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REVIEW

# Hyperemesis gravidarum: current perspectives

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**Abstract:** Hyperemesis gravidarum is a complex condition with a multifactorial etiology characterized by severe intractable nausea and vomiting. Despite a high prevalence, studies exploring underlying etiology and treatments are limited. We performed a literature review, focusing on articles published over the last 10 years, to examine current perspectives and recent developments in hyperemesis gravidarum.

**Keywords:** hyperemesis gravidarum, nausea, vomiting in pregnancy, pregnancy, antiemetics, adverse pregnancy outcomes

## Introduction

Up to 80% of all pregnant women experience some form of nausea and vomiting during their pregnancy.[1–3] The *International Statistical Classification of Disease and Related Health Problems, Tenth Revision*, defines hyperemesis gravidarum (HG) as persistent and excessive vomiting starting before the end of the 22nd week of gestation and further subdivides the condition into mild and severe, with severe being associated with metabolic disturbances such as carbohydrate depletion, dehydration, or electrolyte imbalance.[4] HG is a diagnosis of exclusion, characterized by prolonged and severe nausea and vomiting, dehydration, large ketonuria, and more than 5% body weight loss.[5,6] Affecting approximately 0.3%–2.0% of pregnancies, HG is the commonest indication for admission to hospital in the first half of pregnancy and is second only to preterm labor as a cause of hospitalization during pregnancy.[7–9]

According to the Hyperemesis Education and Research Foundation, conservative estimates indicate that HG can cost a minimum of $200 million annually in in-house hospitalizations in the United States.[10] Taking into account other factors such as emergency department treatments, potential complications of severe HG, and the fact that up to 35% of women with paid employment will lose time from work through nausea, the actual cost of HG to the economy is significantly higher.[3] In a related economic analysis, Piwko et al projected that the United States spends nearly $2 billion in costs attributed to pregnancy-related nausea and vomiting; 60% of this expenditure is a result of direct costs (eg, drugs, hospital admission), and 40% is a result of indirect costs (eg, time lost from work).[11]

To date, studies investigating the association between HG and adverse pregnancy outcomes and maternal morbidities have provided conflicting results.[9,12] In all aspects of research involving HG, the interpretation of results and associations must be with caution, as the majority of the studies have been limited by retrospective study

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design,[10,13–15] small numbers,[16] bias, lack of control for potential confounders, and variable definitions of HG.[15,17,18]

Thus, to examine current clinical perspectives of HG, we performed a review of MEDLINE (1994–January 2014), EMBASE (1994–January 2014), and the Cochrane Library. Articles related to "hyperemesis gravidarum" and/or "nausea and vomiting of pregnancy" were considered for inclusion in our review. Reference lists of selected articles were reviewed to identify additional articles. Although the review focused on articles published in the last 10 years, a second search with unrestricted time limits was performed to identify key papers related to HG that were also considered in the review.

## Risk factors for HG

HG is most likely a multifactorial condition and has been associated with many risk factors.[19] Women with HG are more likely to be younger, primiparous, persons of color, and less likely to drink alcohol.[20,21] Body mass index, smoking, and socioeconomic status do not appear to differ significantly between women with HG and those without.[21] Female infant sex has also been associated with HG.[8,22–25] Paternal genes are not thought to play a role in the occurrence of HG. In contrast, maternal intergenerational effects have been observed, with increased odds of HG among women whose mothers also experienced HG during a previous pregnancy (unadjusted odds ratio [OR], 3.2; 95% confidence interval [CI], 1.6–6.4).[26] Moreover, although recurrence rates are higher in women with HG, they are not 100%, indicating a multifactorial process rather than purely maternal genetics.[27,28]

