GENETIC AND MATERNAL FACTORS IN HYPEREMESIS GRAVIDARUM: A SYSTEMATIC REVIEW

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Abstract

Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting during pregnancy (NVP), which can lead to extreme dehydration, significant weight loss, and electrolyte and metabolic imbalances. Importantly, early identification of HG symptoms can help to reduce its severity and prevent complications. Although HG is associated with many adverse maternal and fetal outcomes, there is limited understanding of the risk factors. This review provides current data on genetic and maternal factors that are linked to HG. All observational studies published in English that investigated the genetic or maternal factors associated with HG from 2011 until 2021 were systematically searched using the PubMed, Scopus, and ProQuest electronic databases. A total of 1462 citation titles was identified, of which 47 potentially relevant abstracts were screened. Of those, 15 studies met the inclusion and exclusion criteria. The genetic variants in the *ryanodine receptor 2* gene (*RYR2*), *growth differentiation factor-15* (*GDF15*), and *protein-coding insulin-like growth factor-binding protein 7* (*IGFBP7*) were found to be associated with HG. On the other hand, several potential maternal factors contributing to the onset of HG were age, *Helicobacter pylori* infection, body mass index (BMI) status, a history of HG in a previous pregnancy, carrying a female fetus, high serotonin levels, and reproductive factors. In view of the lack of strength of the overall evidence for risk factors related to HG, it is first imperative to establish a precise definition for HG in a diverse study population. Nevertheless, to conclude, this review was able to provide current data on genetic and maternal factors that are associated with HG.

Keywords: Hyperemesis Gravidarum, Nausea, Vomiting, Pregnancy, Risk Factors, Genetic

Introduction

The International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) describes HG as excessive and persistent vomiting that begins prior to the 22nd week of gestation. It can be clinically categorized as ranging from mild to severe, whereby severe HG interferes with several metabolic changes such as dehydration, electrolyte deficiencies or carbohydrate depletion (1). In other words, women may experience nausea and vomiting (NVP) during early pregnancy, however, HG represents severe episodes of NVP (2). HG affects approximately less than 3% of pregnant women but this varies according to different study populations and clinical diagnosis (2). Consequently, HG affects maternal physical and psychological well-being, and birth outcomes.

To date, the exact pathogenesis of HG has not been clearly explained. However, many studies have proposed that HG is likely to be multifactorial (2-4) and involves multiple potential etiologies. For example, the disturbance of endocrine hormone levels, genetic factors as well as gastrointestinal factors could be associated with HG (3). Additionally, placental disorders can lead to high levels of human chorionic gonadotrophin (hCG) which can trigger pregnancy nausea (5). It is essential to determine the genetic components that can contribute to this condition throughout pregnancy (6). Thus, in recent years, researchers have developed an interest in discovering the relation between genetic factors and HG by using whole-exome sequencing (WES) and genome-wide association studies (GWAS) to identify specific genes such as placental and appetite genes. Early recognition of pregnant women that have a higher risk of developing HG is necessary to reduce adverse outcomes through the implementation of proper management.

There is limited understanding of the previous evidence regarding genetic components and risk factors linked to HG. Furthermore, current research may have been conducted to identify potential genes and maternal factors. Therefore, this study aims to systematically review the data from existing studies on the genetic components and maternal risk factors that are associated with HG. In addition, the findings of this review may assist researchers who want to do further research about the pathophysiology, prediction, or prevention of HG in the future.

Methods

Search strategy for identification of related studies

In this review, relevant studies that reported on genetic components and maternal factors in HG were selected from three online medical databases, PubMed, Scopus, and ProQuest. For database searching, a combination of the keywords "pregnancy", "pregnant women", "pregnant woman", "gene", "genetic", "risk factor", and "hyperemesis gravidarum" were used to retrieve relevant studies. In addition, BOOLEAN operators such as AND and OR were used to specify the search results.

Inclusion and exclusion criteria

Selection criteria were determined to achieve the objective of this systematic review. Studies had to be published in English between 2011 and 2021, and available as full text. Only observational studies that investigated the genetic or potential maternal risk factors associated with HG were included, therefore any studies that described the level of NVP without mentioning HG were excluded, as NVP is a normal condition whereas HG is usually accompanied by other significant symptoms such as weight loss, dehydration, metabolic deficits, and electrolyte imbalances. Additionally, due to the lack of an international consensus regarding the definition of HG, this review included studies that described any definition or diagnostic criteria for HG. On the other hand, articles were excluded if they were not written in English, were published before 2011, or were case reports, animal studies, in vitro studies, review papers, hand-searched, grey literature, books, or dissertations.

