

Diagnosis and treatment of hyperemesis gravidarum

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■ Cite as: *CMAJ* 2024 April 15;196:E477-85. doi: 10.1503/cmaj.221502

Nausea and vomiting of pregnancy are often considered normal and affect most pregnancies, with 1 meta-analysis finding the average reported rate to be 70%.¹ The severe end of the clinical spectrum of nausea and vomiting of pregnancy is called hyperemesis gravidarum.

Hyperemesis gravidarum leads to an inability to eat and drink sufficiently, resulting in weight loss and dehydration. It can have detrimental effects on maternal quality of life² and may lead to short- and long-term adverse outcomes among offspring. Management of hyperemesis gravidarum requires considerable health care resources, as it is a common reason for hospital admission and emergency department visits in the first trimester.^{3,4} In the absence of curative options, treatments are aimed at symptom reduction and have the potential to improve quality of life and perinatal outcomes, and to reduce the socioeconomic burden.

We provide an overview of the cause, diagnosis, and treatment of hyperemesis gravidarum, as well as its impact on the birthing parent and offspring (Box 1).

What causes hyperemesis gravidarum?

The cause of hyperemesis gravidarum is not fully understood and is most likely multifactorial. Pregnancy at a young age, pregnancy with a female fetus, multiple pregnancy, molar pregnancy, underlying medical conditions (e.g., thyroid and parathyroid dysfunction, hypercholesterolemia, type 1 diabetes), or a history of hyperemesis gravidarum are associated with an increased risk of hyperemesis gravidarum.⁵⁻⁸ Multiple or molar pregnancy can be ruled out at first presentation with hyperemesis gravidarum using ultrasonography.

Reproductive endocrine and placental factors have been the most extensively investigated as biomarkers associated with the diagnosis and severity of hyperemesis gravidarum.^{9,10} The role of human chorionic gonadotropin (hCG) has been a focus of research, although a meta-analysis revealed an inconsistent association between the severity of nausea and vomiting of pregnancy and hyperemesis gravidarum with serum concentration of hCG and markers of thyroid dysfunction.¹¹

Key points

- Diagnosis of hyperemesis gravidarum can be made in the first 16 weeks of pregnancy when a person has nausea and vomiting, at least 1 of which is severe, impairing sufficient intake and affecting tasks of daily living; the presence of ketonuria is not needed to diagnose hyperemesis gravidarum or determine eligibility for medication.
- Hyperemesis gravidarum is associated with increased risks of various adverse health outcomes in the short and long term for both pregnant people and their offspring.
- In the absence of curative options, treatments are aimed at symptom reduction and have the potential to improve quality of life and perinatal outcomes, and to reduce the socioeconomic burden.
- Treatment with antiemetics has been shown to be effective; evidence for other treatment options is limited.
- Hyperemesis gravidarum commonly recurs in subsequent pregnancies.

Box 1: Evidence considered in this review

We searched PubMed from inception to 2023 for studies related to the pathophysiology, diagnosis, impact, and treatment of hyperemesis gravidarum. We limited the search to articles in English and focused on randomized clinical trials or systematic reviews, although we did not apply any restrictions on study type. We supplemented this search by screening bibliographies of retrieved articles to identify other relevant articles.

A recent prospective cohort study showed that 21 (9.8%) of 215 patients with hyperemesis gravidarum had gestational transient thyrotoxicosis, but this was not associated with severity of hyperemesis.¹⁰ Gestational transient thyrotoxicosis is caused by stimulation of the maternal thyroid gland by hCG, is self-limiting, and does not generally require treatment. Furthermore, physiologic changes in thyroid function in early pregnancy do not influence the clinical course of hyperemesis gravidarum.¹⁰ Therefore,

routine testing of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) concentrations is of limited value in patients with hyperemesis gravidarum if no other clinical signs of thyroid disease are present.¹⁰ Recently, growth differentiation factor 15 (GDF-15) — which is produced in the early trophoblast and binds receptors in the brain’s “vomiting centre” in the area postrema — was identified as a prime candidate for the link between early placental growth and nausea and vomiting.^{12,13} A family history of hyperemesis gravidarum is associated with increased risk of the condition, which recent research suggests may be mediated by single nucleotide polymorphisms in the *GDF15* gene and the gene of its receptor in the area postrema.¹⁴ More research is necessary to verify the role of GDF-15 in the pathogenesis and course of hyperemesis gravidarum.

