ORIGINAL ARTICLE

1. Professional School of Human Medicine, Universidad Privada San Juan Bautista, Lima, Peru
   a. Surgeon
   b. ORCID 0000-0002-7161-4128
   c. ORCID 0000-0002-3707-3831
   d. Master in Health Services Management. ORCID 0000-0003-3185-4861

Corresponding author:
Gianina Jesús Ángeles-Olaza
⚲ Pasaje Lanqui 651, San Luis – Lima, Perú
☎ +51 953217213
✉ gianina.angeles@upsjb.edu.pe

Risk factors for hyperemesis gravidarum in the Peruvian maternal-perinatal institute
Factores de riesgo de hiperémesis gravídica en el instituto materno perinatal peruano

Gianina Jesús Ángeles-Olaza[1,a,b], Cristina Nataly García-Borjas[1,a,c], Miguel Ángel Arce-Huamaní[1,d]

ABSTRACT

Introduction: Hyperemesis gravidarum (HG) is a disorder of pregnancy characterized by severe nausea and vomiting that can lead to serious complications. It affects approximately 0.5%-2% of pregnant women globally, being more common in multiple pregnancies and in young women. **Objective:** To identify the risk factors associated with hyperemesis gravidarum in women attended at the Instituto Nacional Materno Perinatal in Lima, Peru, during the year 2022. **Materials and Methods:** A case-control study including 126 pregnant women (63 cases with HG and 63 controls) was performed. Data collected on factors associated with hyperemesis gravidarum such as extreme maternal age, higher education level, maternal obesity, maternal hCG concentrations in the first trimester, parity, multiple pregnancy, female fetus, history of mental illness, hyperthyroidism and hydatidiform mole were analyzed. Logistic regression was used to avoid confounding variables. **Results:** Multivariate analysis adjusted for possible confounding variables indicated that higher education level was a protective factor for hyperemesis gravidarum but was not statistically significant. In contrast, maternal obesity, high hCG concentrations during the first trimester, nulliparity, and having a female fetus were factors that increased the risk of hyperemesis gravidarum and were statistically significant. **Conclusion:** The study found that maternal obesity, high hCG concentrations, nulliparity, and gestation of a female fetus were significant risk factors for hyperemesis gravidarum, while a higher education level could be a protective factor, though not a significant one.
Key words: Risk factors, Hyperemesis gravidarum, Pregnancy

RESUMEN

Introducción. La hiperémesis gravídica (HG) es un trastorno del embarazo caracterizado por náuseas y vómitos severos que puede llevar a complicaciones graves. Afecta aproximadamente del 0,5% al 2% de las gestantes globalmente, siendo más común en embarazos múltiples y en mujeres jóvenes. **Objetivo.** Identificar los factores riesgo asociados con la hiperémesis gravídica en mujeres atendidas en el Instituto Nacional Materno Perinatal en Lima, Perú, durante el año 2022. **Materiales y Métodos.** Se realizó un estudio caso-control que incluyó 126 gestantes (63 casos con HG y 63 controles). Se analizaron datos recopilados sobre factores asociados a hiperémesis gravídica como edad materna extrema, nivel de instrucción superior, obesidad materna, concentraciones de hCG materna en el primer trimestre, paridad, embarazo múltiple, feto de sexo femenino, antecedente de enfermedad mental, hipertiroidismo y mola hidatiforme. Se utilizó la regresión logística para evitar variables confusoras. **Resultados.** El análisis multivariado ajustado por posibles variables confusoras indicó que el nivel de instrucción superior fue un factor protector para la hiperémesis gravídica, pero no fue estadísticamente significativo. En cambio, la obesidad materna, las altas concentraciones de hCG durante el primer trimestre, la nuliparidad y tener un feto de sexo femenino fueron factores que incrementaron el riesgo de hiperémesis gravídica y resultaron estadísticamente significativos. **Conclusión.** El estudio encontró que la obesidad materna, altas concentraciones de hCG, nuliparidad y gestación de un feto femenino fueron factores de riesgo significativos para la hiperémesis gravídica, mientras que un nivel de instrucción superior podría ser factor protector, pero no significativo.
Palabras clave. Factores de riesgo, Hiperémesis gravídica, Embarazo

INTRODUCTION

Hyperemesis gravidarum (HG) is a condition that occurs in pregnancy, characterized by incoercible nausea and vomiting[1]. It is an important condition, hospitalizing approximately 59,000 pregnant women each year, according to U.S. records[2]. This number of admissions is due to the multiple maternal-fetal complications that HG can cause, such as

fetal growth restriction, maternal dehydration, Wernicke's encephalopathy and even death[3]. Its incidence worldwide is 0.5%-2%, and even up to 10.8% described in a study from China[4]. Therefore, HG is an important pathology due to the complications it can cause.

