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Review Article

Beyond Morning Sickness: The Complexities of Hyperemesis Gravidarum

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Abstract

Mobility policies in public transport were guided by the distancing of people during the pandemic. However, its effect on users' risk perception was not fully established as a discussion axis in the research agenda. Therefore, the study aimed to address this gap by comparing the theoretical structure against the empirical structure analyzed in a systematic review. A cross-sectional and correlational work was carried out with a sample of experts who evaluated the prevalence of the categorical dimensions of risk perception in public transport mobility using the Delphi technique. The results confirm a second-order factor that makes the model extension essential to the state of the art where prevention is highlighted, with practical implications for public health and transport policy.

Keywords: confirmatory factor analysis; covid-19; transport mobility; risk perception; confinement and distancing policies

Introduction

Hyperemesis gravidarum (HG) is a severe and often debilitating form of nausea and vomiting that occurs during pregnancy, distinct from the more common and milder nausea and vomiting of pregnancy (NVP). While NVP affects up to 70% of pregnant individuals and is typically self-limited and manageable with conservative measures, HG occurs in a smaller subset—ranging from 0.3% to 10.8% of pregnancies depending on the population studied and diagnostic criteria used—but is far more intense in its clinical presentation and consequences [1,2]. HG is characterized by intractable nausea and persistent vomiting that leads to significant maternal morbidity, including weight loss exceeding 5% of pre-pregnancy body weight, electrolyte abnormalities, dehydration, and the presence of ketonuria or ketonemia [1]. While nausea and vomiting are common in pregnancy, hyperemesis gravidarum represents a serious medical condition requiring separate clinical attention. The significance of HG extends beyond physical health. The relentless symptoms often result in psychological distress, including anxiety, depression, and social isolation [3]. The profound fatigue and inability to maintain daily function can hinder an individual's quality of life during what is otherwise expected to be a joyful period. In more severe cases, the complications from prolonged vomiting—such as Wernicke's encephalopathy, malnutrition, and hospitalization—may escalate risks to both mother and fetus [4]. Given its profound impact on both physical and mental health, hyperemesis gravidarum requires prompt, comprehensive management to mitigate long-term consequences for maternal and fetal well-being. Despite its seriousness, the management of HG remains challenging. There is a lack of robust, evidence-based guidelines for its treatment, resulting in highly variable approaches that rely on physician preference or trial-and-error strategies. Many interventions, including pharmacologic agents, dietary changes, and supportive therapies, are used with inconsistent efficacy across clinical settings [2]. Compounding the issue, patients frequently report insufficient access to care, particularly in outpatient and community settings, as well as limited continuity of care among providers [5]. Additionally, a general lack of awareness and standardized education among healthcare professionals can delay diagnosis and effective management [6]. These ongoing challenges highlight the urgent need for standardized, evidence-based strategies to ensure timely and effective care for individuals affected by hyperemesis gravidarum. Given these challenges, this review aims to evaluate the current landscape of HG management by critically appraising existing treatment strategies—both pharmacologic and non-pharmacologic—and their efficacy and safety profiles. It also highlights the persistent gaps in research, with a focus on underserved populations disproportionately affected by poor access to care. Finally, we propose directions for future investigation to improve clinical outcomes and promote individualized, whole-person care in alignment with the osteopathic tenets of medicine.

Discussion

Pathophysiology and Etiology of HG

The etiology of hyperemesis gravidarum (HG) is multifactorial and remains incompletely defined; however, several converging lines of evidence suggest key contributions from hormonal, genetic, gastrointestinal microbiota, and psychosocial factors. Understanding these biological and environmental interactions is critical for identifying effective and individualized treatment strategies.

