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Review article

Predictive factors of Hyperemesis Gravidarum: A systematic review

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ABSTRACT

Purpose: Hyperemesis gravidarum (HG) is the main cause of hospitalization during the first trimester of pregnancy. Although it has been associated with serious complications, little is known about its predictive factors. The aim of this systematic review was to search for and critically appraise the studies that investigate the predictive factors for HG.

Methods: Search strategy included PubMed, CENTRAL and EMBASE databases (till December 2017). All studies examining risk factors for HG were included. Screening of available studies was carried out by two reviewers, as well as the quality assessment of the included studies, based on the Newcastle-Ottawa Scale for observational studies.

Results: The search located 308 articles, of which 14 observational studies (four low-, eight medium- and two high-quality), involving 1400 women who met the eligibility criteria. In four studies, there was no association between Helicobacte r (H.) Pylori infection and HG, in contrast to two studies which demonstrated such an association. Pre-pregnancy body mass index (BMI), adipose tissue, maternal age, leptin, ghrelin, beta-chorionic gonadotropin (β-hCG), total (T_4) and free thyroxine (fT_4) correlated with HG in various studies, and could be considered as predictive markers. Regarding the high-quality evidence, a cohort study associated leptin and nephatin-1 with HG, whereas a cross-sectional study found no association between H. pylori infection and HG.

Conclusions: More studies of high quality and adequate sample size have to be carried out to identify the predictive factors for HG.

Contents

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Introduction

Hyperemesis Gravidarum (HG) is a rare condition [0.3–3% of pregnancies, according to the diagnostic criteria and the ethnicity [1–3]] characterized by persistent and severe nausea and vomiting during pregnancy leading to dehydration, electrolyte disturbances (hypokalemia, hyponatremia), weight loss (5% of the pre-pregnancy weight) and ketosis [4]. The clinical diagnosis of HG is based on the presence of nausea and vomiting in pregnant women, excluding other pathological conditions that could produce these symptoms (metabolic, gastrointestinal, neurological, infectious and iatrogenic causes [5,6]. HG is the main cause of hospitalization during the first trimester of pregnancy [7]; it is associated with significant morbidity and mortality, as well as a high cost of treatment [7,8].

Early diagnosis of HG is of clinical importance, to avoid maternal [vitamin B1 (thiamine) and K deficiency [9],Wernicke's encephalopathy [10,11] and fetal/neonatal [preterm birth, intrauterine growth restriction (IUGR), increased insulin resistance [12–17], psychiatric disorders in adulthood (12)] complications. The exact pathophysiological mechanism of HG is not known. Many hypotheses [high concentrations of beta-chorionic gonadotropin (β-hCG) and estradiol (E_2), psychological factors] have been proposed, which implies its multifactorial nature [6,8,18,19].

Obviously, the identification of women at a higher risk for developing HG is of particular importance. Many predictive factors have been proposed, such as Helicobacter Pylori (H. Pylori) infection [20–30], genetic predisposition [2,31,32], low body mass index (BMI) [33–35], female embryo [36,37], multiple gestation [37–39], leptin [35,40,41], hyperthyroidism [42,43], increased β-hCG concentrations [42–44] and history of HG in previous pregnancy [45] (Table 1). Two meta-analysis concluded that smoking before and during pregnancy [46] and depression [47] are not risk factors for HG. Despite the conduction of several studies on the identification of HG predictive factors, the presence of conflicting results and the small sample sizes make the role of these factors unclear. The aim of this systematic review was to search for and critically appraise the studies that investigate the predictive factors for HG.

Table 1
Factors that show a strong or a weak association with HG.

Strong association	Weak association
H. Pylori infection	Depression
BMI	Smoking
Genetic predisposition	
Female embryo	
Multiple pregnancy	
Historical HG in a previous pregnancy	
Hyperthyroidism	
β-hCG	

BMI: body mass index; β-hCG: beta-human chorionic gonadotropin; HG: Hyperemesis Gravidarum; H. Pylori: Helicobacter Pylori.

Materials and methods

This systematic review followed the reporting recommendations of the PRISMA statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [48,49]. We did not register a protocol for this systematic review. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Search strategy

A systematic search was conducted on three major electronic databases: PubMed (MEDLINE), CENTRAL (Cochrane) and EMBASE on December 2017. The search string was constructed by combining Medical Subheadings (MeSH) terms with Boolean operators: {("Hyperemesis Gravidarum" [MeSH]) OR ("Nausea and Vomiting" [MeSH]) OR ("Morning Sickness" [MeSH])) AND (("Risk Factors" [MeSH]) OR ("Prognosis" [MeSH])}. The PubMed search strategy is presented in Appendix A. The search was conducted by two authors (PI, DP) independently, in a blinded manner.

Eligibility criteria

Inclusion and exclusion criteria were decided by the researchers, considering the research question, research design and factors recorded in the primary studies. In each primary study, the case group had to include women with ongoing HG diagnosis (pregnant women who, during the first trimester, have ketones in the urine and episodes of vomiting at least four times a day). The control group had to include women without HG or other pregnancy complication. Studies were considered irrespective of publication date and language used. Experimental animal studies or *in vitro* studies, reviews and case reports were excluded from the systematic review (Table 2).