Among the main associated factors are pregnancy, maternal age, gestational age, multiple pregnancy, among others[5]. It has been shown that women in their first gestation with multiple pregnancies are more prone to have HG[6]. Likewise, young pregnant women have a higher risk of HG than older patients[7]. Multiple studies find that an increase in gestational age is less related to the development of HG[3] - HG is more frequent in the first trimester. Regarding psychological factors, several studies consider that the emotional factor is associated with HG, with greater presence of anxiety disorders and depression[8]. For clinical factors, hydatidiform mole and hyperthyroidism are related to HG due to the hormonal increase generated by these pathologies, causing nausea and incoercible vomiting[9-11].

The Instituto Nacional Materno Perinatal (INMP) is a public institution specialized in maternal-perinatal care. The gynecological-obstetrics area is divided into four services -A, B, C and D-, which house pregnant women with different pathologies. Service 'B' is in charge of metabolic pathologies, as well as hemorrhagic pathologies. HG is a pathology admitted only in this service, with low prevalence. There are not many national studies on this pathology. By investigating the problem in a national reference institution will help to update the knowledge about this disease.

Therefore, the aim of this study was to identify the risk factors associated with hyperemesis gravidarum in women attended at the Instituto Nacional Materno Perinatal in Lima, 2022.

MATERIALS AND METHODS

This is an analytical observational case-control study. The study population included all pregnant women attended at the 'B' service of obstetrics and gynecology of the Instituto Nacional Materno Perinatal of Lima, Peru, during the period January-December 2022. The sample consisted of 126 medical records of pregnant women. Using the case-control formula based on a previous study, a sample size of 126 (63 cases and 63 controls) was estimated, assuming an exposure ratio of 48.9%, an OR of 2.9, 95% confidence and 80% power, with a 1:1 ratio between cases and controls. A convenience sampling was chosen due to the low prevalence of hyperemesis gravidarum, selecting pregnant women diagnosed with the condition as cases and pregnant women without the diagnosis as controls, excluding those with second and third trimester pathologies or incomplete medical records.

This retrospective study used a data collection form designed and validated by experts that included eleven items focused on identifying associated factors. The variables analyzed included:

• Dependent variable: diagnosis of hyperemesis gravidarum.

• Independent variables: extreme maternal age, higher education level, maternal obesity, maternal hCG concentrations in the first trimester, parity, multiple pregnancy, female fetus, history of mental illness, hyperthyroidism and hydatidiform mole.

The information collected was stored in Excel 2020 and statistically analyzed with SPSS 25.

We chose to use ultrasound-derived gestational age, as it has been shown to improve the efficiency of the test[12]. We chose to limit our study to women at 13 weeks' gestation, as HG generally occurs at this stage of gestation and the hCG level peaks at the end of the first trimester[13].

The study used univariate analysis to present frequencies and percentages, and bivariate analysis to show frequencies, percentages, and p values. In the multivariate analysis, multiple logistic regression was used to evaluate the odds ratio (OR)[14], p values, and 95% confidence intervals. Analyses were performed using SPSS version 25, at a significance level of 0.05.

Regarding ethical considerations, the study was submitted for evaluation and review by the prestigious CIEI-UPSJB, under registration code N°1302-2023-CIEI-UPSJB, and also by the Ethics Committee of the INMP, with file number N°23-21915-1. It is important to mention that this proj-

ect consisted of a retrospective study based on clinical histories, avoiding the use of invasive methods and without establishing direct contact with the participants. Rigorous measures were implemented to ensure the confidentiality of the participants' data, storing all the information under alphanumeric codes to which only thesis students and their supervisors have access. No face captures were taken and no visual evidence was kept that could lead to the identification of participants. In addition, no names or sensitive information of those involved has been publicly disclosed.

RESULTS

This study analyzed the characteristics of 126 pregnant women attended at the Instituto Nacional Materno Perinatal in Lima, Peru, during the year 2022. In general, the evaluated pregnant women were characterized by obesity (77/126; 61.1%), high first trimester maternal hCG concentrations (86/126; 68.3%) and multiparity (98/126; 77.8%). History of hyperthyroidism and hydatidiform mole was reported in 6.3% (8/126) and 7.9% (10/126) of the patients evaluated, respectively (Table 1).

TABLE 1. DESCRIPTIVE AND BIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH HYPEREMESIS GRAVIDARUM.