2.1 Hormonal Influences

Human chorionic gonadotropin (hCG) has the most consistent association with HG. Serum hCG levels typically peak between 9- and 12-weeks' gestation, which aligns temporally with the period of most severe symptomatology in HG patients [1]. Clinical correlations show a higher incidence of HG in pregnancies characterized by elevated hCG levels, including twin gestations, hydatidiform mole, and Down syndrome pregnancies—conditions in which hCG concentrations may be two to three times higher than in singleton pregnancies [1]. Mechanistically, hCG may act centrally on the area postrema of the medulla, a chemoreceptor trigger zone that regulates vomiting. A related mechanism involves thyroid-stimulating hormone (TSH) receptor cross-reactivity. Due to their structural similarity, hCG can weakly bind and activate TSH receptors, leading to transient gestational thyrotoxicosis. Up to 66% of HG patients exhibit suppressed TSH levels with elevated free T4 in early pregnancy [7], contributing to heightened sympathetic activity, tachycardia, and nausea. Estrogen and progesterone, two hormones significantly elevated in early pregnancy, further exacerbate gastrointestinal symptoms. Estrogen has been shown to increase sensitivity to hCG receptors, while both hormones delay gastric emptying and reduce lower esophageal sphincter (LES) tone, resulting in increased gastric distention, gastroesophageal reflux, and prolonged nausea and vomiting [2]. Progesterone also impairs gastrointestinal motility by directly inhibiting smooth muscle contractility.

2.2 Genetic Predisposition

Epidemiological data support a strong heritable component to HG. A 2011 Norwegian cohort study involving over 2.3 million pregnancies found that women with a first-degree relative (mother or sister) who experienced HG were threefold more likely to develop the condition themselves [6]. This familial aggregation points toward underlying genetic susceptibility. In 2018, a genome-wide association study (GWAS) identified two genes, GDF15 (Growth Differentiation Factor 15) and IGFBP7 (Insulin-like Growth Factor Binding Protein 7), that were significantly associated with HG [4]. GDF15, a stress-induced cytokine secreted by the placenta and the gastrointestinal tract, is known to act on the hindbrain to regulate nausea and feeding behavior. IGFBP7, involved in placental implantation and inflammation, may synergize with GDF15 to amplify emetic signaling. These genes are highly expressed in trophoblastic tissue, which aligns with the early gestational timing of HG symptoms. The identification of these genes provides potential biomarkers for early detection.

2.3 Gut Microbiome Dysbiosis

The gut-brain axis, an intricate communication pathway involving neural, hormonal, and immunological signals between the gastrointestinal tract and the central nervous system, is increasingly implicated in HG pathogenesis. A 2020 case-control study found tha women with HG had significantly reduced microbial diversity and lower abundance of beneficial commensals such as Lactobacillus and Bifidobacterium compared to controls [8]. This dysbiosis may lead to a pro-inflammatory intestinal environment, delayed gastric emptying, and heightened activation of the vagal afferent system, which relays signals from the GI tract to brainstem emetic centers. These findings suggest that the microbiome could serve as both a biomarker and therapeutic target in HG.

2.4 Psychological and Environmental Factors

While psychological stress does not independently cause HG, it can significantly exacerbate symptoms and influence the duration of illness. Women with HG have been shown to have higher rates of anxiety and depression than those experiencing typical NVP [3]. This bidirectional relationship suggests that severe vomiting may contribute to mental health decline, while existing mood disorders may reduce coping mechanisms and increase perceived symptom burden. Furthermore, qualitative studies have reported that women with HG frequently experience post-traumatic stress symptoms due to the extreme physical and emotional toll of the condition, often compounded by lack of social support or medical validation [5]. Perceived dismissal by healthcare providers and disrupted daily functioning contribute to a cycle of helplessness and medical mistrust, which may delay escalation of care.

Pharmacological Treatment Options

3.1 Antiemetics

Pharmacologic treatments for hyperemesis gravidarum (HG) include antiemetics, corticosteroids, and antihistamines. Common antiemetics include ondansetron, metoclopramide, and promethazine. Ondansetron (Zofran) is a selective 5-HT3 serotonin receptor antagonist often used off-label to treat nausea and vomiting in pregnancy. It works both centrally on the brainstem's chemoreceptor trigger zone and peripherally on the vagus nerve terminals, both of which play roles in nausea and vomiting [9]. While ondansetron was previously classified as a "Pregnancy Category B" drug (indicating animal testing showed no fetal risk), there is no adequate research on its use in pregnant women. The American College of Obstetrics and Gynecology (ACOG) guidelines recommend pyridoxine (vitamin B6) with or without doxylamine as the first-line treatment, and ondansetron may be considered for refractory cases, though it is associated with a potential risk of cleft palate if used in the first trimester [10]. Electrolyte and ECG monitoring are advised for patients with risk factors for arrhythmia [9]. Given the potential risks, it is important for healthcare providers to carefully weigh the benefits and risks of ondansetron use in pregnancy and monitor patients accordingly.