Study selection process

All relevant studies were imported in the Mendeley reference manager (version 1.19.2 for Mac). Two researchers (PI, DP) screened independently each one of the studies, based on the predefined eligibility criteria. Both researchers were not blind to study title and authors. Studies that were considered as eligible by both researchers, were screened as full text.

Table 2
Eligibility criteria for study selection.

Inclusion criteria	Exclusion criteria
Human study	Study *in vitro* or in animals
Current pregnancy	
HG diagnosis according to criteria	
Presence of control group (pregnant without HG)	Review studies, case reports
Determination of potential predictive risk factor in both groups by any method	
	Absence of approval by bioethics committee

HG: Hyperemesis Gravidarum.

Quality assessment

Two researchers (PI, DP) assessed the quality of each of the included studies based on the Newcastle-Ottawa Scale (NOS), as only non-randomized studies (cross-sectional, case control and cohort studies) were included in the systematic review. NOS is based on a "star system". Each of the included studies is judged on three categories: selection of study groups; comparability of study groups; and ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively [50]. Studies are rated as of high (8–9 stars), medium (6–7 stars) or low quality (<6 stars). Details of quality assessment of the included studies are provided in Table 3. Any disagreements regarding the quality assessment between the two researchers were arbitrated by a third one (DGG).

Data extraction

Data from the eligible studies was extracted by two researchers independently (PI, DP) into a Microsoft Excel sheet. Due to the great heterogeneity of the results, a meta-analysis was not possible to be conducted.

Results

The systematic search yielded 308 results after removal of the duplicates (PubMed: 296, EMBASE: 257, CENTRAL: 12). Following the screening of the titles and abstracts, 288 studies were excluded as irrelevant. From the remaining 20 studies, two were not available for full text assessment, whereas four were excluded due to eligibility criteria (Table 4). Fourteen studies were eligible for the qualitative synthesis. All of them were written in English and published from 1979 to 2017. A PRISMA flow diagram is included in Appendix B.

Study characteristics

The 14 studies that met the eligibility criteria for this review differed in terms of design, result analysis and the risk factor they examined (Table 5). The total number of participants was 1400 (Table 6). Tables 6 and 7 illustrate the sample size and the descriptive characteristics and the sample size of the included studies, respectively.

Aka et al. [40]

A case-control study of 18 women with HG and 18 healthy pregnant women. When the two groups were compared in regard to leptin levels, HG had higher levels ($p = 0.037$). Therefore, leptin may have a role in HG and can be identified as a marker for the HG.

Demir et al. [35]

A prospective case-control study of 54 women with HG and 42 pregnant women without HG. Gestation week and BMI were significantly lower in the HG group compared with the controls ($p = 0.001$). Also, they developed a novel parameter, Adjusted Leptin Levels (ALL: maternal serum leptin levels/gestational week). ALL was higher in the HG group ($p = 0.009$). A positive correlation was found between ALL and BMI in the HG group ($r = 0.449$,

Table 3
Quality evaluation of the studies included with the Newcastle-Ottawa Quality Scale.

Study	Case definition	Representativeness of cases	Selection of controls	Definition of controls	Cohort representativeness	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present	Sample representativeness	Sample size	Non-respondents	Ascertainment of the exposure	Matched controls	Additional factors	Ascertainment of exposure	Ascertainment of participants	Non-response rate	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	Assessment of the outcome	Statistical test	Total score	Quality of study
Aka et al.	no	*	*	*									*	*	*	*	no						7	**medium**
Demir et al.	no	no	no	no									*	*	*	*	no						4	**low**
Gungor et al.					no	*	*	*					*	*				*	*	*			8	**high**
Al Yatama et al.	no	*	no	*									*	*	*	*	no						6	**medium**
Aytac et al.	no	*	no	*									no	*	*	*	no						5	**low**
Erdem et al.	no	*	no	*									no	*	*	*	no						5	**low**
Frigo et al.	no	*	*	*									*	*	*	*	no						7	**medium**
Karadeniz et al.	no	*	no	*									no	*	*	*	no						6	**medium**
Lee et al.									*	*	no	**	*	*							*	*	8	**high**
Kosus et al.	no	*	*	*									*	*	no	*	no						6	**medium**
Ozturk et al.	no	*	no	*									*	*	*	*	no						6	**medium**
Panesar et al.	no	*	no	*									*	*	*	*	no						6	**medium**
Cevrioglu et al.	no	*	*	*									*	*	*	*	no						7	**medium**
Kauppila et al.	no	*	no	no									*	*	*	*	no						5	**low**

Table 4
Studies excluded from the qualitative synthesis and reasons for their exclusion.

Author	Year	Study	Reason of exclusion
Kjeldgaard et al.	2017	Cohort	Uncertain diagnosis of HG
Sandven et al.	2009	Case-control	Discordance in the criteria used for HG diagnosis
Bagis et al.	2002	Case-control	Uncertain diagnosis of HG
Signorello et al.	1998	Case-control	Uncertain diagnosis of HG

HG: Hyperemesis Gravidarum.

Table 5
Design of the included studies.

