

REVIEW ARTICLE

Obstetrics

The impact and management of hyperemesis gravidarum: Current and future perspectives

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Abstract

Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting in pregnancy affecting around 1%–3% of pregnancies worldwide and is the most common reason for hospital admission in early pregnancy. HG can have lasting consequences for both pregnant individuals and their offspring. Current best-practice management includes symptomatic treatment with anti-emetic pharmacological treatment, rehydration if needed, and psychological support. There is a lack of high-quality evidence on treatment for HG. Future research should focus on understanding the cause, developing effective treatment, and so limiting the burden of disease on patients and healthcare systems.

KEYWORDS

hyperemesis gravidarum, nausea and vomiting of pregnancy, pregnancy disorder

1 | INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is considered a normal symptom of pregnancy. Hyperemesis gravidarum (HG), in contrast to normal NVP, is a rare and debilitating disorder of pregnancy, defined by the Windsor definition as nausea and vomiting, at least one of which is severe, starting in early pregnancy (before 16 weeks gestational age), and which causes an inability to eat and/or drink normally and strongly limits daily living activities.¹ HG has important antenatal and postnatal consequences, some of which are long-lasting, for both parent and child.² Currently, evidence

on treatment options is limited: the Cochrane review, including all trials on HG treatment, included just 2045 participants, of whom 931 had been enrolled in pharmacological trials,³ and the included studies were of low methodological quality. Treatment is, at present, aimed at symptom reduction, but emerging knowledge on the etiological pathways can open new avenues of management. Better recognition and treatment of HG have the potential to amend HG's detrimental effects on maternal, perinatal, and long-term outcomes.

The aim of this narrative review is to highlight what is currently known of HG and provide an overview of consequences of the

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disease and best-practice management, highlight current research, and inform future research.

2 | EPIDEMIOLOGY

While up to 90% of pregnant people worldwide experience NVP, HG is estimated to affect around 1%–3% of pregnancies.^{4,5} Geographically, HG seems to be more prevalent in western countries.⁶ A history of HG is the single largest risk factor for (recurrent) HG.⁷ Recurrence rate estimates range from 15% from registry studies to 89% from cohort studies.^{7,8} Positive family history for HG, multiple pregnancy, primiparity, female fetal sex, younger maternal age, and over- or underweight are each associated with an increased risk of HG.^{9–12} Recent research has shown that Growth Differentiation Factor 15 (GDF-15) is implicated in the pathogenesis of NVP and HG, with feto-placental production of GDF-15 and maternal sensitivity both contributing to the risk of HG.¹³

3 | CONSEQUENCES OF HG

3.1 | Maternal consequences

As described in the Windsor definition of HG, individuals with HG are often unable to tolerate oral fluids and food.¹ HG is associated with insufficient caloric intake and nutrient deficiencies and maternal weight loss, or lack of maternal weight gain.^{14,15} Vitamin deficiencies can have severe consequences for mother and fetus. Thiamine rapidly depletes in people with HG, due to low intake caused by poor dietary intake and increased metabolic demand in pregnancy.¹⁶ Thiamine deficiency can lead to Wernicke's encephalopathy (WE),¹⁷ and ultimately Korsakov, and is associated with a very high rate of fetal demise. Thiamine supplementation, which is critical in preventing WE in HG, is unfortunately not universally provided, as is evident from the steady publication of case reports of HG-associated WE in the literature.^{17–20} In rare cases, HG can lead to vitamin K deficiency, which causes maternal coagulopathy-related hemorrhage, embryopathy, or neonatal intracranial hemorrhage.²¹ Women with at least one admission for HG have an increased risk of venous thromboembolism antepartum, at delivery, and postpartum which can be fatal.^{2,22}