Metoclopramide (Reglan) is a dopamine receptor antagonist approved to treat nausea and vomiting in patients with GERD or diabetic gastroparesis by increasing gastric motility [11]. It is also used off-label for hyperemesis gravidarum (HG). Metoclopramide antagonizes central and peripheral dopamine-two receptors (D2) in the medullary chemoreceptor trigger zone in the area postrema, preventing nausea and vomiting triggered by most stimuli [11]. Due to a lack of research on its effects in pregnant women, metoclopramide should be used cautiously and monitored closely in this population. Like ondansetron, ACOG guidelines recommend metoclopramide only in refractory cases of nausea and vomiting during pregnancy, with the dosage being 5 to 10 mg, every 6 to 8 hours, orally or intramuscularly, in patients who are adequately hydrated [11]. Healthcare providers must also weigh the risks and benefits of using metoclopramide in pregnant patients. Promethazine (Phenergan) is a medication commonly used for the treatment of allergic conditions, nausea and vomiting, motion sickness, and used for sedation. As a phenothiazine derivative, promethazine posessess antidopaminergic, antihistamine, and anticholinergic properties, working as a direct antagonist at both the mesolimbic dopamine receptors and alpha-adrenergic receptors in the brain [12]. It acts as an H1-receptor blocker for its antihistamine effects. Promethazine is used off-label for nausea and vomiting during pregnancy (NVP). According to ACOG, promethazine can be useful in treating NVP and HG when the first-line treatments fail to deliver symptomatic relief [12]. Although it has potential use in refractory cases, the safety profile of promethazine must be carefully considered due to the higher incidence of adverse effects in some patients. A previous double-blind randomized control trial (RCT) comparing intravenous promethazine and metoclopramide in women with HG found similar efficacy between the between the two drugs in controlling nausea and vomiting at 24 hours, but stated increased adverse effects in the promethazine group, including dry mouth, dizziness, drowsiness, and dystonia [12]. Following the trend, all of the risks and benefits of using these antiemetics in pregnant patients must be considered.

3.2 Corticosteroids

Corticosteroids are used in the treatment of HG in refractory cases. Corticosteroids, such as prednisolone, work by binding to the glucocorticoid receptor, promoting anti-inflammatory effects and blocking pro-inflammatory signals. In the literature, the possible beneficial effects of using prednisolone for HG is mentioned, but there is limited data supporting this claim available [13]. Therefore, Asmat et. al conducted an RCT in Lahore, Pakistan, to compare the outcome of prednisolone with placebo in pregnant women presenting with HG during the first trimester of pregnancy. This RCT showed that prednisolone is effective for treating HG in women in their first

trimester of pregnancy, as it reduces the frequency of episodes and severity of episodes of vomiting [13]. As this study was conducted in Asia, there is a need for further studies within different populations.

3.3 Diclegis - the Doxylamine-Pyridoxine Combination

As previously mentioned, ACOG recommends pyridoxine (vitamin B-6) with or without doxylamine as first-line treatment for nausea and vomiting during pregnancy (NVP). The doxylamine-pyridoxine combination, known as Diclegis, is the only FDA-approved prescription medication specifically for NVP and HG. Doxylamine, a first generation H1 receptor antagonist, is commonly used to treat allergies and insomnia and is sold over-the-counter [14]. Antihistamines typically block histamine activity at the H1 receptor and directly influence the vestibular system, thereby reducing stimulation of the vomiting center. Pyridoxine is a water-soluble vitamin, which is essential for the metabolism of proteins, carbohydrates, and fats. The mechanism by which vitamin B6 carries out its antiemetic effects remains unclear.

3.4 Future Directions for Pharmacologic Therapy

Currently, emerging pharmacological studies for HG emphasize GDF15, a hormone that acts on the brainstem and primarily originates from the fetus and placenta during pregnancy [15]. This study found that the severity of NVP is influenced by maternal sensitivity of GDF15, which may be affected by prior exposure to the hormone. Future therapies may involve inhibiting GDF15 signaling to treat HG, including the development of antibodies or other agents to antagonize activity of GDF15. Fejzo et al. (2024) also suggest that pre pregnancy interventions, including safely increasing GDF15 levels before pregnancy with metformin, may reduce the risk of developing HG or decrease the severity of symptoms.