Selection procedure

This review adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 Protocol Guideline (7). There are two phases that should be followed in PRISMA, identification and screening. Firstly, a comprehensive search was conducted by entering the appropriately designed keywords into the selected databases to identify relevant studies about genetic components and maternal factors in HG. The retrieved articles were filtered to remove any duplicated papers within the three databases. Then, the remaining articles were screened according to title and abstract, and full-text articles were assessed for eligibility. Any papers that did not fulfill the inclusion criteria of this review were excluded. After completing the identification and screening phase, the quality of each article was assessed, followed by data extraction.

Data extraction and quality assessment

Data extraction for the included studies was conducted by two authors independently, using Microsoft Excel version 2019. Any discrepancies observed between the data extracted were determined through discussion. The data extracted from the eligible studies included the first author's name, publication year, country, study design, study population, number of participants according to cases and control group, and the definition of HG. Furthermore, genetic and potential maternal factors that were relevant to the study were extracted as the main findings. The selected full-text articles were assessed for quality using the Crowe Critical Appraisal Tool (CCAT) version 4.1 following eight categories, which included title, abstract and text, introduction, study design, sampling, data collection, ethical matters, results, and discussion. The CCAT Form and User guide must be used together when calculating the score (8). Articles were graded based on the total score obtained which was then be converted into a percentage.

Results

Literature search

The literature search process is shown in the PRISMA diagram (Figure 1). The total number of articles acquired through database searching was 1462. Following the removal of duplicated publications within the three databases, 1245 articles were identified. 1137 articles were excluded by title screening. Then, the remaining 108 articles underwent abstract screening, in which 61 articles were excluded. Articles were excluded during the title and abstract screening if the data were unrelated or irrelevant to the objectives of this study. Of the 47 articles that qualified for full-text eligibility, 32 articles were removed as these articles did not meet the inclusion criteria and were not related to the study outcomes. As a result, 15 articles were included in this review.

Description of the included studies

The general characteristics of the studies included in this systematic review are summarized in Table 1. The included studies were published between 2011 and 2021 and were from various countries, Turkey (9-13), South Korea (14), United States (15-17), England (18), Iran (19), Norway (20, 15), Australia (15), and Finland (21). The majority of the included studies were of cohort and case-control study design. In terms of the study population, participants were from registered lists in hospitals (10, 11, 18-22), recruited from a National Health Screening (NHS) programme (14), websites (15-17, 23), volunteer pregnant women (9, 12, 13), and a survey (15). 12 studies categorized the participants into two groups, HG cases and a control group (9, 10, 12, 13, 15-22). One study compared the outcomes between the HG

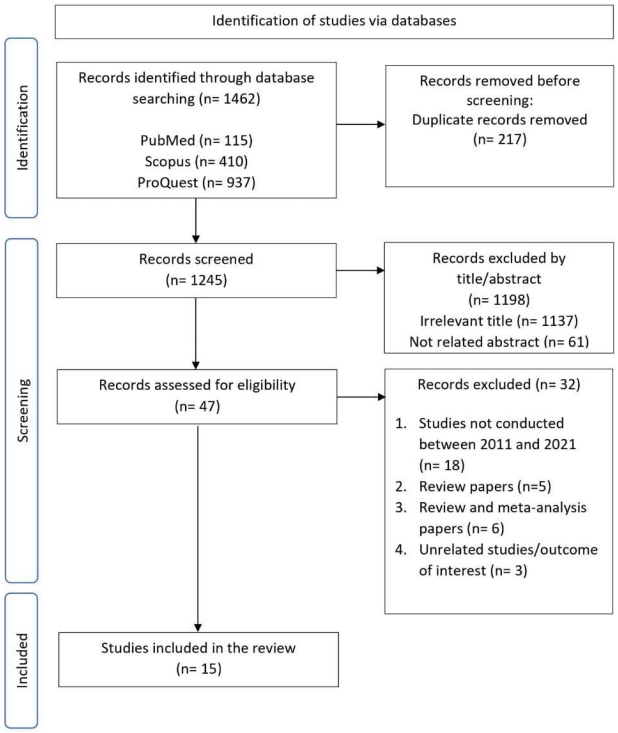

Figure 1: Prisma flow chart

group and two control groups, those with NVP and those without NVP (23), while another study focused only on HG cases and divided them into groups of those who required hospitalization and those who did not (14). Yet another study made a comparison between HG cases, those with morning sickness in pregnancy (MSP), and a control group (11). In addition, as a consensus on the definition of HG has not been established yet, this review included studies that addressed HG as NVP, regardless of how the different diagnoses of HG were defined. Participants for the HG study groups were chosen according to the criteria of ICD-10 diagnosis codes (21), or ICD-10 diagnosis requiring hospital admission (14, 18), while a further eight studies defined HG based on symptoms and clinical findings (9-13, 19, 20, 22). Another study characterized HG based on hospital admission (23), and three studies defined HG based on clinical diagnosis and IV fluid or parenteral treatment (15-17). Thus, it can be observed that different studies described different definitions or diagnoses for HG.