Associated factors	Total		Hyperemesis gravidarum				X^2 Test	p-value
			Yes (N=63)		No (N=63)			
	N	%	n	%	n	%		
Extreme maternal reproductive age								
Yes	23	18.3	12	19.0	11	17.5	6.05	0.08
No	103	81.7	51	81.0	52	82.5		
Higher education level								
Yes	31	24.6	16	25.4	15	23.8	2.83	<0.00*
No	95	75.4	47	74.6	48	76.2		
Maternal obesity								
Yes	77	61.1	59	93.7	18	28.6	5.43	0.03*
No	49	38.9	4	6.3	45	71.4		
Maternal hCG concentrations								
Adequate (< 219 UI/L)	40	31.7	2	3.2	38	60.3		
High (≥ 219 UI/L)	86	68.3	61	96.8	25	39.7	6.83	0.04*
Parity								
Nulliparous	28	22.2	12	19.0	16	25.4	5.07	0.02*
Multiparous	98	77.8	51	81.0	47	74.6		
Multiple pregnancy								
Yes	10	7.9	5	7.9	5	7.9	1.62	0.09
No	116	92.1	58	92.1	58	92.1		
Female fetus	0							
Yes	67	53.2	60	95.2	7	11.1	4.94	0.01*
No	59	46.8	19	30.2	62	40.0		
History of mental illness								
Yes	5	4.0	2	3.2	3	4.8	2.03	0.15
No	121	96.0	61	96.8	60	95.2		
Hyperthyroidism								
Yes	8	6.3	4	6.3	4	6.3	3.13	0.12
No	118	93.7	59	93.7	59	93.7		
Hydatidiform mole								
Yes	10	7.9	8	12.7	2	3.2	2.03	0.47
No	116	92.1	55	87.3	61	96.8		

hCG: human chorionic gonadotropin.
* Statistical significance set at p-value less than 0.05.

Gianina Jesús Ángeles-Olaza, Cristina Nataly García-Borjas, Miguel Ángel Arce-Huamaní

Among the patients reporting hyperemesis gravidarum, 19% (12/63) were found to have extreme reproductive age, 25.4% (16/63) had a higher level of education, 96.8% (61/63) had high maternal hCG concentrations during the first trimester, and 95.2% (60/63) had female fetuses. Therefore, in the bivariate analysis, the chi-square tests indicated statistical significance for higher education level ($p<0.001$), maternal obesity ($p=0.03$), high hCG concentrations in the first trimester ($p=0.04$), nulliparity ($p=0.02$) and female fetus ($p=0.01$). The rest of the variables evaluated did not have statistical significance (Table 1).

In Table 2, in the multivariate analysis adjusted for possible confounding variables, the adjusted ORs were found, concluding that higher education level was a protective factor for hyperemesis gravidarum with an OR of 0.85, being statistically non-significant. Among the factors that increased the risk for hyperemesis gravidarum were maternal obesity (OR: 2.78), high hCG concentrations during the first trimester (OR: 3.19), nulliparity (OR: 3.76) and female fetus (OR: 3.13), all statistically significant.

DISCUSSION

In the present study, 126 pregnant women attended at the Instituto Nacional Materno Perinatal of Lima, Peru, during 2022 were analyzed. Pregnant women with hyperemesis gravidarum presented a high prevalence of obesity, high hCG concentrations in the first trimester and nulliparity. In the bivariate analysis, statistical significance was found for higher education level, maternal obesity, high hCG concentrations in the first trimester, nulliparity and female fetus. Multivariate analysis showed that maternal obesity, high first trimester hCG levels, nulliparity and female fetus increased the risk of hyperemesis gravidarum.

In the study, higher education level was identified as a protective factor, with not statistically significance. This agrees with the study by Demewez Adane K[2] conducted in Ethiopia, which found that low education was more common in women with hyperemesis gravidarum, finding statistically significant (p = 0.02). Similarly, Seid AM[15] found that having a low educational level was a statistically significant risk factor (OR: 5.7). These results could be due to the fact that the study population in Ethiopia was attended in a general hospital and the number of pregnant women was larger, in addition to possible differences in the populations studied or variables not considered in the adjustment.

Another finding of our study was maternal obesity (OR: 2.78) as a statistically significant risk factor. Obese women were almost three times more likely to experience hyperemesis gravidarum compared to those without obesity. This result differs from that found by Yeon Kim H[16], where obese women are 4% more likely to develop hyperemesis gravidarum. The result is not statistically significant, indicating that obesity may not be a relevant risk factor in the population studied. However, Thakur M[17] found that low weight was significantly associated with HG. This variability of results may be due to the type of population, geographic location, and different lifestyles in each.