Non-Pharmacological Treatments

4.1 Dietary Modifications

Non-pharmacological treatments for HG broadly include dietary modifications, IV hydration, enteral nutrition, and other adjunctive therapies. The most common initial dietary advice is to consume small, frequent meals that are high in protein and low in fat. Protein has been shown to help with nausea more than carbohydrates or fats. It stabilizes gastric rhythms and reduces gastric dysrhythmias that are often associated with nausea and vomiting during pregnancy [16]. Fat on the other hand can worsen nausea because it is harder to digest. Eating small meals every 1-2 hours helps prevent an empty stomach which can trigger nausea by maintaining steady blood sugar levels. Although dietary advice is a commonly used management tool, there is a lack of evidence and trial-based research. A randomized control trial in 2023 found that adding watermelon to the diet after hospital discharge for HG improves body weight, HG symptoms, appetite, and overall, wellbeing and satisfaction [17]. Dietary modifications are not only important in intervening currently diagnosed women, but also before the pregnancy in determining the risk of developing HG. A subproject of the Norwegian Mother and Child Cohort Study with 107,000 pregnancies found that consumption of fish, seafood, allium vegetable groups, and moderate amounts of water were associated with a reduced risk of hyperemesis. Another dietary modification can be implementing ginger in the treatment of pregnancy induced nausea and vomiting. Several studies have found ginger to be as effective as vitamin B6 in relieving the severity of nausea and vomiting episodes [18]. However, more observational studies with a larger sample size are required to reproduce and confirm its effectiveness.

4.2 Hydration

Hydration can be used to manage severe dehydration in HG patients. In comparison to oral rehydration therapy, IV hydration remains first line therapy in the early inpatient treatment [19]. Common indications for IV fluid administration in HG are persistent vomiting despite antiemetic medical therapy, 5% or more weight loss of prepregnancy weight, and severe dehydration with the presence of significant fluid loss signs. According to the RCOG guideline, the most appropriate rehydration regime is normal saline while avoiding dextrose containing IV fluids for initial fluid replacement due to increased risk of Wernicke encephalopathy and worsening hypokalemia.

4.3 Enteral Nutrition

Enteral nutrition can be considered in patients with refractory cases of HG in the setting of persistent ketonuria, prerenal AKI, altered mental status, or continued electrolyte abnormalities in which maternal weight is not maintained [20]. Because of no standardized criteria for inpatient admission of patients for treatment of HG, many patients make frequent visits to the emergency department or obstetric care clinic with considerable complications. There are multiple ways to deliver enteral nutrition, such as nasogastric and nasojejunal tubes, and percutaneous endoscopy. This feeding process eliminates the associated risk of sepsis due to mucosal degradation and bacterial translocation when the gut is deprived of enteral feeding [21]. Starting with a nasogastric tube not only provides nutritional support, but may even provide antiemetic support by bypassing the cephalic phase of digestion. However, long-term use of an NG tube can be poorly tolerated by patients and cause chronic sinusitis or become clogged. Percutaneous placement of tubes can be considered in patients requiring prolonged (more than 4-6 weeks) enteral nutrition or unable to tolerate NG tubes. However, they do carry additional risks for infection and tube displacement. Parenteral nutrition can be considered if there are contraindications to enteral nutrition or if it is unsuccessful. Both peripherally and centrally inserted catheters can be used in place of enteral nutrition, however they are associated with complications that can be life threatening [22]. Overall, enteral and parenteral nutrition is well tolerated in HG pregnant patients, and can be used in long term support.

4.4 Acupressure and Acupuncture

Other adjunctive therapies offered in management of HG that include acupuncture and/or acupressure. The use of a low risk acupressure band at the Neiguan point P6 (pericardium 6) during inpatient treatment can offer relief from severe nausea and vomiting [23]. A systematic review and meta-analysis by Haizhen Lu et al., (2021) found that acupuncture leads to a shortened hospitalization time and lower pregnancy termination rate with fewer adverse events [24]. Effectiveness of both acupressure and acupuncture remains to be challenging due to a lack of robust research without underlying publication biases.