In a small pilot study, D'Orazio et al examined personality characteristics between 15 women with HG and 15 matched women without HG and did not detect any differences in personality, psychological, or somatic variables.[29] Mullin et al examined risk factors in 395 women with prolonged HG. Women with prolonged HG were slightly younger and weighed more and had a history of allergies and a restrictive diet.[30] Of those women with HG with a significant weight loss (>15% of prepregnancy weight), HG tended to be more severe, with some symptoms, such as food aversion, continuing through the postpartum period.[14] Ethnicity may play a role, with one study in Germany demonstrating that immigrants were 4.5 times more likely to be treated for HG than native Germans. These women also scored higher on a somatization scale (Symptom Checklist-90-Revised), indicating a higher degree of "psychological distress".[31] Asian ethnicity has also been reported as a risk factor.[32]

One observational study demonstrated that women with HG were more likely to have higher levels of pregnancy-associated plasma protein A (PAPP-A) and free human chorionic gonadotropin (hCG) in the first trimester compared with controls.[34] Maternal serum concentrations of hCG peak during the first trimester, when HG symptoms are often at their worst.[35] Similarly, symptoms of HG are often more severe in multiple pregnancies and molar pregnancies, which are conditions associated with excessively high hCG levels. However, conflicting reports exist,[34–36] and therefore a causal association between HG and hCG has not been established.[36] Infection with *Helicobacter pylori* may play a role in the development of HG in some women. A meta-analysis examining *H. pylori* infection in women with HG reported a significant association (OR, 3.32; 95% CI, 2.25–4.90).[37] The meta-analysis was limited by significant heterogeneity among studies. Therefore, similar to hCG, a causal association between HG and *H. pylori* has not been established. Other factors implicated in the etiology of HG include estrogen,[38] stress, depression, and anxiety.[21]

## HG and adverse fetal pregnancy outcomes

HG has been reported to be associated with an increased risk for adverse pregnancy outcomes such as low birth weight, preterm birth, and small-for-gestational age infants.[10,13,25] A recent systematic review identified no association with Apgar scores, congenital anomalies, or perinatal death.[25]

Several additional studies were not included in the aforementioned review either because of inclusion criteria or because of publication after the review search period. McCarthy et al performed a prospective cohort study of 3,423 nulliparous women.[21] HG was defined as repeated vomiting in early pregnancy not resulting from other causes (eg, gastroenteritis) and requiring any of the following: inpatient admission, day stay with intravenous fluids, nasogastric feeding (at home or in hospital), or vomiting associated with loss of more than 5% of her booking weight. Women with hospitalized HG were considered as having severe HG. Secondary outcomes included spontaneous preterm birth, preeclampsia, birthweight, small-for-gestational age infants, and infant sex ratio. Women with severe HG had an increased risk of having a spontaneous preterm birth compared with women without HG (adjusted OR, 2.6; 95% CI, 1.2–5.7).[21] No significant associations were observed among other secondary outcomes.

Other studies have reported conflicting results. Vikanes et al conducted a retrospective cohort study and identified 814 women with HG during a 10-year period in Norway.[39] Relative to women without HG, no increased risk for adverse

pregnancy outcomes or low birthweight was observed among women with HG. Vandraas et al conducted a population-based cohort study of 2,270,363 births between 1967 and 2009, using the Norwegian Birth Registry.[40] They reported a decreased odds of very preterm birth (OR, 0.66; 95% CI, 0.5–0.9) and large-for-gestational-age infants (OR, 0.9: 95% CI, 0.8–0.9) among women diagnosed with HG. Hastoy et al reviewed obstetric outcomes in a small cohort of 197 women hospitalized for HG in a tertiary maternity hospital in France.[41] Similar to Vikanes et al,[39] no significant associations were observed between HG and adverse perinatal outcomes. However, in contrast, Hastoy et al did observe an increased risk for low birth weight (adjusted relative risk [RR], 1.7; 95% CI, 1.1–2.4).[41]

Fejzo et al performed a study involving 819 women from an HG Web site registry: 16% of babies were born prematurely, and 8% of the women reported infants born weighing less than 2,500 g.[14] Among women with extreme weight loss, 9.3% reported having a child with a behavioral disorder. As with other research in HG, the lack of a robust control group makes these results difficult to interpret. Still, similar results have been reported in women with extreme starvation, suggesting similar underlying pathological processes.[42]