A 2015 systematic review showed that infection with *Helicobacter pylori* can be a risk factor for hyperemesis gravidarum.¹⁵ Clinicians should also rule out urinary tract infection as a potential cause of nausea and vomiting in pregnancy.¹⁶

How is hyperemesis gravidarum defined?

Definitions for hyperemesis gravidarum in clinical and research settings have had a high degree of heterogeneity and historically relied on the presence of ketonuria such as the Fairweather criteria, published in 1968 (Box 2).^{17,18} However, current evidence does not support the notion that the presence of ketonuria is associated with, or a marker of disease severity for, hyperemesis gravidarum.^{11,19}

Recently, a multi-stakeholder, international consensus definition of hyperemesis gravidarum was published, the Windsor definition (Box 2).²⁰ This definition was developed to assist in clinical diagnosis and harmonize identification of hyperemesis gravidarum for study populations in clinical trials.

Box 2: Diagnosing hyperemesis gravidarum

Fairweather criteria (1968)

- More than 3 episodes of vomiting a day
- Weight loss
- Ketonuria
- Electrolyte imbalance
- Volume depletion
- Onset usually at 4–8 weeks of pregnancy

Windsor definition (2021)

- Mandatory features
 - Nausea and vomiting, at least 1 of which is severe
 - Inability to drink or eat normally
 - Strongly affects daily living activities
 - Beginning of symptoms in early pregnancy*
- Contributory features
 - Signs of dehydration

*Early pregnancy was defined as before a gestational age of 16 weeks.

What is the effect of hyperemesis gravidarum on health outcomes?

Birth parents

The risks of hyperemesis gravidarum and potential management approaches are summarized in Table 1.

In the short term, hyperemesis gravidarum can cause substantial weight loss from insufficient caloric intake, as well as dehydration and electrolyte imbalance.^{32,33} Rarely, vitamin deficiencies can cause severe maternal morbidity or death, including thiamine deficiency, which may lead to Wernicke encephalopathy.²³ Malnourishment-related Wernicke encephalopathy in pregnancy is an uncommon, severe, and preventable consequence of hyperemesis gravidarum that warrants attention because of its rapid onset and detrimental course. A systematic review of 177 pregnant patients with hyperemesis gravidarum complicated by Wernicke encephalopathy showed that 50% of fetuses and 5% of the parents died.²³ None of these patients had received thiamine treatment; clinicians should be aware that intravenous glucose treatment can precipitate Wernicke encephalopathy.²³ Symptoms of the classic Wernicke encephalopathy triad include eye movement disorders (e.g., blurred or double vision, nystagmus, ophthalmoplegia), altered mental status (e.g., confusion, reduced alertness, changes in cognition), and ataxia, but only 60% of patients exhibit the full triad of symptoms.²³

Hyperemesis gravidarum increases the risk of both antenatal and postnatal venous thromboembolism.²⁵ Several studies have reported higher rates of depression, anxiety, posttraumatic stress disorder (PTSD), and, in some cases, suicidal ideation among people with hyperemesis gravidarum compared to the general pregnant population.^{2,26} Furthermore, more than 50% of patients with hyperemesis gravidarum consider terminating a wanted pregnancy, and as many as 11% of patients terminate with hyperemesis gravidarum as the sole reason.^{28,34}

Hyperemesis gravidarum can have health effects that outlast the pregnancy, although evidence is limited. Family planning can be affected, leading to pregnancy being postponed or avoided for fear of recurrent hyperemesis gravidarum.⁷ Depression and anxiety can persist after pregnancy and symptoms of PTSD have been estimated to affect about 18% of patients with hyperemesis gravidarum, with symptom duration unknown.²

Offspring

In a recent systematic review of 61 studies, we described consequences of hyperemesis gravidarum for the offspring,³⁰ concluding that people with hyperemesis gravidarum were more likely to have a placental abruption (odds ratio [OR] 1.15), a baby with a weight less than 1500 g (OR 1.43), preterm birth (OR 2.81), a baby admitted to neonatal intensive care (OR 1.20), or a baby that required resuscitation (OR 1.07). Hyperemesis gravidarum was associated with fewer stillbirths (OR 0.92) and babies with a birth weight greater than 4000 g (OR 0.74). Whether effective treatment of hyperemesis gravidarum improves these perinatal outcomes is unknown.