Gaps in Research

There are many gaps in research in the field of HG, such as a lack of standardization in treatment guidelines, limited understanding of long-term outcomes, especially in those with comorbid conditions, and resulting health disparities from insufficient validated research.The lack of standardized protocols has led to many inconsistencies in the clinical and surgical approaches to HG, which often results in delayed escalation of care. There is a wide variation in first-line treatment with some providers starting with pyridoxine/doxylamine while others use ondansetron. The route of administration also varies depending on preference or availability. A lack of severity in grading tools has also made it challenging to standardize care for patients. Although tools like PUQE (Pregnancy-Unique Quantification of Emesis) exist, they are often underutilized, which contributes to uncertain assessments of symptom severity and treatment requirements. Without concrete criteria across settings, patients can go untreated in early stages, which leads to preventable weight loss, malnutrition, or hospitalization. Despite being one of the most severe conditions affecting early pregnancy, HG remains understudied in terms of long-term impact of maternal and fetal outcomes. Of all aspects of maternal health, mental health is possibly the least studied. Those with HG have higher rates of postpartum depression, anxiety, and PTSD-like symptoms, even after HG symptom resolution [25]. The psychological burden of HG outcomes can impact existing conditions, and is underappreciated in longitudinal follow-up studies. Persistent nutritional deficiencies and GI sensitivity can prolong recovery, particularly in cases requiring prolonged parenteral or enteral feeding. Fetal and childhood outcomes are also poorly understood in pregnancies with HG. Emerging data suggest associations between HG and low birth weight, preterm delivery, and small for gestational age (SGA) infants, however findings are inconsistent [26]. Other novel research suggests that children

exposed to HG in utero are associated with neurodevelopmental, cognitive, and neurological deficits. These findings underscore the importance of monitoring and supporting both maternal health during pregnancy and child development in cases of HG.

Patients with HG are often suffering from multiple coexisting conditions that require additional attention when creating a management plan. Variability in symptom severity and unpredictability in treatment response demands for a patient-centered, individualized approach. The most common comorbidities seen in patients with HG are thyroid dysfunction, GI disorders, and nutritional deficiencies, which can complicate diagnosis and treatment. Many women have transient hyperthyroidism that is hCG-mediated that resolves spontaneously in most cases, however can worsen GI symptoms. GERD is often exacerbated by frequent vomiting while gastroparesis may worsen nausea. Resultant thiamine, iron, and B12 deficiencies can increase the risk of Wernickie's encephalopathy in prolonged vomiting and inadequate supplementation. As stated before, the compromised physical health can impact the psychological wellbeing of the patient which increases the risk of developing additional psychiatric conditions. Many pregnant patients have difficulty falling and/or staying asleep leading to anxiety and insomnia; Mirtazapine can be considered in theory for such cases; however, it should be evaluated on a case-by-case basis due to limited pregnancy-specific data. These conditions highlight the significance of developing a tailored patient care plan for those with HG.

HG being under-researched and underfunded contributes to the health disparities that disproportionately impact marginalized populations. Minority populations, particularly Black, Hispanic, Indigenous, and immigrant patients are underrepresented in clinical studies on HG, thus we know little about how it manifests and is best managed across different racial and ethnic groups. There is also a profound gap in understanding how race, gender identity, socioeconomic status, and mental health conditions intersect in the context of HG. Such a narrow landscape can create diagnostic bias, leading to delayed recognition and inadequate treatment. Addressing these gaps through inclusive research, equitable healthcare policies, and culturally competent care is essential to improving outcomes for all individuals affected by HG.

Treatment Guidelines

The management of hyperemesis gravidarum (HG) remains highly variable across clinical settings due to the lack of a universally accepted, standardized protocol. Instead, most guidance is drawn from expert consensus and observational data, supplemented by a limited number of randomized controlled trials. The most widely cited clinical practice guidelines include those from the American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynaecologists (RCOG), and the Society for Maternal-Fetal Medicine (SMFM).

ACOG Practice Bulletin No. 189 (2018)

ACOG identifies doxylamine-pyridoxine (Diclegis) as the first-line pharmacologic therapy for nausea and vomiting of pregnancy (NVP) and mild forms of HG [10]. This combination has Level A evidence based on randomized trials demonstrating safety and efficacy in reducing symptom severity without increased risk to fetal development [10]. If symptoms persist, second-line therapies such as ondansetron, metoclopramide, and promethazine are recommended, though the safety of ondansetron during the first trimester remains debated due to possible associations with orofacial clefts and cardiac defects [27]. Corticosteroids, such as methylprednisolone, are reserved for refractory HG unresponsive to antiemetics. ACOG recommends their use after 10 weeks' gestation due to possible teratogenic risks during organogenesis. Corticosteroids have Level B evidence and are effective in rapidly reducing emesis but carry potential risks including cleft palate and gestational diabetes [28].

