually have a younger age and are more mentally immature, so they are more prone to shock which can cause a lack of attention to nutrition during pregnancy which can make them more likely to experience HEG (9)(10).

Previous research conducted in African countries found that pregnant women in the first trimester have a higher risk of experiencing HEG. Likewise, in this study, it was found that pregnant women in the first trimester were more at risk of 49.63 times developing HEG compared to mothers in the first trimester and second trimester. This is because in the first trimester hCG levels increase so that it can cause excessive nausea and vomiting, (11)(12). HEG can occur in women in the 1st trimester and 2nd trimesters this is because HEG may be a manifestation of women's subconscious efforts to reject pregnancy, (13). Prolonged HEG may be caused by a strict diet, allergies, autoimmune history, a lactose-free diet, and vegetarianism (14). However, research conducted by Ioannidou et al. and Erginbas et al. gestational age did not correlate so it was not detected to be a risk of HEG (15).

In this study it was found that women who did not work were more at risk by 0.42 of experiencing HEG compared to women who worked, this is in line with research conducted by Roseboom et al. 2011 and Mekonnen et al. 2018 found that women who do not work are more at risk of HEG due to the possibility that pregnant women who do not work are more exposed to vomiting triggers such as food while cooking, lack of activity, dirty nappies, fragrances, etc. which can trigger and exacerbate HEG (16),(12).

Mothers who do not work or become housewives have narrower social circles, little information, and no friends to share experiences, so if there is a problem with their pregnancy, they cannot handle it and cause mental stress, which will trigger nausea and vomiting, (17)

Pregnancy distance is a risk factor for HEG, where a pregnancy distance of fewer than 2 years has a higher risk of experiencing HEG, based on research found that pregnant women whose pregnancy distance is too close causes the mother have a short time in restoring the condition of her reproductive organs so that they tend to experience HEG (18).

The highest proportion of deaths occurred in mothers with a parity of 1-3 children and when viewed according to the distance of pregnancy, it turns out that the distance of fewer than 2 years shows a higher proportion of maternal deaths. Pregnancy distance that is too close causes the mother to have a short time to recover the condition of the uterus so that it can return to its previous condition. Pregnant women with too close a distance are at risk of hyperemesis gravidarum and anemia in pregnancy.

Because the iron deficiency of pregnant women recovers, it is finally depleted for the needs of the fetus in the womb(19).

In this study, it was found that anemic pregnant women were 0.422 times more at risk of experiencing HEG than pregnant women who were not anemic, as well as research conducted in Turkey, found a significant relationship between anemia and HEG (20). HEG is associated with anemia because the increase in haemoconcentration can be caused by vomiting. Pregnant women who experience nausea and vomiting continuously will worsen the mother's condition, and the lack of nutrition and iron intake will cause the mother to experience anemia. Pregnant women with HEG will experience a decrease in nutrition so nutritional reserves such as iron in the body of pregnant women will decrease because food reserves have been used due to lack of nutritional intake in the body of pregnant women with HEG(21).

Women with HEG will experience several complications such as vitamin k deficiency, if this is allowed to continue it will cause coagulopathy which can lead to increased blood loss, and vitamin B6 and B12 deficiency will cause anemia (5)

HEG can cause vitamin deficiency, especially vitamin B1, and can cause hypophosphatemia which is a rare cause of intravascular hemolytic anemia. Hypophosphataemia leads to red blood cell (RBC) phosphorus consumption as well as RBC ATP, which is the main energy source for RBC function and plays an important part in structural integrity. The use of ATP changes the shape of red blood cells from deformable biconcave discs to rigid spherocyte or

schistocyte forms. The spheroidal, dehydrated, and poorly filterable condition can shorten the survival time of red blood cells and increase the chance of damage in microvas culture. Thus hypophosphatemia tends to affect the function and survival time of red blood cells through depletion of cellular ATP and eventually results in intravascular hemolytic anemia(6).

In this study, it was found that women with non-ideal BMI status were likely to be at risk of exposure to HEG 2.22 times compared to women with ideal BMI status, this following research conducted by Kim et al. 2021 and Bolin et al. 2013, where the BMI status of pregnant women who are not ideal is a higher risk factor for experiencing HEG because less fat deposits may not be able to neutralize circulating placental factors that cause HEG. Women who have lower body weight have less estrogen levels and this may be the cause of HEG. Therefore, counseling regarding ideal weight should be delivered to pregnant women—(9)(22).

Women with non-ideal BMI status have been associated with higher risk. Many factors cause non-ideal BMI statuses such as leptin and ghrelin levels which are important in regulating food intake and appetite (8).

However, from studies conducted in European countries, the risk factors for BMI status cannot be measured and do not provide constant results in their studies(7)—(23).

CONCLUSION AND RECOMMENDATION

In this study, the risk factors of maternal age, parity, gestational age, maternal employment, pregnancy distance, anemia, and BMI status have a significant relationship with the incidence of HEG, but maternal

education does not have a significant relationship with the incidence of HEG.

By knowing the risk factors, it is hoped that health workers can pay attention to several factors to be able to carry out early detection and anticipate to minimize the severity when pregnant women are exposed to HEG. For further research, it is expected to conduct research using primary data.

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