Quality assessment

All of the studies provided sufficient detail regarding the background of the study, objectives, outcomes, results, interpretation of results, and overall conclusion. Only moderate and high quality articles were included in this review.

Table 1: Characteristics of the included studies

Reference	Year	Country	Study design	Study population	No of participants		HG definition
					HG	Control	
Bezircioğlu et al. (9)	2011	Turkey	Prospective	Pregnant women between 10 and 14 weeks of gestation	36	36	Severe vomiting (> 4 times/day), ≥ 3kg weight loss and ketonuria
Güngören et al. (10)	2013	Turkey	Prospective-controlled	Hospital registration	90	50	Oral intake difficulties, vomiting (3 times/day), weight loss and ketonuria
Cengiz et al. (11)	2014	Turkey		Hospital registration	28	MSP:30 No NVP:29	Nausea and vomiting accompanied with > 5% weight loss, severe dehydration that might require hospitalization and ketonuria
Kosus et al. (12)	2016	Turkey	Case-control	Volunteered pregnant women	54	30	Persistent nausea and vomiting with > 5% weight loss and ketonuria
Aydin et al. (13)	2020	Turkey	Prospective-cohort study	Pregnant women from Turkish communities aged between 16 and 35 years old	24	24	Severe nausea and vomiting, ≥ 5% weight loss, electrolyte imbalance, ketonuria, and dehydration or hospital admission.

Table 1: Characteristics of the included studies (continued)

Reference	Year	Country	Study design	Study population	No of participants		HG definition
					HG	Control	
Kim et al. (14)	2020	South Korea	Cohort	All pregnancies that resulted in a delivery and were registered during national health screening	216373		Hospitalization for HG was described by using ICD-10 for primary or secondary diagnosis
Fejzo et al. (15)	2016	United States	Case-control	HER Foundation website	5 families:15	3	A HG diagnosis (i.e severe NVP, > 5% weight loss, hospital admission or daily routine disruption) and needing IV fluid/feeding tube treatment
		Norway		Norwegian Mother and Child Cohort Study (MoBa)	385	2280	
		Australia		Surveys	269	677	
Fejzo et al. (16)	2018	United States		23andMe research participants	1306	15756	A HG diagnosis and needing IV fluid treatment
				HER Foundation website	First cohort: 789 Second cohort: 110	First cohort: 606 Second cohort: 143	A HG diagnosis (i.e:weight loss, medication or hospital admission) and IV fluid/ total parenteral nutrition treatment
Fejzo et al. (17)	2018	United States		HER Foundation website	5 families:15	5	A HG diagnosis and needing IV fluid treatment
Fiaschi et al. (18)	2016	England	Population-based database cohort	National Health Service (NHS) hospitals	121885	8093653	Hospital admission based on ICD-10 code for primary diagnosis.
Kazemzadeh et al. (19)	2014	Iran	Case-control	Hospital registration	78	97	Vomiting (> 3 times/ day), > 3kg weight loss, ketonuria and PUQE score > 13
Vikanes et al. (20)	2013	Norway	Case-control	Immigrant pregnant women registered at hospital	62	108	Persistent nausea and vomiting, weight loss, and disturbance of electrolytes.
Nurmi et al. (21)	2020	Finland	Population-based database cohort	Healthcare registration	9315	428150	ICD-10 diagnosis codes
Akdemir and Akhin (22)	2011			Hospital registration	37	33	Frequent or recurrent vomiting which is more than three times a day, > 3 kg weight loss and ketonuria
Fejzo et al. (23)	2019			Clinical Gravidity Association Trial and Evaluation (CGATE) programme	11	NVP:20 No NVP:9	Hospital admission due to HG