There is a paucity of data examining the long-term effects of HG throughout childhood and into adulthood.[25] In a retrospective case-control study of 259 adults, psychological and behavioral disorders were more frequently reported among adults exposed to HG in utero (OR, 3.6; 95% CI, 1.9–6.9).[43] Notably, this risk estimate was based on a composite outcome of 17 different disorders because of small numbers for the majority of diagnoses under review (often $<5$ cases observed per individual disorder). Nonetheless, individual analyses of anxiety, depression, and bipolarism revealed no increased odds of anxiety; though in contrast, increased odds of depression and bipolarism were observed. Although other research has reported an increased risk for psychological disorders in adulthood, as well as reduced insulin sensitivity in prepubertal children,[44] prospective longitudinal investigations are warranted to better understand the underlying dynamics of these associations.[45]

## HG and adverse maternal outcomes

HG can be extremely debilitating for women and, if inadequately managed, can cause significant morbidities, including malnutrition and electrolyte imbalances, thrombosis, Wernicke's encephalopathy, depressive illness, and poor pregnancy outcomes such as prematurity and small-for-gestational-age fetuses.[13,46–49] Mullin et al showed that those with HG were more likely to suffer from hematemesis, dizziness, fainting, and antiemetic treatment.[30] Bolin et al observed that women with HG have an increased risk for placental disorders, such as placental abruption, and that this risk was particularly marked among women presenting with HG in the second trimester.[50]

Furthermore, after pregnancy, these women were more likely to develop posttraumatic stress disorder, motion sickness, and muscle weakness and to have infants with colic, irritability, and growth restriction.[30] Jørgensen et al[33] demonstrated that the risk for any autoimmune disorder was significantly increased in women with HG (RR, 1.41; 95% CI, 1.30–1.51). In its extreme forms, HG may cause malnutrition and end organ damage manifesting as oliguria and abnormal liver function tests. Reassuringly, permanent hepatic damage and associated death are rare in women with HG.[51]

In their large, prospective study on women with HG, McCarthy et al demonstrated that women with HG, particularly severe HG, were at increased risk for cognitive, behavioral, and emotional dysfunction in pregnancy.[21] Other studies have linked HG with an increased risk for depression, anxiety, and mental health difficulties,[52,53] and as a result, some advocate psychiatric evaluation.[54] One study reported women with HG meet criteria for anxiety and depression in 47% and 48% of cases, respectively.[12] Despite such associations, care must be taken not to stigmatize the condition of HG.

## Identification and treatment of HG

It is important to emphasize that early assessment of nausea and vomiting in pregnancy is essential to prevent delay in diagnosis and management of HG. Apart from HG, consideration should be given to other underlying complications associated with persistent vomiting, such as gastrointestinal conditions (eg, hepatitis, pancreatitis, or biliary tract disease), pyelonephritis, and metabolic disorders (eg, diabetic ketoacidosis, porphyria, or Addison's disease).[55] If such conditions are ruled out, adherence to obstetrical guidelines for the management of nausea and vomiting in pregnancy is encouraged,[55–58] although disconcertingly, this may not always be followed in practice.[59]

Notably, diagnostic biomarkers for HG have produced inconsistent results. A recent systematic review and meta-analysis found that although ketonuria is often assessed as part of a clinical examination, the robustness of ketonuria as a diagnostic marker for HG remains unclear.[60] Future investigations examining ketonuria levels in the diagnosis and severity of HG are warranted. Lymphocytes were typically

higher in women presenting with HG, although the association between HG and hCG and thyroid hormones, leptin, estradiol, progesterone, and white blood count were less reliable.[60] As previously discussed, *H. pylori* serology may be of diagnostic benefit.[60]

