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## Association between anxiety and hyperemesis gravidarum among pregnant women in Trujillo, Peru: a prospective cohort study

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### ABSTRACT

**Background:** Hyperemesis gravidarum (HG) is a severe pregnancy-related condition that may substantially affect maternal physical and psychological well-being. Anxiety frequently coexists with HG, although evidence regarding whether anxiety precedes its occurrence remains limited, particularly in Peruvian populations. **Objective:** To evaluate the association between anxiety and HG among pregnant women in Trujillo, Peru. **Methods:** A prospective cohort study was conducted among 216 pregnant women receiving antenatal care at public healthcare facilities in Trujillo, Peru, between August and September 2025. Anxiety was assessed at enrollment using the validated Spanish version of the 20-item Zung Self-Rating Anxiety Scale, with scores  $\geq 45$  indicating anxiety. Women with HG diagnosed at enrollment were excluded, and participants were subsequently followed for incident HG through 20 weeks of gestation. HG was identified from physician-recorded diagnoses supported by persistent nausea and vomiting with clinically relevant features. Crude risk ratios (RRs) and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were estimated. **Results:** HG occurred in 56 of 108 women with anxiety (51.9%) and 20 of 108 women without anxiety (18.5%). Anxiety was associated with a higher crude risk of HG (RR, 2.80; 95% CI, 1.81–4.33;  $p < 0.001$ ) and remained significantly associated after multivariable adjustment (aOR, 5.51; 95% CI, 2.66–11.38;  $p < 0.001$ ). **Conclusions:** Anxiety was associated with a higher occurrence of HG in this prospective cohort. These findings support consideration of anxiety assessment as part of comprehensive antenatal care; however, they do not establish a causal relationship.

**Keywords:** Anxiety; Hyperemesis Gravidarum; Pregnancy; Cohort Studies; Maternal Health

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## Introduction

Nausea and vomiting are common during early pregnancy, whereas hyperemesis gravidarum (HG) represents the severe end of this clinical spectrum. HG is characterized by persistent nausea and vomiting that may result in reduced oral intake, dehydration, clinically significant weight loss, and metabolic or electrolyte disturbances. It remains an important cause of healthcare use and hospital admission during the first half of pregnancy and may substantially impair maternal functioning and quality of life [1–3].

The etiology of HG is multifactorial and has been associated with hormonal, genetic, metabolic, gastrointestinal, and psychosocial mechanisms. Reported risk factors include a previous history of HG, multiple gestation, younger maternal age, and selected clinical and sociodemographic characteristics [3–8]. Nevertheless, no single mechanism fully explains its occurrence, and the contribution of psychological factors remains uncertain [4].

Anxiety disorders are common during pregnancy and represent a clinically relevant component of maternal mental health [9,10]. Women with HG frequently report higher levels of anxiety, psychological distress, and post-traumatic stress symptoms than pregnant women without HG [11–13]. However, the temporal relationship between anxiety and HG remains difficult to establish because much of the available evidence has assessed psychological symptoms after HG onset or among women already diagnosed with the condition. Consequently, these findings should not be interpreted as evidence that HG is primarily psychogenic.

The relationship between anxiety and HG may also be bidirectional. Severe and persistent nausea and vomiting may increase emotional distress through nutritional compromise, concern about maternal and fetal well-being, disruption of daily activities, and the potential need for hospitalization [1,2,10]. Conversely, anxiety preceding HG may influence autonomic and neuroendocrine responses, symptom perception, and coping mechanisms, potentially contributing to greater vulnerability to nausea and vomiting. Prospective evidence in which anxiety is assessed before incident HG remains comparatively limited.

Studying this association in Peru is particularly relevant because access to timely antenatal care, socioeconomic conditions, cultural perceptions of mental health, and availability of perinatal mental healthcare may influence the identification and management of both anxiety and

HG [4,7]. Recent Peruvian evidence has identified clinical and sociodemographic factors associated with HG; however, evidence specifically evaluating anxiety as a preceding exposure remains scarce [4]. This knowledge gap supports the need for prospective studies capable of establishing a clearer temporal sequence between psychological exposure and subsequent HG occurrence. Therefore, the objective of this study was to evaluate the association between anxiety and hyperemesis gravidarum among pregnant women receiving antenatal care in Trujillo, Peru.