Main findings of the included studies

Genetic factors of HG

As illustrated in Table 2, the findings from the included studies show that genetic variants in *RYR2* (15), *GDF15* (16, 17), and *IGFBP7* (16) have been found to have an association with HG. These included studies are the current research findings of the Hyperemesis Education and Research (HER) Foundation that aims to indicate whether there is a potential genetic component linked to HG development. First of all, Fejzo et al. (15) discovered *RYR2* gene expression in two of five families in the HG group of a United States study population using the WES method. The *RYR2* gene was found to be associated with the emesis pathway. Through genotyping, Fejzo et al. (15) identified the novel and rare variants of the *RYR2* gene among 15 affected individuals. The two confirmed variants in the *RYR2* gene were L3277R and G1886S located at exon 37. However, the L3277R variant could not be identified in the other HG affected group. While G1886S could be found in the HG group, surprisingly this variant could also be observed among women in the control group. Moreover, Fejzo et al. (15) also analysed the *RYR2* variants among Norwegian and Australian populations. They found two common variants of *RYR2* associated with HG. These two *RYR2* single-nucleotide polymorphisms (SNPs) were rs790899 and rs1891246. Besides, by using copy-number analysis, they also identified exon 16 deletion in *RYR2* in a pregnant woman who had experienced severe HG and required tube feeding treatment (15).

Moreover, Fejzo et al. (16) conducted two separate GWAS scans for loci associated with HG, and the findings were independently replicated in two larger cohort studies. This study revealed that two loci, which were chr19p13.11 and chr4q12, had the most significant association with HG ($p < 5 \times 10\text{-}8$). Interestingly, chr19p13.11 contained genes *GDF15* and *LRRC25*, and a high linkage disequilibrium (LD) was found between *GDF15* common missense variant (rs1058587) and the lead SNP rs45543339. LD refers to the non-random allelic association at different loci (24), therefore LD was used to study the correlation between an allele of one SNP with an allele of another SNP in a given population (25). Moreover, Fejzo et al. (16) also discovered that the *GDF15* receptor, which is GDNF-family receptor α-like (GFRAL), was linked with NVP. This finding established a remarkable association between the expression of *GDF15* and the pathogenesis of HG. Apart from that, the second finding of GWAS demonstrated that *IGFBP7* near the locus chr4q12 might be involved in NVP (16). The *GDF15* and *IGFBP7* genes are known to be linked to placenta development and play important roles in appetite regulation. Nevertheless, there was little evidence from this study to determine the relationship between *IGFBP7* gene expression and HG.

In addition, Fejzo et al. (17) examined whether *GDF15* gene expression could be involved in familial susceptibility and recurrent HG in a subsequent pregnancy. This study revealed that SNPs were associated with an elevated *GDF15* level among HG affected family members compared to unaffected family members. Besides, about 80% of the women in the HG group who carried the *GDF15* risk allele, rs16982345 had a higher probability of a subsequent pregnancy with HG symptoms (17). In their recent study, the serum protein levels of *GDF15*, *IGFBP7* and hCG were compared between women admitted to hospital for HG, women with normal NVP and women without NVP. The results showed a significant increase in serum *GDF15* and *IGFBP7* levels in women admitted to hospital for HG compared to women with NVP at 12 weeks of gestation ($p < 0.001$). In contrast, no significant association could be observed between serum *GDF15* and *IGFBP7* levels in HG cases compared to the control group at 24 weeks' gestation after HG symptoms gradually disappeared (23).

Maternal Factors Related to HG

Review findings from 11 studies showed that HG could be associated with many maternal risk factors. Details of the risk factors related to HG are presented in Table 3. There were five studies that assessed whether *H. pylori* infection might be involved in the development of HG (9, 10, 13, 19, 20), whilst three other studies were large population cohort studies which identified many statistically significant risk factors for HG (14, 18, 21). The remaining papers explored serum asymmetric dimethylarginine (ADMA) levels (22), serotonin levels (11), and maternal body fat composition (12).

Akdemir and Akhin (22) examined ADMA levels and reported that HG patients were more likely to have a higher level of ADMA compared to healthy pregnant women. This study suggested that an abnormal level of ADMA may disrupt the normal function of endothelial cells and eventually cause HG among pregnant women in early pregnancy.

Additionally, Cengiz et al. (11) carried out a study to investigate the relationship between plasma serotonin levels and HG. The results showed serotonin levels in pregnant women with HG were significantly higher in comparison to pregnant women with morning sickness in pregnancy (MSP) and control groups ($p = 0.001$).

One study was carried out to investigate the relationship between maternal body fat composition by measuring maternal visceral and subcutaneous fat tissue, and BMI status in pregnant women with HG and pregnant women without HG (12). The results showed that, in the HG group, the percentage of visceral adipose tissue (VAT) and pre-pregnancy BMI were significantly higher compared to the control group. In contrast, it can be observed that there was no significant difference in subcutaneous fat thickness (SCFT) between the HG and control group.