Author	Year	Country	Type of study	Aim
Aka *et et al.*	2006	Turkey	Case-control	Leptin and leptin receptor in pregnant women with HG.
Demir et al.	2006	Turkey	Case-control	Adjusted Leptin Level (ALL) as a predictor for HG.
Gungor et al.	2013	Turkey	Cohort	Ghrelin, obestatin, nesfatin-1, leptin in pregnant women with HG.
Al Yatama et al.	2002	Kuwait	Case-control	Hormone profile of women with HG.
Aytac et al.	2007	Turkey	Case-control	H. Pylori stool antigen assay in HG.
Erdem et al.	2002	Turkey	Case-control	H. Pylori (+) in HG and correlation with symptoms.
Frigo et al.	1998	Austria	Case-control	HG associated with H. Pylori.
Karadeniz et al.	2006	Turkey	Case-control	H. Pylori stool antigen assay in HG.
Lee et al.	2005	Los Angeles	Cross-sectional	H. Pylori in Hispanic population affected by HG.
Kosus et al.	2016	Turkey	Case-control	HG and maternal body fat composition.
Ozturk et al.	2017	Turkey	Case-control	HG and prealbumin, nesfatin-1, ghrelin, obestatin.
Panesar et al.	2001	Hong Kong	Case-control	Thyroid hormones/hCG responsible and HG.
Cevrioglu et al.	2004	Turkey	Case-control	H. Pylori in gravida with HG: H. Pylori stool antigen test.
Kauppila et al.	1979	Finland	Case-control	hCG serum concentrations in HG.

hCG: human chorionic gonadotropin; HG: Hyperemesis Gravidarum; H. Pylori: Helicobacter Pylori.

Table 6
Number of cases (Hyperemesis Gravidarum) and controls of the included studies.

Author	Participants	Cases / Controls
Aka et al.	36	18/18
Demir et al.	96	54/42
Gungor et al.	40	20/20
Al Yatama et al.	100	50/50
Aytac et al.	107	52/55
Erdem et al.	86	47/39
Frigo et al.	234	105/129
Karadeniz et al.	60	31/29
Lee et al.	82	40/42
Kosus et al.	84	54/30
Ozturk et al.	78	40/38
Panesar et al.	116	58/58
Cevrioglu et al.	124	27/97
Kauppila et al.	157	42/115

$p = 0.001$); leptin levels were also positively correlated with BMI in the HG group ($r = 0.313$, $p = 0.025$). The authors concluded that leptin can be a good prognostic marker for HG, as values of ALL > 2.5 in the first trimester were associated with severe nausea and vomiting.

Gungor et al. [41]

A cohort study of 40 patients, 20 women with HG and 20 pregnant women without gestational pathology. Nesfatine-1 concentrations in the HG group were higher compared with the controls, while leptin concentrations were lower in the HG group. The authors suggested that leptin and Nesfatine-1 may play a role in the pathology of the HG.

Al Yatama et al. [43]

A case-control study on the levels of 50 patients with HG and 50 women without HG. The values of β-hCG, T_4, and fT_4 were higher in the HG compared with the control group ($p < 0.0001$, $p = 0.004$ and $p = 0.01$, respectively). TSH levels were lower in the HG group ($p < 0.0001$). None of the patients were diagnosed with hyperthyroidism.

Aytac et al. [30]

A prospective study of 107 pregnant women (52 with HG and 55 asymptomatic), which focused on H. Pylori stool antigen (HpSA). In total, the incidence of HpSA was 41.1%. Regarding the two groups, 22 women with HG (42.3%) and 22 without HG (40%) were positive for HpSA ($p > 0.05$). As the specific antigen test demonstrated, the HG was not related to the H. Pylori infection.

Erdem et al. [28]

A prospective study of 47 women with HG and 39 controls group, assessed for the H. Pylori specific IgG (HpIgG) antibodies by using an ELISA method. The incidence of infection with H. Pylori was 85.1% and 64.1%, respectively ($p < 0.05$).

Frigo et al. [24]

A total of 105 women with HG were compared with 129 controls. H. Pylori seropositivity was examined by HpIgG concentrations. Positive IgG were found in 95 H G women (90.5%) and in 60 controls (46.5%), while mean index percentages of IgG were 74.2% and 24.3%, respectively ($p < 0.01$). The authors suggested that H. Pylori seropositivity may cause HG.

Table 7
Descriptive characteristics of the included studies.