Due to severely restricted fluid intake and/or excessive vomiting, HG often leads to dehydration and electrolyte imbalances, including hyponatremia, hypochloremia, and hypokalemia.²³ In rare cases, HG patients can develop severe consequences such as acute kidney injury secondary to hypovolemia and arrhythmia-related cardiac arrest secondary to severe hypokalemia.²² Treatment with intravenous dextrose can precipitate severe hypokalemia in those with existing mild hypokalemia, as well as bringing on acute WE. Furthermore, secondary to extended periods of severely restricted food intake, individuals with HG who are rapidly reintroduced to nutrition are susceptible to refeeding syndrome, a condition of

electrolyte imbalances, including hypophosphatemia, hypokalemia, and hypomagnesemia.^{24–26}

Individuals with HG have a slightly increased risk of severe complications during pregnancy, including placental abruption and pre-eclampsia, particularly if HG persists into the second trimester, as well as venous thromboembolism antenatally.^{2,22,27}

Studies have shown that HG adversely impacts concurrent, as well as future, mental health.²⁸ However, the notion that HG is psychogenic in its origins, while unsubstantiated, is pervasive and can have detrimental effects on outcomes^{29–31}: an uncaring attitude or unawareness of the severity of the symptoms among their health-care providers is associated with increased psychiatric burden and emotional distress among those with HG,^{32–34} as well as delays in appropriate treatment as outlined earlier. In general, those affected by HG report increased rates of depression, anxiety, and post-traumatic stress disorder (PTSD),^{28,35} and those with higher nausea and vomiting scores have higher rates of negative mental health outcomes during and up to 4.5 years after pregnancy. Depression and anxiety symptoms and PTSD can outlast the pregnancy period.³⁵ Many individuals with HG experience suicidal ideation while they are suffering from HG.^{36,37} Termination of planned and wanted pregnancies is not uncommon, as are postponing or curtailing future pregnancies.³⁶ Not being offered adequate treatment and negative attitudes from their caregiver are potential influencing factors for considering termination.^{38,39}

3.2 | Offspring consequences

A systematic review, including 61 studies, found that HG was associated with low birth weight, preterm birth, and neonatal intensive care unit admission, or need for neonatal resuscitation.⁴⁰ By contrast, HG was associated with reductions in macrosomia and reductions in stillbirth.⁴⁰

The consequences of HG for offspring are not limited to the direct perinatal period. A systematic review and meta-analysis including 1814785 offspring reported the long-term health outcomes of children born to mothers with HG.⁴¹ HG was associated with anxiety disorder and sleep problems in offspring.⁴¹ The extent of the impact of HG on long-term fetal health is still unclear; nor is it clear what impact HG treatment may have on improving offspring health.

These findings align with wider research, which found that effects of exposure in utero to maternal malnutrition due to famine leads to a wide range of unfavorable outcomes later in life, including an increased risk of cardiovascular events, obesity, psychiatric outcomes, and cancer.^{42–47}

3.3 | Societal consequences

In addition to physical and psychological suffering, HG presents an economic and societal burden. The National Health Service (NHS) in the UK estimates an annual cost of up to £62 million due to

NVP-related healthcare, including hospital admissions, general practice visits, and ambulance call-outs.⁴⁸ Studies have shown that costs increase with the severity of NVP.⁴⁹ Besides healthcare utilization costs, work absenteeism is not uncommon among individuals with HG.⁵⁰ Specifically, hospital admissions lead to increased costs and longer sick leave. Day care management of NVP is less costly and equivalent in effectiveness to inpatient management.⁵¹ Therefore, improved or more effective treatments hold a sizeable societal and economic benefit, besides the medical advantages.