On the other hand, an *H. pylori* gram-negative bacterium infection could be a risk factor for HG in some women. Bezircioğlu et al. (9) evaluated the correlation between *H. pylori* infection and HG by measuring the *H. pylori* stool antigen (HpSA). About 22.2% of pregnant women with HG were found to have a markedly higher prevalence rate of

Table 2: Genes associated with HG

Genes	Location	Findings	Reference
RYR2		• Novel variant L3277R and rare variant G1886S • A significant association between common variants rs790899 and rs1891246 with HG and weight loss • Exon 16 deletion in RYR2 in woman with total parenteral nutrition treatment for HG	Fejzo et al. (15)
GDF15	chr19p13.11	• High LD of common missense variant in *GDF15* (rs1058587) and lead SNP rs45543339 (r^2= 0.98, *D'*=0.99) • Other variants that are linked to HG include *GDF15*(rs16982345, rs1054221) and GFRAL (rs7761177) • There is an association between GDF15-GFRAL and NVP	Fejzo et al. (16)
		• Variant rs16982345 was associated with higher risk of recurrence of HG • High *GDF15* expression among affected family members compared to unaffected family members	Fejzo et al. (17)
		• At 12 weeks of pregnancy, GDF15 serum levels were significantly increased in women affected by HG • At 24 weeks of pregnancy, there was no difference in GDF15 serum levels between women affected by HG and control group	Fejzo et al. (23)
IGFBP7	chr4q12	• Variants linked to HG are rs143409503 and rs4865234	Fejzo et al. (16)
		• At 12 weeks of pregnancy, IGFBP7 serum levels were significantly increased in women affected by HG • At 24 weeks of pregnancy, there was no difference in IGFBP7 serum levels between women affected by HG and control group	Fejzo et al. (23)

H. pylori infection compared to 2.8% in the control group. In terms of severity of HG symptoms, it was found that *H. pylori* did not cause any serious conditions in the HG group. Next, Güngören et al. (10) identified a positive relationship between *H. pylori* positivity and the severity of HG. Positive *H. pylori* IgM was found to be higher in 26.1% of women with severe HG while no positive *H. pylori* IgM was found in women with mild and moderate HG symptoms (10). Also, positive *H. pylori* IgG was found in 78.6% of the mild HG, 84.9% of the moderate HG, and 82.6% of the severe HG group. Only 4.2% of the mild HG group, and 8.3% of the moderate HG group had positive *H. pylori* polymerase chain reaction (PCR) DNA, while the highest rate could be observed in 87.5% of the severe HG group. Similarly, Kazemzadeh et al. (19) also investigated the relationship between *H. pylori* infection and pregnant women with HG. This study demonstrated that positive serum IgG levels were much greater in 65.4% of women with HG. In contrast, only 44.3% of control group had positive IgG levels. Also, the results indicated that the HG patients showed a significantly higher rate of infection with *H. pylori* (p = 0.05). The current study by Aydın et al. (13) which investigated *H. pylori* infection rates has added more evidence to support the role of *H. pylori* in the development of HG. The results showed a higher rate of detection of *H. pylori* infection in pregnant women with HG symptoms. Vikanes et al. (20) examined the role of infection with *H. pylori* among pregnant women by measuring IgG antibodies, vacuolating cytotoxin A (VacA), and cytotoxin-associated gene A product (CagA) in blood, and by HpSA test. Severe HG included HG patients that required hospitalization due to prolonged nausea and vomiting, loss of weight, rehydration, and parenteral nutrition. This study reported that *H. pylori* IgG, positive VacA, CagA, and HpSA were not significantly associated with either the severe HG or the control group. In other words, this study implied that there was no significant association between *H. pylori* infection and severe HG.

In addition, Kim et al. (14) evaluated pre-pregnancy risk factors for hospital admission caused by HG among women in South Korea who had undergone health screening assessment. Women admitted to hospital due to HG were slightly older, had an underweight pre-pregnancy BMI, were carrying a female infant, were primiparous, or had a multiple pregnancy compared to women with HG without hospitalization. Similarly, Fiaschi et al. (18) analysed risk factors in 8 215 538 pregnancies based on Hospital Episode Statistics. The results showed women admitted to hospital due to HG were slightly younger (< 30 years old), and were of low socioeconomic status. HG also has been associated with multiple pregnancies, carrying a female infant, women who have experienced HG during a previous pregnancy and pre-existing maternal health problems such as dysfunction of the parathyroid and thyroid, type I diabetes, and high levels of cholesterol (18). Ethnicity also may play a role in HG, whereby those of Asian or African ethnicity have an increased risk of recurrence (18).