	Cases			Controls		
	Age (years)	BMI/Weight (kg/m^2 / kg)	Gestational age (weeks)	Age (years)	BMI/Weight (kg/m^2 / kg)	Gestational age (weeks)
Aka et al.	27.0 ± 4.4	25.4 ± 3.8	8.5 ± 2.2	28.1 ± 6.01	25.9 ± 4.9	8.6 ± 2.3
Demir et al.	25.9 ± 4.0	21.4 ± 3.4	8.6 ± 1.74	26.0 ± 5.2	24.0 ± 13.5	9.8 ± 1.5
Gungor et al.	27.3 ± 6.4	22.3 ± 2.3	9.6 ± 3.3	26.8 ± 5.3	26.8 ± 5.3	11.3 ± 1.9
Al Yatama et al.	27.1 ± 4.4	61.2 ± 21.5 (kg)	10.3 ± 2.2	29.0 ± 4.6	69.8 ± 12.6 (kg)	10.3 ± 2.3
Aytac et al.	28.9 ± 4.6		10.5 ± 2.7	28.8 ± 3.9		10.0 ± 2.7
Erdem et al.	27.5 ± 4.0		9.4 ± 2.1	27.9 ± 4.6		9.3 ± 1.9
Frigo et al.	24.0 ± 2.3		8.0 ± 1.0	25.0 ± 3.1		9.0 ± 1.2
Karadeniz et al.	25.8 ± 4.7		9.6 ± 2.4	26.3 ± 6.0		11.8 ± 2.7
Lee et al.	25.4 ± 4.9			25.8 ± 4.9		
Kosus et al.	27 (21-39)	22.9 (16.2 - 38.1)	9 (6 - 13)	30 (24 - 37)	23 (22 - 34)	8 (6 - 12)
Ozturk et al.	28.7 ± 4.7	22.8 ± 3.4	8.5 ± 2.2	26.5 ± 5.8	27.2 ± 5.4	8.7 ± 1.8
Panesar et al.	28 (24.8 - 31)		10.1 (8.1 - 13.1)	32 (29 - 35)		10.1 (8.0- 13.1)
Cevrioglu et al.	26.6 ± 0.7	22.9 ± 0.7	8.8 ± 0.8	27.9 ± 0.5	24.5 ± 0.9	10.4 ± 0.5
Kauppila et al.	26.2 (19 - 38)		7 - 17			

Data are given as mean ± standard deviation (SD) or as median (range).

Karadeniz et al. [27]

A prospective, case-control study focused on the role of H. Pylori infection. The authors checked for the presence of HpIgG and HpSA. They included 31 women with HG and 29 pregnant women without HG. HpIgG seropositivity was 67.7% for HG women and 79.3% for controls ($p = 0.31$), while HpSA was detected in 22.6% and 6.9%, respectively ($p = 0.08$). No correlation was found between H. Pylori infection and HG.

Lee et al. [51]

A cross-sectional study of 82 women of Spanish descent, checked for HpIgG. Of the 40 women with HG, 26 were seropositive compared with 28 of the 42 controls ($p = 1.0$).

Kosus et al. [34]

A study of 54 women with HG and 30 healthy pregnant women (singleton pregnancy, gestational week 6^{th}-14^{th}). The pre-pregnancy BMI and the visceral adipose tissue (VAT) were higher in the HG group compared with the controls. Specifically, VAT and pre-pregnancy BMI predicted 83.8% and 67.1% of HG cases, respectively. The authors concluded that both pre-pregnancy BMI and VAT are associated with HG and can be considered predictive markers for HG.

Ozturk et al. [52]

A study of 78 pregnant women (40 with HG and 38 healthy controls). BMI was lower in the HG compared with the control group. Furthermore, concentrations of ghrelin and pro-albumin were lower in the HG group ($p = 0.011$ and $p < 0.001$, respectively), whereas obestatin and nesfatin-1 had no difference. No association was found between BMI and ghrelin and pro-albumin levels. The authors suggested that ghrelin may play a role in the pathogenesis of the HG.

Panesar et al. [42]

A logistic regression analysis to check for factors associated with HG. A receiver operating characteristic (ROC) curve was constructed to predict the onset of HG. Women with HG were younger compared with controls ($p < 0.001$), while fT_3, fT_4 and β-hCG were higher in the HG group ($p < 0.05$, $p < 0.001$, $p = 0.051$, respectively). In contrast, TSH was higher in the control group ($p < 0.001$).

Cevrioglu et al. [25]

The study investigated the association between H. Pylori infection and HG, by measuring HpSA and HpIgG. HpSA was found in the serum of 40.7% of HG women, while only 12.4% of the controls were positive ($p = 0.001$). HpIgG were detected in 85.2% and 73.2% of HG and controls, respectively ($p = 0.05$). The authors suggested a correlation between H. Pylori infection and HG.

Kauppila et al. [44]

In a study of 42 pregnant women with HG, β-hCG concentrations were higher at 7^{th}-8^{th},9^{th}-11^{th} and 12^{th}-14^{th} gestational weeks compared with controls ($p < 0.001$, $p < 0.05$ and $p < 0.05$, respectively). The authors suggested a causal association between β-hCG and HG.

Details regarding the risk factors that were assessed and the methods used to measure them in each included study are presented in Table 8. A summary of the results is presented in Table 9.

Methodologic quality assessment

Quality assessment was conducted by NOS. Four of them were low-quality studies, eight medium- and two high-quality. Table 3 summarizes the quality evaluation of the included studies.

Discussion

This is the first systematic review that evaluated the studies that investigated the prognostic factors for the onset of HG. It provided evidence obtained from observational studies and it was conducted in accordance with the MOOSE guidelines.

The results of the included studies differ; sometimes, they were even conflicting. Three studies indicated a causal association between increased concentration of β-hCG and HG. Regarding T_4 and fT_4 concentrations, higher levels were found in HG women in two studies. Six studies focused on the association of H. Pylori infection with HG, with contradictory results. In four of them, no correlation was found, while two studies concluded that H. Pylori infection is associated with HG. Detection of HpSA confirmed an association between H. Pylori and HG. One study found that women with HG were of younger age, while three studies concluded that leptin is a good prognostic marker for the onset of HG.

Table 8
Risk factors and methods used to identify them in the included studies.