Our study also identified that being nulliparous (OR: 3.76) was a statistically significant risk factor. This suggests that women who have not had children are almost four times more likely to develop hyperemesis gravidarum compared to those who had children. Similar result was found by Yeon Kim H[16], in which being nulliparous was a statistically significant risk factor with 18% higher odds of developing hyperemesis gravidarum (OR: 1.18). Both studies agree that nulliparity is a risk factor for HG, but our study shows a stronger association, possibly due to differences in sample size or demographic characteristics. Likewise, Thakur M[17] found that be-

TABLE 2. MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH HYPEREMESIS GRAVIDARUM.

Associated factor	p-value	Crude OR (95% CI)	Adjusted OR (95% CI)
Higher educational level	<0.00	0.81 (0.40–2.06)	0.85 (0.63–1.44)
Maternal obesity	0.03*	2.64 (1.17–3.40)	2.78 (1.36–4.71)
High maternal hCG concentrations	0.04*	3.14 (2.62–7.37)	3.19 (2.81–8.74)
Nulliparity	0.02*	3.12 (1.98–8.34)	3.76 (1.99–9.35)
Female fetus	0.01*	2.58 (1.94–5.28)	3.13 (2.01–6.93)

OR: odds ratio; hCG: human chorionic gonadotropin
* Statistical significance set at p-value less than 0.05

ing nulliparous was significantly associated with HG. It is important to consider that variations in ORs could reflect differences in study methodology or heterogeneity of the populations studied, underscoring the need for further research to confirm these findings.

On the other hand, having a female fetus (OR: 3.13) was also a statistically significant risk factor. This implies that women expecting a female baby are more than three times more likely to develop hyperemesis gravidarum compared to those expecting a male baby. Similar result was found by Yeon Kim H[16] and Miina Nurmi[18], in which women expecting a female baby are respectively 34% and 26% more likely to develop hyperemesis gravidarum (OR: 1.34), with statistical significance. Although all studies agree that fetal sex is a risk factor for HG, our study indicated a higher risk, which could reflect variations in diagnostic criteria or in the characteristics of the populations studied.

This study provides a contribution to the existing knowledge on hyperemesis gravidarum (HG) by identifying specific risk factors associated with its development in pregnant women attended at the Instituto Nacional Materno Perinatal in Lima, Peru. Through multivariate analysis it was determined that maternal obesity high hCG concentrations in the first trimester, nulliparity and gestation of a female fetus significantly increased the risk of HG. These findings not only confirm previous results from other studies but also provide specific local data that can be used to improve prevention strategies and clinical management of HG in the Peruvian population.

The study performed has several limitations, including the use of a convenience sampling design which may not be representative of the general population and could bias the results. In addition, being a retrospective case-control study there are inherent limitations such as the possible lack of information in the medical records and the difficulty in establishing causality between the factors studied and hyperemesis gravidarum. To mitigate these limitations, the authors collected the medical records that had complete data.

Regarding the strengths of the study, we highlight the robust analytical methodology employed, which included a well-structured case-control design and the use of advanced statistical analyses such as logistic regression to adjust for possible confounding variables. In addition, the study used the SPSS 25 software for data analysis, ensuring rigorous statistical treatment. Data collection was carried out using a data sheet designed and validated by experts which guarantees the accuracy and relevance of the information collected for the objectives of the study. These methodological characteristics strengthen the reliability of the findings and support their potential applicability in other clinical and research contexts.

Conclusion

The present study identified that maternal obesity, high hCG concentrations in the first trimester, nulliparity and gestation of a female fetus were significant risk factors for the development of hyperemesis gravidarum in women attended at the Instituto Nacional Materno Perinatal in Lima, Peru. In addition, it was observed that a higher level of education could act as a protective factor, although it did not reach statistical significance. These findings provide valuable information for the prevention and management of hyperemesis gravidarum in the Peruvian population, suggesting the need for educational programs and more rigorous monitoring of pregnant women with these risk factors.