Table 1: The risks of hyperemesis gravidarum for pregnant people and their offspring

Risk	Management
Short-term maternal outcomes	
Weight loss ²¹	Refer to a dietitian (preferably with experience in treating hyperemesis gravidarum) ²¹
Dehydration ²¹	Administer IV fluids in either an outpatient clinic or inpatient setting ²²
Electrolyte imbalances ²¹	Hospital admission to correct electrolyte imbalances ²¹
Wernicke encephalopathy ²³	Offer thiamine supplementation to patients admitted with prolonged lack of nutrient intake, especially before administration of dextrose or enteral or parenteral nutrition ²²
Vitamin K deficiency ²⁴	Consider vitamin K supplementation (150 µg IV)
Thromboembolism ²⁵	Consider thrombosis prophylaxis in patients admitted to hospital or in patients with other risk factors for thromboembolism ²¹
Depression, anxiety, or PTSD ^{2,26,27}	Ask about depressive symptoms and offer psychosocial help ²¹
Suicidal ideation ²⁸	Ask about suicidal ideation and refer if necessary
Consideration of pregnancy termination ²⁸	Ask if patient is considering pregnancy termination, talk about recurrence risks, expand antiemetic treatment, and refer if necessary
Long-term maternal outcomes	
Changes to family planning ⁷	After a pregnancy affected by hyperemesis gravidarum, suggest follow-up to discuss future pregnancy and, if desired, make a plan for treatment of hyperemesis gravidarum in a next pregnancy ⁷
Depression, anxiety, or PTSD ^{2,29}	Offer psychosocial help ²¹
Perinatal outcomes	
Placental abruption ³⁰	
Birth weight < 1500 g ³⁰	Offer ultrasonography to measure fetal growth in pregnancy if symptoms persist beyond second trimester
Preterm delivery ³⁰	
Resuscitation or admission to NICU ³⁰	
Long-term outcomes to offspring	
Reduced insulin sensitivity ³⁰	
Anxiety disorders ³¹	
Sleep problems ³¹	
Attention-deficit/hyperactivity disorder ³¹	
Autism spectrum disorder ³¹	
Testicular cancer ³¹	
Note: IV = intravenous, NICU = neonatal intensive care unit, PTSD = posttraumatic stress disorder.	

Maternal vitamin deficiency as a consequence of hyperemesis gravidarum may lead to neonatal vitamin K deficiency, which results in disordered clotting after birth, and fetal congenital abnormalities.²⁴ Parental undernutrition and weight loss creates a fetal environment that can lead to health effects for offspring over the life course.³⁵ A recent systematic review showed that hyperemesis gravidarum may be associated with small increases in adverse health outcomes among children, including mental health disorders such as anxiety disorders (OR 1.74), sleep problems (OR 2.94) and, possibly, testicular cancer (OR 1.60), although this evidence is based on few studies of low quality.³¹

When should hyperemesis gravidarum be treated?

Treatment to prevent dehydration and malnutrition is required when nausea and vomiting become so severe as to interfere with normal eating and drinking. Treatment should also be considered when symptoms affect quality of life and activities of daily living.²⁰ Research in the treatment of hyperemesis gravidarum is limited and studies are often small. For instance, comparative effectiveness studies of the 3 most commonly prescribed drugs to treat hyperemesis gravidarum (i.e., antihistamines, metoclopramide, and ondansetron) involved only 552 patients with hyperemesis gravidarum.³⁶

What is the optimal approach to management?

A 2018 Cochrane review of treatments for hyperemesis gravidarum concluded that little high-quality and consistent evidence supports any 1 intervention.³⁷ Management of nausea and vomiting in other conditions can inform strategies for managing hyperemesis gravidarum, although safety considerations for medications used during pregnancy need to be taken into consideration.³⁸ Treatment of hyperemesis gravidarum should initially start with 1 antiemetic drug, and if this is not sufficient to ameliorate nausea, addition of another antiemetic drug of another class has been suggested.²¹ If the patient shows signs or symptoms of dehydration (e.g., thirst, concentrated urine, dry skin, weakness, lightheadedness, fainting, inability to keep fluids down), clinicians should investigate for electrolyte disturbances and, if necessary, administer intravenous fluid therapy, which should include 100 mg intravenous thiamine supplementation.²¹ Hospital admission is usually necessary for those with dehydration and marked electrolyte abnormalities, and should be considered if oral and sublingual drugs are insufficiently tolerated or are ineffective, or to facilitate parenteral or intravenous treatment. Thrombosis prophylaxis may be considered in admitted patients, but not all agents used for thrombosis prophylaxis are safe in pregnancy.