4 | BEST-PRACTICE MANAGEMENT

4.1 | Diagnosis

Hyperemesis gravidarum is a clinical diagnosis. The lack of a laboratory test to aid diagnosis, in combination with the fact that nausea and vomiting is so common in pregnancy, contributes to the clinical challenge of differentiating normal NVP from HG. The Windsor definition for HG highlights the most important characteristics of the disease and was partly created to assist in consistency in clinical diagnosis.¹ The Pregnancy Unique Quantification of Emesis 24 h (PUQE-24) score is a short and easy-to-use validated scoring tool to quantify NVP severity and is most commonly used in clinical and research settings to track symptom improvements following treatment.⁵² Recently, a promising new tool containing 12 questions, called the HyperEmesis Level Prediction (HELP) score, has been developed to measure NVP severity; however, further validation is needed to determine its role in HG care.⁵³

4.2 | Medical treatment

Treatment of HG is mainly aimed at symptom reduction to prevent dehydration and malnutrition. In 2018, a Cochrane review of treatments of HG, including 25 trials involving 2052 participants, of whom only 931 patients were involved in pharmacological trials, showed a lack of high-quality evidence for HG treatments.³ The lack of high-quality evidence was mainly due to the small sample size of individual studies and comparisons.³ The little available evidence applied different diagnosis definitions and measured a broad range of outcomes, hampering aggregation of data.

In cases of threatening dehydration, rehydration therapy should be started. Various rehydration regimens have proved to be effective, with outpatient day-case management often being chosen.⁵⁴⁻⁵⁷ In areas where there are services available to provide intravenous (IV) treatment at home, these services may be utilized for IV rehydration at home for HG patients, as it has been associated with high patient satisfaction in a pilot study.⁵⁸ Clear criteria need to be established for who is eligible for at-home rehydration treatment and what treatment regimen is most appropriate.

According to the 2024 Royal College of Obstetricians and Gynecologists (RCOG) guideline, the most appropriate rehydration

regime for HG patients is normal saline.⁴⁸ Additional potassium chloride in each bag is recommended by the RCOG and is often pragmatically chosen based on a daily need of 60mmol. A frequently used regimen is 3L of 0.9% NaCl with 20mmol of potassium chloride administered IV over the course of 4h.⁵⁷ The use of dextrose infusions as fluid replacement could be an acceptable form of partial parental nutrition, as long as electrolytes are carefully monitored before and after infusion to prohibit the risk of dextrose solutions exacerbating hypokalemia, triggering refeeding syndrome, or triggering WE in thiamine-deficient states.^{48,59} As hypovolemic HG patients can be hyponatremic, hypochloremic, and hypokalemic, monitoring of electrolytes is recommended during rehydration treatment in such cases. Renal function monitoring should also be considered in severe cases of HG as acute kidney failure induced by HG has been described.⁶⁰ Furthermore, in cases of severe hypokalemia, ECG analysis should be considered to rule out arrhythmia.²²

Antiemetic treatment is the current cornerstone of treatment of HG (Table 1), although many drugs are not registered for use in pregnancy and data on effectiveness and safety are limited. First-line antiemetic treatment for HG consists of antihistamines or phenothiazines, so-called H1 receptor antagonists, as their safety profiles are well established during the first trimester of pregnancy.⁶¹ These medications have not been demonstrated to be effective in people with HG.^{3,48} However, another first-line antiemetic, the delayed-release combination of doxylamine and pyridoxine (vitamin B6) has shown an improvement in PUQE score when compared with placebo in the treatment of mild-to-moderate NVP.⁶²⁻⁶⁴ Delayed-release doxylamine and pyridoxine is the only licensed treatment of NVP and the RCOG guideline recommends it as a first-line option.^{48,62}

Metoclopramide and ondansetron are considered second-line antiemetic treatments for HG.⁴⁸ Metoclopramide is considered safe and effective; however, due to a risk of extrapyramidal effects, a prescription should be provided with information on the potential side effects, and treatment should be discontinued if such side effects arise.³ Ondansetron should be considered as a second-line treatment. One study found a slightly increased risk of orofacial

TABLE 1 Antiemetics used in the treatment of hyperemesis gravidarum (HG).