Author	Risk factor	Method	Details
Aka et al.	Leptin, leptin receptor, cortisol, insulin, T_3, fT_4, T_4, β-hCG	ELISA	Leptin:Intra-assay 2.6 and 4.9%, Inter-assay 3.7 and 6.6%, Sensitivity 0.01 ng/ml. Leptin receptor:Intra-assay 4.8 and 13.3%, Inter-assay 7.0 and 9.6%, Sensitivity 0.12 ng/ml.
Demir et al.	Leptin, TSH, fT_3, fT_4, T_4	ELISA	Leptin:Intra-assay 2.6 and 4.9%, Inter-assay 3.7 and 6.6%, Sensitivity 0.01 ng/ml. TSH: Intra-assay 0.6 and 6.0%, Inter-assay 2.1 and 4.1%, Sensitivity 0.025 mIU/ml. fT_3:Intra-assay<6.4%, Inter-assay<5.5%, Sensitivity 0.5 pM. fT_4: Intra-assay <6.7%, Inter-assay<6.5%, Sensitivity 0.4 pM.
Gungor et al.	Leptin, nesfatin-1	ELISA	The lowest leptin concentration measured is 2 ng/ml. Intra-assay 7.8%, Inter-assay 9.3%. The lowest nesfatin-1 concentration measured is 0.1 ng/ml. Intra-assay 10%, Inter-assay 15%.
Al Yatama et al.	TSH, fT_4, T_4, β-hCG	MPIA, TPO	Lower detection level: ß-hCG 2.0 mIU/ml, T_4 1.05 μ/dl. TSH0.03 μl/ml, $fT_4$0.4 nd/dl.
Aytac et al.	H.Pylori	HpAg, stool	
Erdem et al.	H.Pylori	ELISA HpIgG	A calibration curve was used in the results.
Frigo et al.	H.Pylori	ELISA HpIgG	IgG: <18% negative, >22% positive. IgG between 18-22% required repeat testing in 2-4 weeks. Intra-assay 7.4, 4.4 και 3.5%, Inter-assay 4.4, 4.2 and 4.2%.
Karadeniz et al.	H.Pylori	HpIgG, HpSA, stool	Positive: >1.00, Negative: <0.90. Values between 0.91-0.99 were interpreted as marginal. Positive: >298 (at 450 nm), Negative: <298.
Lee et al.	H.Pylori	ELISA HpIgG	Sensitivity 94.9%, Specificity 4%, Inter-assay 10%.
Kosus et al.	Fat composition (subcutaneous fat tissue, SCFT) (visceral adipose tissue, VAT)	SCFT, VAT	The subcutaneous fat depth was measured to the outer border of the rectus abdominus muscle at the level of the white line. The visceral fat depth was measured from the inner border of rectus abdominus muscle at the level of the white line to the anterior wall of the abdominal aorta.
Ozturk et al.	Pre-albumin, ghrelin, nesfatin-1, ostestatin	ELISA	Analytical ranges: Ghrelin: 0-100 ng/ml, Ostestatin: 0.412-100 ng/ml. Nesfatin-1: 0.78-50 ng/ml, Pre-albumin: 50-500 mg/l.
Panesar et al.	β-hCG, TSH, fT_4, fT_3	ELISA	The lower detection limit for TSH was 0.03 mIU/l, Inter-assay<10%.
Cevrioglu et al.	H.Pylori	ELISA HpIgG, HpIgA, stool	IgG index (Arbitrary Unit, Au): >11 Au/mL positive, <9 Au/ml negative. Levels between 9-11 Au/ml required repeat testing in 2-4 weeks.
Kauppila et al.	β-hCG	Blood sample	Inter-assay ± 13%.

In the Kosus et al. study, both pre-pregnancy BMI and adipose tissue were correlated with HG and could be considered predictive markers for HG. However, despite the fact that the patients were volunteers (selection bias), the small sample size does not allow generalization of the results. In the Ozturk et al. study, ghrelin was associated in the pathogenesis of the HG. The control group and the study group consisted of hospital patients and the women with possible confounding factors that could influence the results were excluded.

In the case-control studies of Aka et al. and Demir et al. and in the cohort study of Gungor et al., the association between leptin, leptin receptor and HG was examined. The authors concluded that leptin levels can be used as a prognostic marker of HG. However, in the study of Aka et al. the small sample size does not allow generalization of the results, while in their study Demir et al. did not avoid potential confounding factors. Regarding the study of Gungor et al., both the design and the methodology were satisfactory. However, the sample sizes of both groups were quite small.

The studies of Aytac et al., Erdem et al., Karadeniz et al., and Lee et al. suggested that H. Pylori infection is not a risk factor for HG, contradicting the studies by Frigo et al. and Cevrioglu et al. Aytac et al. managed to avoid confounding factors, both from the initial study design and from the final analysis. However, BMI (a probable confounding factor) was not assessed in neither group. The results of the Erdem et al. study should also be reproduced with caution as BMI was not measured. Over and above, the HG group was bigger than the control group, and the results were assessed by quantitative estimation using a calibration curve. In the study by Karadeniz et al. there was no BMI measurement and the small sample size did not allow for generalization of the results. Finally, in the Lee et al. study, HG women were selected from the general Spanish population, while the control group was selected from an obstetrics clinic. Both the design and the methodology of the study were reliable.