Acknowledgments

References

1. Bidary N, Aulya Y, WidowatI R. Analysis Of The Event Of Hyperemesis Gravidarum In Pregnant Women. J Kebidanan Malahayati. 2022;8(4):651-61. doi: 10.33024/jkm.v8i4.5015

2. Adane KD, Zerga AA, Gebeyehu FB, Ayele FY. Proportion of hyperemesis gravidarum and associated factors among pregnant women admitted into the obstetrics ward at Akesta general hospital, North East Ethiopia. PloS One. 2023;18(2). doi: 10.1371/journal.pone.0281433

3. Thakur M, Gautam J, Dangal G. Severity of Hyperemesis Gravidarum and Associated Maternal factors. J Nepal Health Res Counc. 2019;17(3):293-6. doi: 10.33314/jnhrc.v17i3.2113

4. Morgan H, Ahmed H, Williamson C. Hyperemesis gravidarum in the primary care setting: cross-sectional study of GPs. BJGP Open. 2022;6(1):1-10. doi: 10.3399/BJGPO.2021.0119

5. Liu C, Zhao G, Qiao D, Wang L, He Y, Zhao M, et al. Emerging Progress in Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum: Challenges and Opportunities. Front Med. 2021;8:809270. doi: 10.3389/fmed.2021.809270

6. Suhartat S. The Relation of Age and Parity with the Incidence of Hypermesis Gravidarum in Pregnant Woman in Dr. H. Moch Ansari Saleh Banjarmasin Hospital. 2020. https://eudl.eu/doi/10.4108/eai.23-11-2019.2298361

7. Dinberu MT, Mohammed MA, Tekelab T, Yimer NB, Desta M, Habtewold TD. Burden, risk factors and outcomes of hyperemesis gravidarum in low-income and middle-income countries (LMICs): systematic review and meta-analysis protocol. BMJ Open. 2019;9(4). doi: 10.1136/bmjopen-2018-025841

8. Topalahmetoğlu Y, Altay MM, Cırık DA, Tohma YA, Çolak E, Çoşkun B, et al. Depression and anxiety disorder in hyperemesis gravidarum: A prospective case-control study. Turk J Obstet Gynecol. 2017;14(4):214-9. doi: 10.4274/tjod.78477

9. Tsakiridis I, Giouleka S, Kourtis A, Mamopoulos A, Athanasiadis A, Dagklis T. Thyroid Disease in Pregnancy: A Descriptive Review of Guidelines. Obstet Gynecol Surv. 2022;77(1):45-62. doi: 10.1097/OGX.0000000000000960

10. González Nava P, Rangel Flores Y, Hernández Ibarra E. Retos en la prevención del embarazo adolescente subsiguiente, un estudio desde la perspectiva de madres adolescentes. Saúde E Soc. 2020;29(3):e181032. https://doi.org/10.1590/S0104-12902020181032

11. Macías Villa HLG, Moguel Hernández A, Iglesias Leboreiro J, Bernárdez Zapata I, Braverman Bronstein A, Macías Villa HLG, et al. Edad materna avanzada como factor de riesgo perinatal y del recién nacido. Acta Médica Grupo Ángeles. 2018;16(2):125-32. https://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S1870-72032018000200125

12. Simionescu AA, Stanescu AMA. Missed Down Syndrome Cases after First Trimester False-Negative Screening-Lessons to be Learned. Medicina (Kaunas). 2020; 56(4):199. doi: 10.3390/medicina56040199

13. Tal R, Taylor HS. Endocrinology of Pregnancy. [Updated 2021 Mar 18]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. https://www.ncbi.nlm.nih.gov/books/NBK278962/

14. Tenny S, Hoffman MR. Odds Ratio. En: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [citado 16 de abril de 2024]. http://www.ncbi.nlm.nih.gov/books/NBK431098/

15. Mohammed Seid A, Mehari EA, Bekalu AF, Dula Sema F, Limenh LW, Geremew DT, et al. Prevalence of hyperemesis gravidarum and associated factors among pregnant women at comprehensive specialized hospitals in northwest Ethiopia: Multicenter cross-sectional study. SAGE Open Med. 2024 Jun 5;12:20503121241257163. doi: 10.1177/20503121241257163

16. Kim HY, Cho GJ, Kim SY, Lee KM, Ahn KH, Han SW, Hong SC, Ryu HM, Oh MJ, Kim HJ, Kim SC. Pre-Pregnancy Risk Factors for Severe Hyperemesis Gravidarum: Korean Population Based Cohort Study. Life (Basel). 2020 Dec 26;11(1):12. doi: 10.3390/life11010012

17. Thakur M, Gautam J, Dangal G. Severity of Hyperemesis Gravidarum and Associated Maternal factors. J Nepal Health Res Counc. 2019;17(3):293-6. doi: 10.33314/jnhrc.v17i3.2113. PMID: 31735920.

18. Nurmi M, Rautava P, Gissler M, Vahlberg T, Polo-Kantola P. Incidence and risk factors of hyperemesis gravidarum: A national register-based study in Finland, 2005-2017. Acta Obstet Gynecol Scand. 2020;99(8):1003-013. doi: 10.1111/aogs.13820