First-line antiemetics	<ul style="list-style-type: none"> • Doxylamine-pyridoxine (10 mg doxylamine +10mg pyridoxine every 6h) • Cyclizine (50 mg every 8h) • Promethazine (25 mg every 8h) • Dimenhydrinate (25-50mg every 6h)
Second-line antiemetics	<ul style="list-style-type: none"> • Metoclopramide (10 mg every 8h) • Ondansetron (4 mg every 8h)
If conventional treatment is ineffective	<ul style="list-style-type: none"> • Corticosteroids (intravenous hydrocortisone 100 mg every 12 h, methylprednisolone 125 mg; as soon as there is clinical improvement, switch to oral prednisolone, tapering schedule 40 mg (day 1), 20 mg (days 2-3), 10 mg (days 4-6), 5 mg (days 7-14))

clefting in babies born to individuals using ondansetron during the first trimester.⁶⁵ However, due to extremely low absolute incidence (14 per 10000 pregnancies compared with 11.4 per 10000 pregnancies) some guidelines, including the RCOG guideline, state that use should not be discouraged if first-line antiemetics are insufficiently effective.^{48,65} Individuals should be informed of potential side effects, which should be weighed against the risks of poorly managed HG (including termination of pregnancy), and healthcare professionals should not avoid ondansetron as a second- or third-line treatment in the first trimester.

If symptoms cannot be adequately contained with (combination) antiemetic treatment, corticosteroids should be considered.⁴⁸ Corticosteroids may reduce the frequency of vomiting and need for readmission.^{3,66} Due to well-known side effects of corticosteroids, which include their effect on immune, metabolic, and adrenal function as well as fetal growth, this therapy is reserved for cases in which other antiemetics have not provided sufficient relief.⁴⁸ Individuals using corticosteroids should have their blood pressure monitored and should be screened for gestational diabetes mellitus.⁴⁸ Fetal growth monitoring should be considered in cases with prolonged use.

Combination of drugs should be used in individuals who have not responded to single antiemetic treatment.⁴⁸ Despite the fact that there is an absolute dearth of studies comparing multi-drug combination antiemetic treatment in HG, synergism of antiemetics from different classes has been the established best practice in other conditions, including postoperative nausea and vomiting or chemotherapy-induced nausea and vomiting.^{67,68} It is also important to consider the route of administration of drugs for people with HG, as oral medication is often poorly tolerated due to frequent vomiting. For individuals with HG, antiemetic formulations, including buccal melts, transdermal patches, and rectal administrations, should be considered, if possible. In severe cases, parenteral or intramuscular route of administration may be necessary.⁴⁸

People with HG have insufficient nutritional intake.^{14,15,69} Dietetic consultation may be helpful in expanding food choices, prescribing oral nutritional support, monitoring nutritional deficiencies, and optimizing intake.^{70,71} If rehydration therapy and antiemetics do not reduce nausea and vomiting to normalize nutritional intake, parenteral or enteral nutrition supplementation should be considered.⁴⁸ Results on the efficacy of tube feeding vary, with the result that there are no defined criteria for starting parenteral or enteral tube feeding. A retrospective cohort in Norway found that enteral nutrition provided for patients with insufficient rehydration and partial parenteral supplementation was associated with adequate maternal and favorable pregnancy outcomes.⁷² Contrarily, a trial investigating tube feeding started on the first day of admission in addition to standard care did not find an improvement in birth weight or secondary outcomes.⁷³ Both the RCOG and American College of Obstetricians and Gynecologists recommend enteral tube feeding to provide nutritional support in those with HG who do not respond to antiemetic therapy.^{74,75} Parenteral nutrition may be applicable to individuals with a long

course of HG and significant weight loss, but should only be used as a last resort in those in whom enteral tube feeding is not possible due to the associated risk of complications.⁷⁰

4.3 | Hospital admission and discharge

Hyperemesis gravidarum is the most common cause of hospital admission in early pregnancy.^{50,76,77} Per country, the care for individuals with HG may be organized in different ways. In general, mild cases of NVP can be cared for with single-agent transient antiemetic treatment, oral hydration, sick days from work, and dietary counseling. More extensive care is appropriate when primary care measures have failed or if symptoms include dehydration and inability to tolerate food or fluids. Secondary care should be considered in the following cases of nausea and vomiting with:

1. Clinical dehydration or weight loss (greater than 5% of body weight), despite single agent or combination first line antiemetics.
2. Electrolyte imbalances.
3. Confirmed or suspected comorbidity in which HG symptoms hamper intake of medications (e.g., urinary tract infection and inability to tolerate oral antibiotics).
4. Comorbidities such as epilepsy, HIV, type 1 diabetes, or psychiatric disease in which HG symptoms hamper timely intake and uptake of necessary medications

Hospital admission consists of rehydration therapy and review of antiemetic treatment, and can often be completed as a day-admission or in an outpatient setting. If individuals are admitted to the hospital with prolonged vomiting and/or reduced intake and/or weight loss, high single-dose parenteral thiamine supplementation should be administered in order to prevent WE and refeeding syndrome.^{17,48} Ketones have unjustly been considered a measure of dehydration and thus been used to inform necessity for hospital admission. However, ketonuria is not associated with HG disease severity and should not be used to diagnose HG, or determine admission indication or length of hospitalization.⁷⁸

Among those admitted for HG, the chance of readmission is high, between 28% and 60%,^{7,79} which should be discussed with patients and accommodated for in care pathways. Antiemetic treatment will need to be continued after discharge.^{80,81} People with symptoms persisting in the second and third trimesters should be offered serial scans to monitor fetal growth, as babies born to mothers with persistent HG and/or low weight gain have an increased risk low birth weight.⁴⁰

4.4 | Psychological support

The care for HG should include offering professional psychological care.⁸² Healthcare professionals should assess people's mental health during pregnancy and refer to psychological support

if necessary.⁴⁸ Clinical assessment should be performed if there is suspicion of depression, anxiety, postnatal depression, and/or PTSD. Information from patient support groups, such as Pregnancy Sickness Support in the UK or the HER foundation in the USA, should be provided to individuals and their partners.⁸³⁻⁸⁵ As many as 25.5% of individuals with HG suffer from occasional suicidal ideation,³⁶ thus suicidal ideation should specifically be assessed by healthcare providers when assessing mental health status of individuals with HG. As HG poses an increased risk of depression, anxiety, and PTSD as long as 4.5 years after pregnancy with HG,³⁵ consideration should be given to follow-up psychological care of individuals with HG beyond pregnancy. Pregnancy sickness-specific counseling may be appropriate in people with HG.⁸⁶ As many as 10% of people with HG will terminate a wanted pregnancy due to their condition.^{37,39} The full range of therapeutic options should be offered to an HG patient before deciding that termination of pregnancy is the only option.³⁸ Few data are available on the best way to organize psychological care for people with HG.

4.5 | Multidisciplinary care

Care for individuals with HG ideally is based on a holistic approach with a multidisciplinary team. A study has shown that involvement of a mental health professional in the care team of a person with HG resulted in an improvement in quality of life and coping with the impact of pregnancy.⁸⁷ Emotional support and psychological and psychiatric care should be available to persons with HG if requested or required. Dietitians should be consulted to monitor their intake and give nutritional advice, including supplementations via various routes if indicated. If complications arise, designated subspecialties should be consulted.

5 | HIGHLIGHTS OF CURRENT RESEARCH AND FUTURE AREAS OF INTEREST

While the HG field of research has been expanding in recent years, evidence on best-practice management of HG is still scarce. As the prioritized list of HG research questions shows, the causes of HG, more effective treatments, and the impact of HG on mothers and babies are considered pivotal areas of future research.⁸⁸