Continuity of health care providers over the first and second trimester, as well as between inpatient and outpatient care, can positively affect patients' physical and mental well-being, and may reduce their requirement for hospital admission and emergency department attendance.^{4,39} As has been previously suggested,⁴ an individualized care plan could benefit patients with severe nausea and vomiting in pregnancy.

Evidence on the effectiveness and safety of treatment options for hyperemesis gravidarum are summarized in Table 2 and Table 3.

Antiemetic treatments

Most antiemetic drugs used to treat nausea and vomiting of pregnancy and hyperemesis gravidarum are not approved for use in pregnancy. The only drug approved (in Canada and the United Kingdom) specifically for the treatment of nausea and vomiting of pregnancy is the delayed-release formulation of doxylamine succinate (10 mg) and pyridoxine hydrochloride (10 mg), as this combination has been shown to be more effective than placebo in reducing nausea and vomiting.^{40,42} A subsequent publication⁶⁴ questioned the statistical and clinical significance of findings of the study by Koren and colleagues.⁴⁰ A recent randomized trial found doxylamine–pyridoxine was more effective than placebo in reducing nausea and vomiting.⁴³ However, the clinical importance of this effect is uncertain because of its modest magnitude.

Other first-generation antihistamines such as cyclizine, dimenhydrinate, and promethazine are recommended by some sources, and have been investigated in studies of nausea and vomiting of pregnancy and hyperemesis gravidarum but have not been shown to be more effective than placebo or other treatments.^{22,37} However, antihistamines can provide an additional anticholinergic benefit to those distressed by hypersalivation in pregnancy.⁴⁵

If these options fail to control symptoms adequately, other treatments are available, including metoclopramide and ondansetron (Table 2). Concerns about safety have largely been allayed for metoclopramide, but whether use of ondansetron is associated with a slightly increased risk of cleft palate and heart defects — or whether the severity of the indication plays a role in this risk — is unclear. Although route of administration has not been investigated in hyperemesis gravidarum, sublingual or per rectum routes offer the same advantages in other conditions with vomiting.^{22,65,66}

The use of corticosteroids is reserved, especially in the first trimester, for patients for whom symptoms are not adequately controlled with other antiemetics (Table 2).²²

Treatment for dehydration

Dehydration, as a consequence of the nausea and vomiting, can be treated by intravenous fluid treatment in either outpatient clinic or inpatient settings, according to local resources and service delivery models.²² Recently, daily intravenous treatment in an outpatient setting (e.g., 2 L of 0.9% sodium chloride solution with 20 mmol of potassium chloride intravenously over 4 h)³⁹ has been shown to be as effective in resolving dehydration as hospital admission and can reduce the length of stay per patient admission and the total number of inpatient nights per year.⁶⁷ To prevent Wernicke encephalopathy, thiamine supplementation (100 mg/d intravenously) should be offered to all pregnant people with prolonged lack of nutrient intake, especially before administration of dextrose or enteral or parenteral nutrition.²²

Nonpharmacologic therapies

People with hyperemesis gravidarum can benefit from avoiding exposure to triggers such as specific odours and particular foods. Old evidence suggests that low-energy, high-protein diets may be associated with a reduction of nausea and vomiting in pregnancy compared with a diet high in carbohydrates.⁶⁸ Referral to a dietitian could help reduce weight loss and prevent malnutrition.⁶⁹ Psychosocial support could alleviate the consequences of hyperemesis gravidarum on mood and of limited ability to complete activities of daily living, including caring for young children.⁷⁰

A 2015 Cochrane review concluded that ginger products, which are considered safe in pregnancy, may be helpful to pregnant people with mild nausea and vomiting, but the evidence of effectiveness was limited and inconsistent for those with hyperemesis gravidarum.^{44,57} A large online survey study of a self-selected sample of 512 patients admitted to hospital for hyperemesis gravidarum found that the use of ginger produced unpleasant physical adverse effects (e.g., exacerbation of nausea and vomiting, pain or burning during vomiting, acid reflux caused by ginger products) in around half of those who tried it, and was associated with a negative psychological effect in 82% of participants.⁵⁸

Table 3 lists other nonpharmacologic therapies like acupuncture and psychotherapeutic treatment and describes data on their effectiveness and safety.