## Materials and methods

### Study design and setting

A quantitative, observational, analytical, prospective cohort study was conducted among pregnant women receiving antenatal care at public healthcare facilities in Trujillo, Peru. Recruitment and follow-up were carried out between August and September 2025, with surveillance for incident hyperemesis gravidarum (HG) extending through 20 weeks of gestation. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies [14].

### Participants

Eligible participants were pregnant women between 5 and 20 weeks of gestation who attended antenatal care, agreed to participate, and provided written informed consent. Women with a documented current or previous anxiety disorder before the index pregnancy, those with HG already diagnosed at enrollment, and those unable to complete the anxiety questionnaire were excluded.

A non-probability convenience sampling strategy was used. The required sample size was estimated at 208 participants, corresponding to 104 women per exposure group. Recruitment continued until 216 eligible pregnant women were enrolled, resulting in two equally sized groups: 108 women with anxiety and 108 women without anxiety. All enrolled participants completed follow-up and were included in the final analysis; no losses to follow-up or missing values were recorded for the variables analyzed.

### Exposure assessment

Maternal anxiety was assessed at enrollment and before incident HG ascertainment using the validated Spanish

version of the 20-item Zung Self-Rating Anxiety Scale [15]. Each item was scored from 1 to 4, yielding a total score ranging from 20 to 80. Scores  $\leq 44$  were classified as absent or minimal anxiety, 45–59 as mild anxiety, 60–74 as moderate anxiety, and  $\geq 75$  as severe anxiety.

For the primary analysis, participants with scores  $\geq 45$  were classified as having anxiety, whereas those with scores  $\leq 44$  were classified as not having anxiety.

### Outcome assessment

The primary outcome was incident hyperemesis gravidarum. HG was identified through review of clinical records when a general physician or obstetrician-gynecologist documented the diagnosis based on persistent nausea and vomiting accompanied by clinically relevant manifestations such as significant weight loss, dehydration, ketonuria, or the need for hospital admission [2].

Women with HG already documented at enrollment were excluded to preserve the temporal sequence between anxiety assessment and subsequent outcome ascertainment.

### Covariates

Sociodemographic, obstetric, and clinical covariates were collected using a structured data-recording form. These variables included occupation, marital status, education, personal medical history, timing of antenatal-care initiation, family history, body mass index, previous hospitalization, gender-based violence, gravidity, previous abortion, laboratory-test findings, supplementation, socioeconomic status, social support, previous history of HG, and planned pregnancy.

Timely initiation of antenatal care was defined as the first antenatal visit occurring before 14 completed weeks of gestation. Supplementation was coded in mutually exclusive categories according to the principal supplement recorded at enrollment: ferrous sulfate or folic acid. Social support referred to regular emotional or practical assistance reported by the participant.

### Potential sources of bias

The use of a standardized anxiety instrument reduced variability in exposure assessment, while ascertainment of HG from clinical records reduced dependence on participant recall. Nevertheless, differential healthcare use, residual confounding, and possible misclassification

of exposure or outcome could not be completely excluded.

### Statistical Analysis

Categorical variables were summarized using absolute frequencies and percentages, whereas maternal age was summarized using the mean and standard deviation (SD).

The crude association between anxiety and HG was initially evaluated using Pearson's chi-square test. The cumulative incidence of HG was calculated separately for women with and without anxiety. A crude risk ratio (RR) with its 95% confidence interval (CI) was estimated from the  $2 \times 2$  cohort table.

A multivariable binary logistic regression model was subsequently fitted to evaluate the independent association between anxiety and HG while simultaneously adjusting for the prespecified sociodemographic, obstetric, and clinical covariates. Adjusted odds ratios (aORs) with 95% CIs were obtained from the exponentiated regression coefficients. Because logistic regression estimates odds rather than risk, the adjusted estimates were interpreted as odds ratios and not as adjusted risk ratios.

All statistical tests were two-sided, and statistical significance was established at  $p < 0.05$ .