The pathophysiology of HG was always considered multifactorial, although little was known about the mechanisms involved. In recent years, however, emerging evidence has demonstrated that variants in the GDF-15 gene, a gene coding for the hormone that causes nausea and vomiting, and its receptor GFRAL-RET are associated with HG.¹³ GDF-15 in pregnant persons is derived from trophoblast production of GDF-15. Higher GDF-15 levels in maternal blood are associated with an increased risk of vomiting.¹³ Conversely, in the non-pregnant state, higher levels of circulating GDF-15 were associated with a lower risk of developing NVP or HG, establishing the hypothesis that maternal sensitivity

to GDF-15 levels is influenced significantly by prior exposure to the hormone before pregnancy.¹³ New insights into the etiology can be harnessed to provide the base for new treatment options such as GDF-15 receptor antagonists, or treatments targeting a preconception increase in GDF-15 levels,⁸⁹ although given the delicate timing of HG during embryonic development and organogenesis, safety aspects of any novel treatments need to be rigorously investigated and balanced against efficacy and side effects. Pre-emptive intervention may significantly impact the incidence, severity, and duration of HG pregnancies. Currently, NGM pharmaceuticals is completing a phase 2 trial testing NGM120, a GFRAL antagonist antibody, to see if it is safe and effective for treating HG, which could be the first medical treatment using the knowledge of GDF-15 for the basis of new treatment.⁹⁰

Furthermore, studies highlighting the consequences of HG are bringing light to the scale of such sequelae. A recent prospective study from the UK aimed to quantify the extent of nutritional deficiencies in HG.¹⁴ This study found that intake of energy, carbohydrates, protein, fat, fiber, calcium, iron, zinc, thiamine, riboflavin, folate, and vitamin C were all significantly lower in people with severe NVP in their first trimester of pregnancy.¹⁴ The effects of nutritional deficiencies in the first trimester on fetal health have been studied in other cohorts, such as the Dutch famine cohorts.⁴² Undernutrition during the early gestational period is an established contributor to chronic noncommunicable disease in adulthood, suggesting that HG may cause similar effects.⁴² Clinicians should be aware that people with HG are deficient in many nutrients, and proactive supplementation of at minimum folate and thiamine should be considered. Nutritional intake should be optimized with the help of a dietician. The optimal management for nutritional deficiencies in people with HG should be better studied, as well as postpartum nutritional status recovery and breastfeeding nutritional content following a pregnancy with HG.

Not only have consequences of HG been noted, but consequences of suboptimal management of the disease have also been described. A large retrospective cohort study from Denmark found that only 50% of people with HG received any antiemetic treatment pre-hospitalization for the disease.⁸¹ The 2013 European Medical Agency (EMA) warning on metoclopramide, limiting its use to 5 days, further decreased the percentage of people receiving antiemetic treatment pre-hospitalization.⁸¹ After the EMA restriction on duration of metoclopramide usage was issued, a decrease in gestational age at first hospitalization and an indication of increased rate of termination of pregnancy among individuals with HG was observed.⁸¹ This suggests that suboptimal management of people with HG can lead to earlier hospitalization during pregnancy as well as a potential increase in termination of pregnancy. Optimal management of HG, including optimal timing of treatment, is vital in minimizing consequences of HG. A similar caution on the use of ondansetron, warning against its use in the first trimester, based on a small increased risk of orofacial clefting, was issued by the EMA in 2019.⁹¹ Whether the 2019 EMA