Table 2: Evidence of the effectiveness and adverse effects of antiemetic treatments for hyperemesis gravidarum

Drug or therapy	Dose*	Effectiveness	Safety in pregnancy	Other comments
Doxylamine–pyridoxine†	10 mg doxylamine + 10 mg pyridoxine every 6 h	More effective than placebo in reducing nausea and vomiting scores. However, the clinical importance of this effect is uncertain because of its modest magnitude. ^{40–44}	Doxylamine has been extensively studied in more than 60 000 pregnancies. The studies do not reveal a higher risk of congenital abnormalities or specific abnormalities. ²¹	Antihistamines can provide an additional anticholinergic benefit to those distressed by ptyalism. ⁴⁵
Cyclizine††	50 mg every 8 h	Has not been shown to be more effective than placebo or other treatments. ^{22,37}	Almost 3500 pregnancies have been studied with cyclizine. No evidence indicates that this drug increases the risk of birth defects. ⁴⁶	Antihistamines can provide an additional anticholinergic benefit to those distressed by ptyalism. ⁴⁵
Promethazine†	25 mg every 8 h	More effective than placebo in relief of nausea and vomiting. ²¹	Promethazine has been extensively studied in more than 25 000 pregnancies. The studies do not reveal a higher risk of congenital abnormalities or specific abnormalities. ²¹	Promethazine is a strong sedative. When used just before delivery, sedation and respiratory depression of the newborn is a theoretical risk. ²¹
Dimenhydrinate†	25–50 mg every 6 h	More effective than placebo in relief of nausea and vomiting. ²¹	Dimenhydrinate is commonly used and safety data are generally reassuring that it is not a teratogen. ²¹	If the patient is taking doxylamine, the total dose of dimenhydrinate should not exceed 200 mg/d to reduce the risk of adverse effects, or doxylamine should be stopped.
Metoclopramide	10 mg every 8 h	More effective than placebo in reducing the intensity of nausea and vomiting. ^{21,47}	Metoclopramide has been extensively studied in more than 90 000 pregnancies. ⁴⁸ Only 1 study ⁴⁹ (<i>n</i> = 958 pregnancies) reported a small increase of genital organ defects; all other studies showed no increase in prevalence of congenital abnormalities. Metoclopramide may therefore be safely prescribed.	Metoclopramide can give tardive dyskinesia, but this is uncommon in young patients. Early detection and discontinuation of metoclopramide is important. If metoclopramide is prescribed, clinicians should warn for this adverse effect. ²¹
Ondansetron	4 mg every 8 h	In a small RCT, use of ondansetron resulted in clinically significant reductions in both nausea and vomiting compared with the combination of doxylamine and pyridoxine. ⁵⁰ In another RCT, it was more effective than metoclopramide for reducing vomiting but not nausea. ⁵¹	Because the results of the studies are contradictory, whether ondansetron is associated with a slightly increased risk of cleft palate and heart defects, or whether the severity of the indication plays a role, is unclear. ^{21,52,53}	Ondansetron should only be used in the first trimester if other antiemetics are insufficiently effective. Clinicians should weigh the risk of untreated severe hyperemesis gravidarum and small increased risk of congenital abnormalities, in consultation with the patient.
Steroids	IV hydrocortisone 100 mg every 12 h or methylprednisolone 125 mg; switch from IV to oral as soon as clinical improvement occurs: oral prednisolone 40 mg (day 1), 20 mg (day 2–3), 10 mg (day 4–6), 5 mg (day 7–14)	More effective than placebo, the rate of hospital readmission is lower. ^{21,37}	No higher risk of congenital abnormalities has been clearly shown; therefore, corticosteroids can be used during pregnancy if necessary. Preference is given to prednisolone and hydrocortisone as these corticosteroids are least likely to reach the unborn child; these should be used for as short a time and dosed as low as possible.	Long-term use of high doses of corticosteroids can slow the growth of the unborn child and inhibit the child's adrenal cortex. As a result, the child may have low blood glucose levels, low blood pressure, and electrolyte disturbances in the first days after birth.

Note: IV = intravenous, RCT = randomized controlled trial.

*Oral route, unless otherwise noted.

†Antihistamine.

‡In Canada, cyclizine is only available as intramuscular formulation.