Furthermore, Nurmi et al. (21) studied risk factors by making two comparisons. The first comparison found that pregnant women suffering from HG were more likely to be younger, underweight or overweight and with a higher gravidity than those without HG. The second comparison

between women with HG pregnancies and those with non-hyperemesis pregnancies showed that increased age and an obese BMI status were associated with the risk of developing HG. Also, both comparison groups found that carrying a female infant, multiple gestation and the use of assisted reproductive technology were reported to have an increased risk of HG.

Table 3: Maternal risk factors in the included studies

Risk factor	Findings	Reference
Serum ADMA levels	• The level of ADMA of 0.79 ± 0.39 µM in HG was higher than the 0.68±0.21 µM in control group (p = 0.001)	Akdemir & Akhin (22)
H. pylori	• 22.8% of HG group reported positive HpSA test while 2.8% of control group reported positive HpSA test • The association of positive HpSA test between HG and control group was statistically significant (p = 0.037) • *H. pylori* infection could be a risk factor for HG	Bezircioğlu et al. (9)
H. pylori	• Positive *H. pylori* IgG antibodies: - 78.6% in mild HG, 84.9% in moderate HG and 82.6% in severe HG, 60% in control group (p = 0.005) • Only 26.1% positive *H. pylori* IgM antibodies in severe HG (p = 0.001) • Positive *H. pylori* PCR DNA was: - 7.2% in mild HG, 3.8% in moderate HG and 91.3% in severe HG (p = 0.001) • Positive relationship between *H. pylori* infection and severity of HG symptoms	Güngören et al. (10)
H. pylori	• Positive IgG, negative VacA and CagA OR:1.26 (95% CI:0.57-2.82) • Positive IgG, positive VacA and CagA OR:0.82 (95% CI:0.40-1.68) • There was no significant difference between *H. pylori* IgG antibodies, CagA and VacA, and HG group	Vikanes et al. (20)
Plasma serotonin	The level of serotonin was markedly high in pregnant women with HG compared to MSP and control group (p = 0.001)	Cengiz et al. (11)
H. pylori	There was a significant difference between *H. pylori* IgG antibodies in HG and control group (p = 0.05)	Kazemzadeh et al. (19)
Maternal risk factors	Maternal age (20-24 years old 25.94%, 25-29 years old 30.55%), female baby, multiple pregnancies, nulliparous women, low socioeconomic status, ethnicity, HG history in previous pregnancy, and comorbidities	Fiaschi et al. (18)
Body fat composition which are visceral adipose tissue (VAT) and subcutaneous fat tissue (SCFT)	• The association of VAT measurement between HG and control group was statistically significant (p = 0.042) • The association of SCFT measurement between HG and control group was not statistically significant (p = 0.498)	Kosus et al. (12)
H. pylori	The HG rate for positive *H. pylori* test was significantly higher than negative *H. pylori* test in patients with HG (p < 0.001)	Aydin et al. (13)
Pre-pregnancy risk factors	Hospital admission for HG were due to pre-pregnancy underweight BMI status (AOR=1.16, 95% CI:1.03-1.31), lower waist circumference (AOR=1.01, 95% CI:1.00-1.02), primiparity (AOR=1.18, 95% CI:1.06-1.30), multiple pregnancies (AOR=2.43, 95% CI:2.00-2.95) and female baby (AOR=1.34, 95% CI:1.23-1.46)	Kim et al. (14)
Maternal, environmental and pregnancy-related factors	Younger maternal age (AOR=1.44, 95% CI: 1.38-1.52), BMI status (overweight: AOR=1.33, 95% CI:1.24-1.43) or (underweight: AOR=1.21, 95% CI:1.10-1.34), low socioeconomic status, pregnant with a female baby (AOR=1.20,95% CI:1.16-1.24), multiple gestation, higher gravidity (AOR: 2.04, 95% CI: 1.83-2.28)	Nurmi et al. (21)

Discussion

Genes related to HG

RYR2 is a calcium channel that is located mainly in cardiac tissue and is involved in the excitation-coupling of cardiac muscle by regulating the Ca^{2+} release (26). The function of the *RYR2* gene is to encode a ryanodine receptor in the sarcoplasmic reticulum of cardiac cells. It is known that *RYR2* has been widely associated with several diseases such as heart failure, arrhythmia and metabolic-related

problems (27). Interestingly, a recent study showed that *RYR2* was significantly associated with cyclic vomiting syndrome (CVS), which has similar symptoms to HG (28). CVS is sudden and frequent severe nausea and vomiting that often occurs in children. This study discovered that *RYR2* was the only gene that was commonly found in the sequencing of more than 1000 genes in the CVS group compared to the healthy control group (28). Further, Fejzo et al. (15) suggested that impaired thyroid normal function or mutant *RYR2* might stimulate nausea or vomiting symptoms and disrupt the normal signaling of *RYR2* Ca^{2+}, and this would lead to mild to severe NVP. Hence, *RYR2* is a potential gene to be investigated in relation to HG.