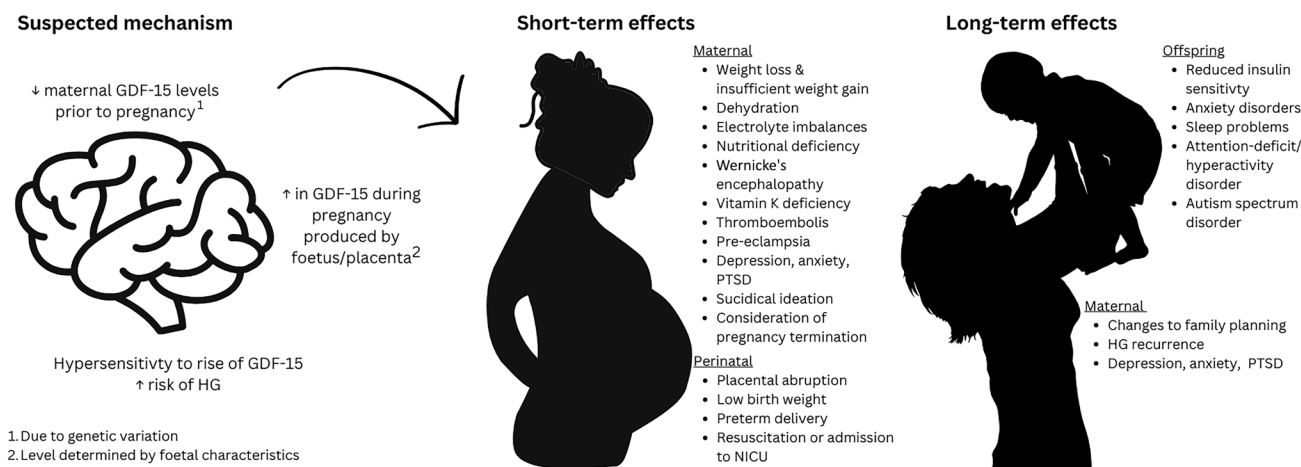


FIGURE 1 Suspected mechanism of hyperemesis gravidarum (HG) and associated adverse maternal and offspring effects. NICU, neonatal intensive care unit; PTSD, post-traumatic stress disorder.

warnings on ondansetron mimic the effects of the 2013 EMA warnings on metoclopramide is the subject of ongoing studies.

In order to better answer the research priorities for HG, steps have been taken to standardize research in this field. First, the Windsor definition for HG was published in order to assist in clinical diagnosis and homogenize the definition of HG in study populations to enable the possibility for meta-analysis.¹ Next, an international consensus was achieved on a core outcome set for trials on HG.⁹² This core outcome set contains a list of 24 outcomes in 10 domains that will help to standardize outcome reporting in HG research, furthering the opportunity for meta-analyses and therefore providing more robust evidence on the effectiveness of treatment options for HG.⁹² A core measurement set, a list of instruments recommended to measure core outcomes, is also in development. Improving outcome reporting in the field of HG will provide more robust evidence to answer the questions still facing the field today.

There is a lack of international guidelines for the treatment of HG. Some countries lack a national guideline. By standardizing care for persons with HG and exchanging information between countries on optimal care through an international guideline, we can increase the quality of care.⁹³ The most appropriate combination of medical treatment should be further investigated with consideration for efficacy and adverse effects. Individuals with HG should be offered medical treatment based on robust evidence in the future. Furthermore, how to best organize care for people with HG is an important factor to consider. Evaluation of the feasibility and patient satisfaction with home or community-based care should be further investigated. Medical care for individuals with HG often ends once symptoms subside or once delivery has taken place. With the potential for long-term effects, there should be some follow-up available to people with HG. This follow-up should include help with family planning in case this is desired, and psychological follow-up given that 20% of HG patients are left with PTSD postpartum. Lastly, due to the high recurrence rate of HG

preconception, counseling should be offered to those wanting to get pregnant after a previous HG pregnancy.

6 | CONCLUSION

Hyperemesis gravidarum is a severe condition of pregnancy and should not be left untreated. HG has a high burden on individuals, their offspring, and the healthcare system. Antiemetics are the cornerstone for treatment (Table 1). Future research should be aimed at providing robust evidence regarding effective treatment for HG. Current research has started to answer questions surrounding the etiology and effects of HG. Perhaps with this knowledge, future treatments can aim at specific biological targets in order to limit maternal and offspring consequences of HG (Figure 1).

AUTHOR CONTRIBUTIONS

LvdM, CD, and RCP conceived the project. LvdM drafted and revised the manuscript. All authors made substantial contributions to the design of the work and revision of the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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