RCOG Green-top Guideline No. 69 (2016)

The RCOG provides more detailed guidance for inpatient management of HG. It recommends intravenous (IV) fluid therapy with normal saline as the preferred rehydration strategy. Dextrose-containing fluids should be avoided initially due to the risk of Wernicke's encephalopathy in thiamine-deficient patients and potential worsening of hypokalemia [29]. This represents Level C evidence, based on case reports and physiological principles. Enteral nutrition, particularly via nasogastric (NG) or nasojejunal (NJ) tubes, is suggested when oral intake fails to meet nutritional needs and weight loss or electrolyte abnormalities persist. Tube feeding may alleviate symptoms by bypassing gastric distention and improving metabolic status [30]. Parenteral nutrition is discouraged due to its high complication risk.

SMFM Consult Series (2018)

SMFM echoes many of ACOG's pharmacologic recommendations and emphasizes early escalation of therapy in cases of refractory vomiting. They also underscore the importance of shared decision-making and individualized care, particularly in women with comorbid conditions such as thyrotoxicosis or anxiety/depression, where treatment approaches may need to be modified.

Adjunctive Therapies

Both ACOG and Cochrane reviews recognize the potential role of low-risk adjunctive therapies, such as acupressure at the P6 (Neiguan) point, which may reduce nausea through modulation of vagal pathways and central neurotransmitter release. This has Level B evidence based on small randomized controlled trials [31].

Summary of Recommendations

Below is a summarized table of selected treatments with corresponding recommendations, governing bodies, evidence levels, and sources:

Treatment Modality	Recommendation	Governing Body	Evidence Level	PubMed Link
Doxylamine-Pyridoxine (Diclegis)	First-line for NVP and mild HG	ACOG	Level A	PMID: 27054920
Ondansetron	Second-line; use with caution in first trimester	ACOG / SMFM	Level B	PMID: 29985511
IV Hydration (Normal Saline)	First-line for moderate/severe dehydration	RCOG	Level C	PMID: 38358264
Avoid Dextrose in Initial IV Fluids	Prevent Wernicke's encephalopathy	RCOG	Level C	PMID: 33721035
Corticosteroids (Methylprednisolone)	For refractory HG	ACOG	Level B	PMID: 22832477
Enteral Feeding (NG/NJ tube)	Refractory cases with malnutrition or electrolyte imbalance	RCOG / SMFM	Level C	PMID: 25581215

Acupressure (P6 point)	Considered low-risk adjunctive therapy	Cochrane Review	Level B	PMID: 28418209

This structured approach highlights the heterogeneity in current practice, the lack of large-scale comparative trials, and the reliance on expert opinion for many commonly used treatments. It also emphasizes the need for early escalation of care and a patient-centered framework, particularly for underserved populations disproportionately affected by access barriers.

Future Directions

The development of targeted therapies could significantly improve the quality of life and care for those diagnosed with Hyperemesis Gravidarum (HG). Precision medicine involves the investigation of genetic markers or specific pathways associated with HG in order to develop treatments tailored to individual patients. In 2018, the first genome-wide association study (GWAS) on nausea and vomiting during pregnancy (NVP) and hyperemesis gravidarum (HG), was completed, revealing that the placenta and the appetite hormone gene GDF15 is a genetic risk factor [33]. This discovery is crucial for the future treatment and management of HG, as it may provide insights into the molecular pathogenesis of the disorder. Further research is needed, as Turco et al. (2018) published an organoid model for placental development [34]. Their method of culturing trophoblast organoids, reflecting the physiological cellular orientation in the placenta, can help better understand the genetic associations with placental biology. By combining genetic research with innovative models like the trophoblast organoid, future therapies could be more precisely developed to target specific genetic factors and pathways implicated in HG, offering a more personalized treatment approach.Further research should also focus on the role of hormones in pregnancy, such as hCG, estrogen, and progesterone, which are implicated in HG. Rising hormone levels seem to play a role in HG, as hCG peaks around 10 weeks of pregnancy, coinciding with the time that pregnant women typically report the worst HG symptoms. The development of drugs that balance these hormone effects could result in improved management and treatment of HG. Studies have identified inflammatory markers in HG, including C-reactive protein (CRP), vaspin, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [35]. Future therapies targeting these inflammatory pathways may help reduce the debilitating symptoms of HG.