### Ethical considerations

The study was conducted in accordance with the institutional ethical principles applicable to research involving human participants and with the principles of the Declaration of Helsinki [16]. Participation was voluntary, and written informed consent was obtained from all participants before enrollment.

Confidentiality and privacy were protected throughout the study. Personal information was handled securely and used exclusively for scientific purposes. The research followed the University Research Ethics Code approved by University Council Resolution No. 0470-2022-UCV.

### Results

The mean age of the 216 participants was 27.31 years (SD, 6.33). Most participants were homemakers (52.8%), were married or cohabiting (67.1%), had some formal education (96.3%), and had no relevant personal medical history (63.4%) (Table 1).

**Table 1.** Categorical sociodemographic and clinical characteristics of the study population

| Characteristic                      | Category                           | n   | %    |
|-------------------------------------|------------------------------------|-----|------|
| Occupation                          | Homemaker                          | 114 | 52.8 |
| Occupation                          | All other occupations              | 102 | 47.2 |
| Marital status                      | Single                             | 71  | 32.9 |
| Marital status                      | Married/cohabiting or other status | 145 | 67.1 |
| Education                           | No formal education                | 8   | 3.7  |
| Education                           | Any formal education               | 208 | 96.3 |
| Personal medical history            | Absent                             | 137 | 63.4 |
| Personal medical history            | Present                            | 79  | 36.6 |
| Timely initiation of antenatal care | No                                 | 168 | 77.8 |
| Timely initiation of antenatal care | Yes                                | 48  | 22.2 |
| Family history                      | Absent                             | 111 | 51.4 |
| Family history                      | Present                            | 105 | 48.6 |
| Body mass index                     | Normal                             | 88  | 40.7 |
| Body mass index                     | Other BMI category                 | 128 | 59.3 |
| Previous hospitalization            | No                                 | 213 | 98.6 |
| Previous hospitalization            | Yes                                | 3   | 1.4  |
| Gender-based violence               | No                                 | 208 | 96.3 |
| Gender-based violence               | Yes                                | 8   | 3.7  |
| Gravidity                           | Primigravida                       | 89  | 41.2 |
| Gravidity                           | Multigravida                       | 127 | 58.8 |
| Previous abortion                   | No                                 | 169 | 78.2 |
| Previous abortion                   | Yes                                | 47  | 21.8 |
| Laboratory tests                    | No abnormality                     | 174 | 80.6 |
| Laboratory tests                    | Abnormal                           | 42  | 19.4 |
| Supplementation                     | Ferrous sulfate                    | 114 | 52.8 |
| Supplementation                     | Folic acid                         | 102 | 47.2 |
| Socioeconomic status                | Low                                | 171 | 79.2 |
| Socioeconomic status                | Other socioeconomic status         | 45  | 20.8 |
| Social support                      | No                                 | 208 | 96.3 |
| Social support                      | Yes                                | 8   | 3.7  |
| History of HG                       | No                                 | 192 | 88.9 |
| History of HG                       | Yes                                | 24  | 11.1 |
| Planned pregnancy                   | No                                 | 142 | 65.7 |
| Planned pregnancy                   | Yes                                | 74  | 34.3 |

HG occurred in 51.9% of women with anxiety and 18.5% of women without anxiety. Anxiety was associated with a 2.80-fold higher crude risk of HG (95% CI, 1.81–4.33; Pearson  $\chi^2$ ,  $p < 0.001$ ) (Table 2).

**Table 2.** Occurrence of hyperemesis gravidarum according to anxiety status

| Anxiety | No HG, n | HG, n | Total, n | HG risk, % |
|---------|----------|-------|----------|------------|
| Absent  | 88       | 20    | 108      | 18.5       |
| Present | 52       | 56    | 108      | 51.9       |
| Total   | 140      | 76    | 216      | 35.2       |

In the multivariable logistic regression model, anxiety remained associated with HG (aOR, 5.51; 95% CI, 2.66–11.38;  $p < 0.001$ ). Formal education was associated with lower odds of HG than no formal education (aOR, 0.08; 95% CI, 0.01–0.52), late initiation of antenatal care was associated with higher odds than timely initiation (aOR, 2.53; 95% CI, 1.15–5.56), and normal BMI was associated with lower odds than a non-normal BMI (aOR, 0.48; 95% CI, 0.23–0.98) (Table 3).