GDF15 is also known as macrophage inhibitory cytokine 1, non-steroidal drug-activated gene, prostate-derived factor (PDF), and placental bone morphogenetic protein (PLAB), which is also known as a member of the transforming growth factor-beta (TGF-β) superfamily (29). *GDF15* is predominantly expressed in the reproductive organs, which are the placenta and the prostate (29). Previous research has shown that *GDF15* is highly expressed in the trophoblast of the placenta (30) and high concentrations of *GDF15* have been found in amniotic fluid that is produced by amnion, chorion and decidua cells (31). In this review, *GDF15* has been found to be associated with HG through the identification of *GDF15* signaling with brainstem-restricted receptor (GFRAL) (16). GFRAL is known as a high affinity receptor for *GDF15* that originates from a distant member of the TGF-β family (32). The signaling of *GDF15* through the GFRAL receptor has recently been identified to stimulate the activation of the chemoreceptor trigger zone of the medulla, which leads to the anorexia eating disorder (33), and decreases body weight and food intake in mice (32, 34-36). Besides, a significant increase of *GDF15* levels has been observed among pregnant women affected by HG compared to the control group during the first trimester (23). *GDF15* becomes elevated in response to nutritional states, including over nutrition, like prolonged high-fat feeding or improper amino acid dietary intake (36), and undernutrition (37) in mice. This suggests that *GDF15* might be associated with other factors. Therefore, it can be implied that *GDF15* is likely to play a significant role in the development of HG among pregnant women.

Apart from that, the *IGFBP7* gene has been found to be associated with HG. *IGFBP7* is a protein coding gene to make IGFBP7 protein. *IGFBP7* protein belongs to the IGFBP family that is necessary for the regulation of insulin-like growth factors (IGF) in the human body (38). Previous findings have shown that *IGFBP7* is involved in the tumour progression of many types of cancer such as breast, gastric, prostate, hepatocellular carcinoma, colorectal, lung, oesophageal, melanoma, and glioma, in which *IGFBP7* can act as either a tumour suppressor gene or oncogene (38). In this review, the severity of NVP symptoms and pregnancy loss can be influenced by *IGFBP7* expression, and therefore indicates the presence of a genetic mechanism (16). It has been found that *IGFBP7* is involved in feeding regulation and metabolic status in *Drosophila sp.* brain (39). As HG can affect the food and nutrient intake needed for a healthy pregnancy, *IGFBP7* may interfere with the appetite regulation of pregnant women. This is because pregnant women with HG usually present with weight loss as a result of constant vomiting that can cause loss of appetite and lower calorie and nutrient intake (40). Nonetheless, there is a lack of evidence to explain the association between *IGFBP7* and HG during pregnancy. Hence, *IGFBP7* is an interesting candidate gene for investigation in the possible association between abnormal expression of *IGFBP7* among pregnant women with HG.

In short, the *GDF15* and *IGFBP7* genes are the ones most likely to increase the risk of HG during pregnancy as these genes may influence placentation and maternal appetite. Moreover, measurement of abnormal expression levels of both the *GDF15* and *IGFBP7* proteins can become a potential predictor to diagnose and predict HG (23). Hence, future studies can be done to determine and understand their role in the development of HG.

Maternal factors contributing to HG

In this review, three cohort studies did not reveal constant results regarding maternal age. Fiaschi et al. (18) and Nurmi et al. (21) found that young mothers aged 20 to 29 years old were more likely to have HG. Conversely, Kim et al. (14) found that increased age was associated with hospitalization due to HG. Other studies with a smaller sample size reported no association between age and the risk of developing HG. Hence, the possibility of experiencing HG during pregnancy might be associated with other factors.

Women with higher serotonin levels were noted to have HG. Abundant production of this hormone will trigger nausea and the vomiting response (11). Nonetheless, there is no available evidence which can explain further the relationship between serotonin and HG. One study noted that impaired endothelial function was involved in the pathogenesis of HG, which might be due to a number of causes such as the reduction of estradiol levels by ADMA (22). Thus, there is a need for further investigation of endothelial dysfunction and HG.