Additionally, improved diagnostic tools could revolutionize HG management. Developing reliable biomarkers, such as proteins or microRNAs, to diagnose HG early and assess its severity could guide treatment, leading to better outcomes. Identification of these biomarkers in urine, blood, or even saliva could help differentiate HG from other causes of NVP. Once established, a scoring system incorporating biomarkers, symptoms, and patient-reported outcomes could help predict the course and severity of the disease, informing individualized care plans.

The integration of patient perspectives into future research of HG could prove highly valuable, as there are limited studies which have explored the experiences of patients with this condition. One such study reported that women described HG as “one of their worst experiences, with profound morbidity and severe psychosocial consequences” [36]. Developing patient-centered outcome measures to assess the impact of HG on quality of life, encompassing physical, emotional, and social well-being, will direct treatment decisions and support more tailored management approaches. In the same study, half the women reported feeling that their healthcare professionals had no knowledge about the condition [36]. Not only can these patient perspectives inform individualized treatment methods, but they can also direct educational approaches for residencies and other training programs to better train healthcare professionals in diagnosing and managing HG. Incorporating these patient perspectives, along with improved diagnostic tools, will help shape a comprehensive approach to HG care.

Healthcare professionals are not the only ones with limited knowledge about HG; patients may also struggle to tell the difference between NVP and HG. To address this, increased patient education highlighting the severity of HG is essential to ensure patients recognize when they should seek medical help. Additionally, creating support groups, whether online or in-person, can provide women with a valuable outlet to share experiences, access information on current research and treatment, and receive emotional support. The integration of these support groups can also improve their pregnancy experiences overall. Given the psychological toll HG can have on patients, it is crucial for healthcare providers to acknowledge and address this aspect of care. Incorporating mental health support into treatment plans can significantly benefit those affected by HG. Providing information about resources like cognitive-behavioral therapy (CBT) for coping strategies and mental health support for patients dealing with anxiety, depression, or PTSD related to HG could greatly improve their mental well-being and overall outlook.

Larger, more diverse clinical trials are needed to assess the effectiveness of different treatments across varied populations. These trials should include pregnant women of different ethnicities, with varying comorbidities and pregnancy complications. Increasing the size of these trials could also elucidate the safety profile of current and experimental treatments. Long-term outcomes research is critical to assess the lasting effects of HG on both maternal and fetal health, as well as its impact on future pregnancies. Systematic reviews suggest that maternal HG is associated with slight increases in adverse outcomes among children, including neurodevelopmental disorders, mental health disorders, and possibly testicular cancer [37] However, the researchers state that this evidence is found from only a few lower quality studies. Continued research with higher quality studies will improve understanding of the long-term impact of HG treatments. Going forward, developing evidence-based guidelines and treatment protocols for managing that can be applied across various healthcare settings is crucial. Currently, the lack of standardized treatment guidelines contributes to inconsistencies in clinical approaches. To optimize these protocols, it is essential to integrate interdisciplinary teams, including obstetricians, gastroenterologists, dietitians, psychologists, and therapists, to address and manage the physical and psychological effects of HG. This collaborative care framework will ensure all aspects of HG are comprehensively managed.

Conclusion

Hyperemesis gravidarum (HG) remains a complex and challenging condition that substantially affects the quality of life of pregnant individuals. Despite its severe symptoms and potential bad outcomes, HG management lacks standardized, evidence-based treatment guidelines, resulting in varied trial-and-error approaches across clinical settings. Current pharmacological and

non-pharmacological treatments show promise for treating HG, but their efficacy and safety profiles are inconsistent across research studies. Further research is necessary to optimize treatment and better develop personalized treatment plans for patients. Important areas for future research include the development of targeted therapies, personalized treatment plans, and improved diagnostic markers to diagnose early and better treat symptoms. In addition, bridging the gaps in research, especially those associated with the long-term outcomes on both maternal and fetal health, as well as the underrepresentation of underserved populations, will be vital in guaranteeing fair and effective care for all patients with HG. By incorporating genetic, hormonal, and environmental factors into treatment with a greater focus on mental health and patient centered care, we can strive for better outcomes for HG patients and their families.

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