**Table 3.** Multivariable binary logistic regression for hyperemesis gravidarum

| Variable                                                      | B      | SE    | Wald   | p      | aOR   | 95% CI       |
|---------------------------------------------------------------|--------|-------|--------|--------|-------|--------------|
| Anxiety: yes (reference: no)                                  | 1.706  | 0.370 | 21.199 | <0.001 | 5.505 | 2.663–11.379 |
| Other occupation (reference: homemaker)                       | 0.176  | 0.364 | 0.233  | 0.629  | 1.192 | 0.584–2.434  |
| Other marital status (reference: single)                      | 0.273  | 0.389 | 0.494  | 0.482  | 1.314 | 0.613–2.816  |
| Any formal education (reference: no formal education)         | –2.576 | 0.983 | 6.862  | 0.009  | 0.076 | 0.011–0.523  |
| Personal history: yes (reference: no)                         | 0.634  | 0.427 | 2.210  | 0.137  | 1.886 | 0.817–4.352  |
| Late antenatal-care initiation (reference: timely initiation) | 0.926  | 0.402 | 5.296  | 0.021  | 2.525 | 1.147–5.556  |
| Family history: present (reference: absent)                   | –0.157 | 0.351 | 0.200  | 0.654  | 0.855 | 0.430–1.700  |
| Normal BMI (reference: other BMI category)                    | –0.741 | 0.368 | 4.067  | 0.044  | 0.476 | 0.232–0.979  |
| Previous hospitalization: yes (reference: no)                 | 1.482  | 1.326 | 1.248  | 0.264  | 4.402 | 0.327–59.243 |
| Gender-based violence: yes (reference: no)                    | 0.224  | 0.935 | 0.057  | 0.811  | 1.251 | 0.200–7.822  |
| Multigravida (reference: primigravida)                        | –0.230 | 0.476 | 0.233  | 0.629  | 0.795 | 0.313–2.019  |
| Previous abortion: yes (reference: no)                        | 0.727  | 0.471 | 2.382  | 0.123  | 2.069 | 0.822–5.212  |
| Abnormal ancillary tests (reference: no abnormality)          | 0.594  | 0.423 | 1.971  | 0.160  | 1.812 | 0.790–4.154  |
| Folic acid (reference: ferrous sulfate)                       | –0.345 | 0.372 | 0.861  | 0.353  | 0.708 | 0.342–1.467  |
| Other socioeconomic status (reference: low)                   | –0.450 | 0.442 | 1.037  | 0.309  | 0.638 | 0.268–1.516  |
| Social support: yes (reference: no)                           | 1.421  | 0.979 | 2.105  | 0.147  | 4.140 | 0.607–28.210 |
| History of HG: yes (reference: no)                            | 0.208  | 0.556 | 0.140  | 0.708  | 1.232 | 0.414–3.665  |
| Planned pregnancy: yes (reference: no)                        | 0.703  | 0.400 | 3.091  | 0.079  | 2.019 | 0.923–4.419  |

## Discussion

In this prospective cohort, women with anxiety had a substantially higher occurrence of HG than women

without anxiety. The crude cohort analysis indicated a 2.80-fold higher risk, and the association persisted in the multivariable logistic model. Direct comparison of effect sizes with previous studies is limited because most available investigations have reported anxiety scores or

psychological symptoms after HG diagnosis rather than prospective RRs or aORs [11–13]. Thus, the present estimate suggests a strong association but should be interpreted cautiously because the observational design does not establish causality.

The findings are consistent with reports of greater anxiety and reduced psychological resilience among women diagnosed with HG [11]. Nijsten et al. documented depression, anxiety, and post-traumatic stress disorder symptoms following HG [12], while El-Skaan et al. described a marked psychological impact among women hospitalized with the condition [13]. These studies support the integration of psychological assessment with obstetric care. Nevertheless, much of the existing evidence evaluates psychological symptoms after HG onset; therefore, reverse causation remains plausible.