In contrast, Frigo et al. and Cevrioglu et al. concluded that H. Pylori infection can cause HG. Frigo et al. minimized the systematic errors: the selection of patients in both groups was randomized, while strict eligibility criteria eliminated women with confounding factors that could affect the results. The main drawback of this study is that BMI was not measured. Nevertheless, the large sample size permits generalization of the results. In the study of Cevrioglu et al., specific antibodies against H. Pylori (HpIgG) were measured by ELISA and HpSA was detected in stool. The measurements were objective, and the same method of analysis was used for both groups. However, the small size of the study group does not allow generalization of the results. Furthermore, there are many methodological issues regarding H. Pylori antibody testing and H. Pylori infection diagnosis. Generally, they are characterized by low sensitivity and specificity which limit their clinical usefulness. Additionally, they require local validation as different antigens may be more prevalent in different parts of the world, and they remain positive even after eradication of the infection [53].

Table 9
Results of the included studies.

Author	Results	Conclusion
Aka et al.	Leptin: Cases 34.0 ± 29.8, Controls 18.2 ± 7.3 Leptin receptor: Cases 13.0 ± 12.7, Controls 11.1 ± 7.8 Cortisol: Cases 15.2 ± 7.1, Controls 12.9 ± 5.3 β-hCG: Cases 101.1 ± 54.7, Controls 72.5 ± 48.5 Insulin: Cases 18.2 ± 20.6, Controls 11.6 ± 12.4 T_3: Cases 1.7 ± 0.5, Controls 2.0 ± 1.9 fT_4: Cases 1.5 ± 0.6, Controls 1.2 ± 0.16 TSH: Cases 1.4 ± 1.6, Controls 1.6 ± 1.1	Higher leptin in HG vs. normal pregnant women (p = 0.037). No difference in leptin receptor in HG vs. controls (p = 0.743). No difference in β-hCG, cortisol, insulin, TSH, T_3 and fT_4.
Demir et al.	Adjusted leptin: Cases 4.3 ± 2.3, Controls 3.6 ± 2.3 Leptin: Cases 11.8 ± 11.5, Controls 8.4 ± 7.4 TSH: Cases 0.7 ± 1.0, Controls 1.6 ± 2.5 fT_3: Cases 3.4 ± 1.3, Controls 2.7 ± 0.9 fT_4: Cases 5.1 ± 7.1, Controls 2.3 ± 2.9 Relationship of adjusted leptin with: BMI: Cases 0.45, Controls 0.12 TSH: Cases 0.27, Controls -0.38 fT_3: Cases -0.01, Controls 0.30 fT_4: Cases -0.04, Controls 0.05	Gestational age and BMI lower in HG vs. control (p = 0.001). Leptin similar between groups (p = 0.099). Adjusted leptin higher in HG vs. controls (p = 0.009). TSH, fT_3, fT_4 different in HG vs. controls (p = 0.003, 0.013, 0.012, respectively). Positive association between adjusted leptin and BMI in HG group (r = 0.449, p = 0.001). Positive correlation between leptin and BMI in HG group (p = 0.025).
Gungor et al.	Triglycerides: Cases 0.86 ± 0.34, Controls 1.25 ± 0.36 Total cholesterol: Cases 4.07 ± 1.07, Controls 4.49 ± 1.02 HDL-cholesterol: Cases 1.38 ± 0.31, Controls 1.72 ± 0.43 Leptin-BMI: r = 0.39, BMI-triglycerides: r = 0.60, BMI-VLDL: r = 0.51	Significant differences in triglycerides (p < 0.01). No difference in cholesterol VLDL or LDL (p = 0.05). Positive correlation between leptin and BMI (r = 0.39, p = 0.01). Positive correlation between BMI and triglycerides (r = 0.60, p = 0.01) and VLDL (r = 0.51, p = 0.02). Leptin lower in HG vs. controls (p = 0.01). Nephatin-1 higher in HG vs. controls (p = 0.01); no difference in obestatin.
Al Yatama et al.	T_4: Cases 11.10 ± 3.66, Controls 9.21 ± 2.30 fT_4: Cases 1.45 ± 0.39, Controls 1,28 ± 0.23 TSH: Cases 0.34, Controls 1.17 β-hCG: Cases 133.4 ± 59.5, Controls 61.8 ± 53.0	β-hCG(p < 0.01), T_4 (p < 0.0004) and fT_4 (p < 0.01) higher in HG vs. controls. TSH lower in HG vs. controls(p < 0.0001). In the HG group, positive correlation between gestational age and β-hCG. β-hCG/T_4 (p < 0.0001) and β-hCG/fT_4 (p = 0.0001) higher in HG vs. controls.
Aytac et al.	H. Pylori (+) antigen in the stool: 41.1% (44 of 107). HG group: 42.3% (22 of 52). Control group: 40% (22 of 55).	Difference not significant (p > 0.05).
Erdem et al.	Cases with HG: H. Pylori (+) 85.1% (40 of 47), H. Pylori (-) 14.9% (7 of 47) Duration of symptoms (weeks): H. Pylori (+) 6.95 ± 1.55, H. Pylori (-) 6.58 ± 1.78 Hospitalization (weeks): H. Pylori (+) 8.83 ± 1.96, H. Pylori (-) 9.47 ± 2.09 Duration of symptoms (weeks): H. Pylori (+) 8.35 ± 5.28, H. Pylori (-) 11.4 ± 7.17	No correlation between H. Pylori (+) and gestational age.
Frigo et al.	H. Pylori (+) Cases: 90.5% (95 of 105), Controls: 46.5% (60 of 129) H. Pylori (+) Cases 7 of 8, Controls 5 of 7	Difference between groups (p < 0.001) in Austria, Turkey, Yugoslavia and Poland. Higher incidence of H. Pylori in southern Europe (p < 0.001).
Karadeniz et al.	Cases: HpIgG (+) 21 (67.7%), HpIgG (-)10 (32.3%) HpSA (+) 7 (22.6%), HpSA (-) 24 (77.4%) Controls: HpIgG (+) 23 (79.3%), HpIgG (-) 6 (20.7%) HpSA (+) 2 (6.9%), HpSA (-) 27 (93.1%)	No difference between the two groups for HpIgG, HpSA.
Lee et al.	Cases: Age 25.4 ± 4.9, Number of births 2.5 ± 1.4, H. Pylori (+): 26/40 (65%), Place of birth: California 8, Mexico 23, Central/South America 9 Controls: Age 25.8 ± 4.9, Number of births 2.5 ± 1.2, H. Pylori (+) 28/42 (66,7%), Place of birth: California 6, Mexico 27, Central / South America 9	No difference in H. Pylori (+) among groups (p = 1.0). Age, pregnancy, number of previous births and place of birth not related to HG. H. Pylori (+) independent of age, pregnancy and place of birth.
Kosus et al.	VAT > 33 mm: 76.3% in cases, 23.7% in controls SCFT >16 mm: 68.2% in cases, 31.8% in controls	Pre-pregnancy BMI (p = 0.004) and VAT (p = 0.042) higher in HG vs. controls. SCFT not different in HG vs. controls.
Ozturk et al.	Ghrelin (ng/ml): Cases 57.8 ± 11.2, Controls 63.5 ± 8.8 (p < 0.05) Nesfatin-1 (ng/ml): Cases 5.09 ± 2.03, Controls 5.50 ± 2.82 (p = 0.463) Obestatin (ng/ml): Cases 4.8 ± 0,7, Controls 4.9 ± 0.4, (p = 0.443) Pre-albumin (mg/l): Cases 152 ± 37, Controls 204 ± 30 (p < 0.001)	BMI lower in HG. No difference between the groups in creatinine, AST, ALT. Higher Ht, Hb and urea in HG vs. controls. Ghrelin and pre-albumin lower in HG vs. controls. No difference in nesfatin-1 and obestatin between the two groups. In the control group, positive correlation between ghrelin-nesfatin-1, obestatin and gestational age.
Panesar et al.	β-hCG (IU/l): Cases 117.5 (76.43 - 169.3), Controls 98.9 (46.5 - 138.2) TSH (mIU/l): Cases 0.18 (0.03 - 0.61), Controls 0.93 (0.24 - 1.56) fT_3 (pmol/l): Cases 4.35 (3.7 - 5.73), Controls 4.0 (3.7 - 4.43) fT_4 (pmol/l): Cases 19.3 (15.4 - 22.4), Controls 14.9 (13.0 - 17.6)	The age of the mother and all the hormones different between HG and controls.