Treatment strategies for HG include inpatient and outpatient care involving intravenous fluids, antiemetics, and dietary advice. Care for women with HG centers around early intervention and support. A lack of support may prevent women from accessing timely and appropriate care.[61] A recently published systematic review involving 37 trials and 5,049 women investigated interventions for the treatment for HG. Interventions examined included acupressure, acustimulation, acupuncture, ginger, chamomile, lemon oil, mint oil, vitamin B6, and several antiemetic drugs. Again, the review was significantly limited by heterogeneity in study participants, interventions, comparison groups, and outcomes measured or reported. Acupuncture showed no significant benefit to women in pregnancy. Ginger may have some benefits, but the evidence was limited. Pharmacological agents including vitamin B6 and antiemetic drugs may help relieve mild or moderate nausea and vomiting.[62] Administration of promethazine and metoclopramide may yield comparable therapeutic effects.[63] Although research is limited, preemptive treatment with Diclectin (Duchesnay, Blainville, Québec, Canada) in women with a history of severe nausea and vomiting in pregnancy may decrease the onset of HG.[64] Overall, however, evidence is lacking as to which pharmacological agent is more effective and less dangerous to both mother and fetus.[62,65–68]

The management of HG is therefore based on correcting electrolyte imbalance and dehydration, prophylaxis against recognized complications, and providing symptomatic relief. Tan et al randomized women with HG to either treatment with 5% dextrose saline or normal saline for rehydration. Outcomes were resolution of ketonuria and the woman's well-being.[69] Short-term benefits (<24 hours) were observed in those treated with 5% dextrose, but these had dissipated by 24 hours. There is an understandable reluctance to prescribe antiemetics for symptomatic relief, but extensive data exist to show a lack of teratogenesis with dopamine antagonists, phenothiazines, and histamine H1 receptor blockers.[70–72] Although most women respond well to rehydration, if necessary, enteral tube feeding may be initiated to serve as either as a supplemental or primary source of nutrition.[73] Consideration may also be given to total parenteral nutrition, although increased risk for infectious complications is a potential concern.[73,74]

Day care has proven to be a beneficial and safe mode of care for women in other clinical settings.[75] Studies have demonstrated that day care management of women with nausea and vomiting during pregnancy appears acceptable and feasible,[76] but no systematic reviews or randomized controlled trials have been performed that examine the effects of introducing day care on rates of hospital admission, duration of inpatient stay, and patient satisfaction.

## Potential research topics and interventions

A randomized controlled trial comparing day patient and inpatient management has finished recruiting approximately 100 women and will soon publish its findings.[77] Further studies are needed that focus on safe alternative treatments, preventative measures in high-risk women, new biomarkers underlying the etiology of HG, and interventions that may reduce adverse pregnancy outcomes.

Further research is also required to determine whether the provision of emotional support for women with HG is beneficial. Although studies are limited in this area, in general, there is a demand for support for women suffering from nausea and vomiting in pregnancy.[51] As shown in a recent study evaluating a nausea and vomiting in pregnancy hotline in the United States, women primarily seek support in the management of the nausea and vomiting as well as understanding drug risks for the fetus.[78] Given that much of the information available on the Internet uses complicated language, there is a clear need to improve Web resources for HG; this may be a complementary strategy to providing support for women.[79] Any new interventions, however, must be shown to be safe from both a maternal and fetal point of view, to be acceptable to mothers, and to be cost-effective.

## Conclusion

Despite the prevalence and considerable morbidity associated with HG, good-quality research investigating the underlying etiology and interventions to treat and prevent HG remains scarce. Exploring new pharmacological interventions in pregnant women for the prevention and treatment of HG remains elusive, and this may be a result of avoiding inducing unnecessary risk for the developing fetus. Controversies such as that involving the administration of thalidomide to women with morning sickness, which subsequently resulted in significant congenital malformations, has likely discouraged researchers from investigating other interventions for HG.[80] As a result, the current mainstay of treatment remains regular hydration and antiemetics. Nonetheless, because of

the prevalence and morbidity associated with this condition, safe, well-conducted, good-quality research is needed to investigate and clarify the etiology, prevention, and treatment of this condition.

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