Several mechanisms may explain the observed association. Anxiety may alter autonomic and neuroendocrine responses, intensify the perception of nausea, and reduce coping capacity. Conversely, persistent vomiting, nutritional compromise, concern about maternal and fetal well-being, disruption of daily activities, and hospitalization may provoke or aggravate anxiety [1,2,10].

The association should therefore be interpreted as potentially bidirectional and should not be used to characterize HG as a purely psychogenic disorder. Recent research has also explored biological markers potentially involved in HG, including ischemia-modified albumin as a possible predictor of the condition [18]. This evidence further supports understanding HG as a multifactorial disorder rather than as a primarily psychogenic condition.

The sociodemographic and clinical profile was broadly consistent with studies reporting HG among women of reproductive age and populations with heterogeneous clinical risk factors [3,5,7,8]. In the adjusted model, formal education was associated with lower odds of HG, whereas late initiation of antenatal care was associated with higher odds. Normal BMI was also associated with lower odds of HG compared with other BMI categories. These findings are broadly consistent with previous evidence showing that sociodemographic characteristics, nutritional status, and access to timely care may contribute to differences in HG occurrence [4,5,7]. However, these secondary associations should be interpreted cautiously because some categories contained relatively few participants.

### *Strengths and limitations*

The strengths of this study include its prospective cohort framework, balanced exposure groups, complete follow-up, use of a standardized anxiety scale, and multivariable adjustment for several potential confounders. The analysis also distinguishes the crude RR from the aOR, thereby avoiding interpretation of logistic-regression coefficients as relative risks.

This study also has several limitations. Outcome ascertainment from routine clinical records may have introduced misclassification, and anxiety levels may vary throughout gestation. Residual confounding cannot be excluded. Convenience sampling and the relatively short follow-up period may limit generalizability. In addition, the multivariable model included several covariates with infrequent categories, resulting in wide confidence intervals for some estimates and potentially reducing model stability. Consequently, secondary adjusted associations should be interpreted cautiously, and the findings should not be considered evidence of causal relationships.

### *Clinical and research implications*

Antenatal services should consider anxiety assessment and timely referral when clinically indicated, particularly among women presenting with severe nausea and vomiting. Psychological assessment should complement, rather than replace, medical evaluation and evidence-based management of HG. Recent clinical research has also evaluated supportive interventions addressing both nausea-vomiting severity and anxiety among women with HG [17], reflecting increasing interest in integrated approaches to the physical and psychological burden of the condition.

Future studies should establish exposure before outcome onset, use standardized HG diagnostic criteria and validated severity measures, prespecify clinically relevant confounders, and report participant flow and missing data transparently. Larger prospective cohorts and more parsimonious multivariable models would also help obtain more precise adjusted estimates. Further research should evaluate whether early psychological assessment or supportive interventions are associated with clinically relevant maternal outcomes.

### **Conclusions**

Anxiety was associated with a higher occurrence of HG among pregnant women in Trujillo. The association

remained statistically significant after multivariable adjustment, but the findings do not establish causality. Integrating mental health assessment into antenatal care may facilitate more comprehensive management, while further longitudinal research with clearly documented temporality and validated outcome definitions is warranted.

### Author Contributions Statement (CrediT)

**J.P.C.:** Conceptualization, Methodology, Investigation, Data Curation, Resources, Project Administration, and Writing – Original Draft. **J.F.Q.:** Methodology, Validation, Investigation, Supervision, and Writing – Review & Editing. **M.D.M.:** Formal Analysis, Data Curation, Visualization, Validation, and Writing – Review & Editing. All authors reviewed and approved the final version of the manuscript.

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### Conflict of Interest

The author declares no financial or non-financial conflicts of interest that could have influenced the conception, conduct, analysis, interpretation, or publication of this research.

### Data Availability

The de-identified data supporting the findings of this study are available from the corresponding author upon reasonable academic request. The dataset has not been deposited in a public repository because it contains clinical information obtained from pregnant participants and its dissemination requires appropriate safeguards to preserve confidentiality and privacy. Any request for access will therefore be considered in accordance with applicable ethical and data-protection requirements.

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