Table 9 (*Continued*)

Author	Results	Conclusion
Cevrioglu et al.	IgG: Cases 85.2%, Controls 73.2% IgA: Cases 48.1%, Controls 41.2% H. Pylori stool antigen: Cases 40.7%, Controls 12.4%	HpSA in stools: 40.7% in HG,12.4% in controls ($p = 0.001$). H. Pylori (+) for IgG and IgA not different between HG and controls ($p > 0.05$).
Kauppila et al.	7^{th}-8^{th} gestational week: Cases 40.8 ± 5.2 IU/ml, Controls 22.1 ± 1.4 IU/ml 9^{th}-11^{th} gestational week: Cases 38.1 ± 2.3 IU/ml, Controls 27.1 ± 2.1 IU/ml 12^{th}-14^{th} gestational week: Cases 35.9 ± 4.2 IU/ml, Controls 25.1 ± 1.7 IU/ml	β-hCG higher in HG vs. controls at 7^{th}-8^{th}, 9^{th}-11^{th}, 12^{th}-14^{th} week of gestation ($p < 0.001$, <0.05, <0.05, respectively). No differences between the groups during the 15^{th}-20^{th} week of gestation.

The results from the studies by Al Yatama et al., Panesar et al., and Kauppila et al. were similar. The levels of β-hCG, T_4 and fT_4 were higher in women with HG, indicating a strong, reproducible association between these parameters and HG. The detailed description by Al Yatama et al. of the sample analysis and the application of the same method in both groups leaves no room for subjectivity. However, the sample size was not large enough, as in the study by Panesar et al. The latter partially avoided confounders in both the design and the final analysis of the study. However, there was no BMI measurement in the women of both groups. Finally, the study of Kauppila et al., indicated a causal association between β-hCG and HG. However, the difference in sample size between the HG and the control groups undermines the validity of the study.