Focusing on pre-pregnancy BMI, it can be observed that there are conflicting results. Despite the results from two large population database studies which observed that BMI was associated with the occurrence of HG (14, 21), some studies with a smaller sample size reported no association between BMI and the risk of developing HG (9-11, 19, 22). Kim et al. (14) indicated that a lower pre-pregnancy BMI was associated with HG while Nurmi et al. (21) reported that both low and high BMI were associated with HG. Also, Kosus et al. (12) found that having ≥ 33mm of visceral fat and a higher BMI were significantly associated in pregnant women with HG. This is possibly due to the different dietary patterns of different population groups or lifestyle factors. Hence, a maternal pre-pregnancy BMI status of being either underweight or overweight and having a greater body

visceral fat distribution could be considered maternal risk factors for HG.

In addition, women presenting with HG are more likely to have a female than a male fetus (18, 21). These data are comparable with other studies. Likewise, two more recent studies reported a markedly higher rate of NVP symptoms, which can be explained by a high hCG concentration in women having a female fetus during pregnancy (41, 42). Although female fetal sex is classified as an uncontrollable risk factor, women can make early pre-pregnancy planning to reduce the severity of NVP symptoms.

Some studies reported that reproductive factors such as multiple pregnancies, gravidity, and parity were associated with the risk of HG. The findings of the selected studies showed conflicting results as Fiaschi et al. (18) reported a higher proportion of nulliparous women being admitted to hospital due to HG whereas Kim et al. (14) found that being a primiparous woman was associated with an increased risk of HG. Whilst, Nurmi et al. (21) found that higher gravidity was linked to an elevated risk of HG. In multiple pregnancies, multiple female fetal sex was associated with HG (14, 18, 21). If pregnant women had a history of HG in an earlier pregnancy, there was a higher risk of developing HG in a future pregnancy (18). Nevertheless, it can be suggested that inconsistent data might be due to different study populations.

In total, four papers determined that women with *H. pylori* infection had a higher risk of developing HG during their pregnancy (9, 10, 13, 19). In contrast, one study found no significant association between *H. pylori* infection and HG (20). A possible mechanism underlying the association between *H. pylori* and HG is that *H. pylori* is able to respond to pH changes and gastrointestinal motility in the stomach due to increased levels of hCG, estrogen, and progesterone (9). As a result, this favourable condition activates the infection. The prevalence rates of *H. pylori* differ according to study population. Hooi et al. (43) reported that approximately over 4 billion individuals are infected by *H. pylori* globally. Generally, higher prevalence rates can be observed in developing countries in comparison to developed countries (43). Risk factors for *H. pylori* are correlated to hygiene, food consumption, ethnicity, region, living in crowded areas, family members' infection status, and poor sanitation facilities. Consequently, the majority of studies have shown that *H. pylori* infection can be considered as a risk factor for HG.

Limitations

This systematic review has several limitations. Firstly, there is a limited number of relevant studies that discuss the genetic component related to HG. Moreover, most of the risk factors were investigated through small sample size studies, as a result the association of these factors and the incidence of HG was insufficiently explained. The lack of consistency in the findings has made probable comparisons between studies difficult due to the heterogenous definition of HG and differing methodologies. The heterogeneity of the definition of HG might have affected the characteristics of the case groups, which consequently contributed to the conflicting results.

Conclusion

In short, this systematic review has been able to provide available evidence regarding the genetic components and maternal factors of HG. However, the existing evidence is not sufficient to infer a firm relationship between these factors and the onset of HG. The findings showed three genes that are likely to play a role in HG, which are *RYR2*, *GDF15,* and *IGFBP7*. Apart from that, this review suggests that age, maternal body fat composition, body mass index status, a history of HG in a previous pregnancy, carrying a female fetus, impaired endothelial function, high serotonin levels, reproductive factors, and *H. pylori* infection can be considered as potential maternal risk factors for HG. Despite this, the relationship between maternal risk factors and HG is unclear as the included studies revealed conflicting results; only several studies suggested exposure to *H. pylori* and carrying a female fetus to be associated with an increased risk of HG during pregnancy. Further studies are necessary to address more evidence regarding the genetic variants and consistent risk factors linked to HG. Hence, it is imperative to establish a precise definition for HG in a diverse study population to achieve consistency and avoid conflicting results.

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Competing interest

The authors report no conflicts of interest.

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