The present systematic review tried to be as concise as possible, adhering to the PRISMA statement and MOOSE report guidelines. As it consists only of observational studies, its results can be applied to the general population. However, the review has several limitations. First, the included studies showed high heterogeneity both in their design and method of analyzing the results; therefore, a meta-analysis was not possible. Second, as they were observational studies, they have inherited biases. To better assess those biases, two different researchers carried out this task using the NOS and were assisted by a third one, when needed. In this regard, it was found that the selection of patients and controls in most of the included studies was based on hospital populations, which might affect the validity of their results. Finally, regarding literature search, the strategy did not include "grey literature", potentially missing relevant information.

After evaluating the quality of the included studies, the most reliable were the cohort study of Gungor et al. and the cross-sectional study of Lee et al. According to Gungor et al., leptin and nesfatin-1 play a role in the pathogenesis of the HG. Lee et al. found no difference in the incidence of H. Pylori infection between the study groups.

Conclusion

In conclusion, HG is a rare condition, characterized by persistent and severe nausea and vomiting during pregnancy leading to dehydration, electrolyte disturbances, weight loss and ketosis. The exact pathophysiological mechanism is not known. The most important risk factors for HG are H. Pylori infection, genetic predisposition, low BMI, female embryo, multiple pregnancy, hyperthyroidism, β-hCG, and history of HG in a previous pregnancy. In a time when research focuses in the treatment of HG, the recognition of the factors associated with its onset of HG is particularly important. In this regard, it is imperative to conduct studies, with larger population samples and appropriate design (prospective cohorts) to identify prognostic factors prior to the onset of HG. In this way, causality could be inferred. The results of the studies regarding the role of H. Pylori infection vary, making the conduction of additional studies a necessity.

Contribution to authorship

P. Ioannidou: Protocol Development, Data Collection, Data Analysis, Manuscript Writing

D. Papanikolaou: Data Collection, Data Analysis, Manuscript Writing

T. Mikos: Protocol Development, Manuscript Revision

G. Mastorakos: Protocol Development, Manuscript Revision

D.G. Goulis: Protocol development, Data Analysis, Manuscript Revision

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Conflict of interest

The authors declare they have no conflicts of interest.

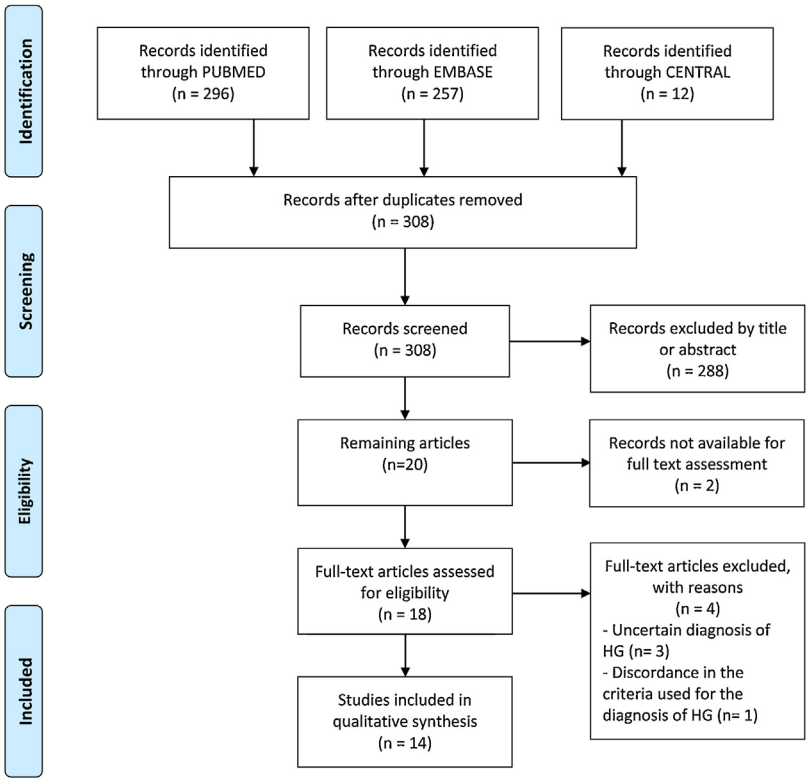
Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Appendix A. PubMed search string

1.	"Hyperemesis Gravidarum"[MeSH]	1.503
2.	"Morning Sickness"[MeSH]	1.639
3.	Nausea and Vomiting"[MeSH]	13.584
4.	1 OR 2 OR 3 ("Hyperemesis Gravidarum"[MeSH]) OR ("Morning Sickness"[MeSH]) OR ("Nausea and Vomiting"[MeSH])	1.640
5.	"Risk Factors"[MeSH]	715.971
6.	"Prognosis"[MeSH]	1.403.702
7.	5 OR 6 ("Risk Factors"[MeSH]) OR ("Prognosis"[MeSH])	1.982.445
8.	4 AND 7 {(("Hyperemesis Gravidarum"[MeSH]) OR ("Morning Sickness"[MeSH]) OR ("Nausea and Vomiting"[MeSH]))) AND (("Risk Factors"[MeSH]) OR ("Prognosis"[MeSH])}	296
9.	NOT animals	296

Appendix B. PRISMA flow diagram of literature search and selection process



Footnotes: The flow diagram template was adopted from the PRISMA statement.

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