Table 3: Evidence of the effectiveness and adverse effects of other treatments for hyperemesis gravidarum

Drug or therapy	Dose	Effectiveness	Safety in pregnancy	Other comments
Cannabis		Research has suggested that cannabis may provide an anti-nausea effect in adults with cancer receiving chemotherapy. ⁵⁴	In pregnancy, prenatal cannabis is suggested to be associated with adverse neurocognitive outcomes in offspring. ^{55,56}	The use of cannabis is not advised
Ginger		May be helpful to patients with mild nausea and vomiting, but the evidence of effectiveness was limited and inconsistent for patients with hyperemesis gravidarum. ^{44,57}	Ginger is not known to cause any problems related to pregnancy. ⁵⁷	Relevant adverse effects of ginger were reported in a large self-selected online survey of 512 patients hospitalized for hyperemesis gravidarum, namely unpleasant physical effects in around half of those who tried it and negative psychological effects in 82% of participants. ⁵⁸
Acupressure and acupuncture		Acupressure may be helpful in some patients and was associated with less need for additional antiemetics and a larger reduction in PUQE score than placebo. ^{43,44}	A systematic review showed adverse events were all mild–moderate in severity, with needling pain being the most frequent. ⁵⁹	
Psychotherapeutic treatment		Few studies have evaluated psychotherapeutic treatment for hyperemesis gravidarum; most have been evaluated as being of poor methodological quality. Several report a positive effect of psychotherapeutic treatment on symptoms of hyperemesis gravidarum. ⁶⁰		
Eradication of <i>Helicobacter pylori</i>	Triple drug therapy, 3 times daily for 7–10 d	Whether eradication of <i>H. pylori</i> might improve or prevent symptoms of hyperemesis gravidarum remains unclear. ¹⁵ Eradication of <i>H. pylori</i> requires high doses, making this approach poorly feasible among patients with hyperemesis gravidarum.	If <i>H. pylori</i> is present, treatment is typically deferred until after delivery. However, with the exception of bismuth, fluoroquinolones, and tetracycline, the other medications used for <i>H. pylori</i> eradication are low risk in pregnancy, especially after 14 weeks.	<i>H. pylori</i> eradication before conception may be an attractive method of ameliorating risk of recurrent hyperemesis gravidarum in subsequent pregnancies, but its possible effectiveness in achieving this goal remains unproven.
Laxatives		Laxatives do not affect nausea or vomiting, but are prescribed for constipation, which can be an adverse effect of antiemetics or dehydration	Laxatives are considered safe in pregnancy for treatment of constipation.	
Proton pump inhibitors		Acid-reducing drugs resulted in significant decreases in PUQE and well-being scores. After intervention with acid-reducing pharmacotherapy, a reduction in acid symptoms correlated with significant reductions in nausea and vomiting of pregnancy. ²¹	Proton pump inhibitors are considered safe in pregnancy, especially omeprazole and lansoprazole. Studies have not shown an elevated risk of birth defects or other adverse effects in pregnancy. ⁶¹	
Antidepressants		Recent case reports suggest that mirtazapine could be considered in refractory hyperemesis gravidarum. The results of a recent double-blind placebo-controlled RCT investigating mirtazapine as a treatment for hyperemesis gravidarum have yet to be published. ⁶²	SSRIs are generally considered an option during pregnancy. Potential complications include maternal weight changes and preterm birth. Most studies show that SSRIs are not associated with birth defects. ⁶³	Antidepressants can be prescribed as an adjunct when nausea causes sleep disorders, or when sleep disorder worsens nausea.

Note: PUQE = Pregnancy-Unique Quantification of Emesis and Nausea, RCT = randomized controlled trial, SSRI = selective serotonin reuptake inhibitor.

Other treatment options

Whether eradication of *H. pylori* prevents or improves symptoms of hyperemesis gravidarum is unclear.¹⁵ Eradication of *H. pylori* requires triple drug therapy (e.g., oral proton pump inhibitor, clarithromycin, and amoxicillin) taken 3 times daily for 7–10 days, so this approach is difficult for those with hyperemesis gravidarum. Eradication before conception may be an attractive method of reducing the risk of recurrent hyperemesis gravidarum in subsequent pregnancies, but its effectiveness in achieving this goal remains unproven and more research is needed.

Other therapeutic agents that can help to manage the condition throughout the pregnancy include proton pump inhibitors, laxatives (particularly if ondansetron causes constipation), and antidepressants (if the condition causes substantial psychological distress).⁷¹ Research has suggested that cannabis may provide an anti-nausea effect in adults with cancer receiving chemotherapy.⁵⁴ However, use of cannabis in pregnancy has been associated with adverse neurocognitive outcomes in offspring, as well as other adverse pregnancy outcomes.^{55,56} Therefore, we advise against the use of cannabis in pregnancy.

Iron, frequently prescribed in pregnancy to prevent or treat anemia, may exacerbate nausea, particularly when taken on an empty stomach. One study suggested that the tablet size and not the iron content may affect adherence among patients with nausea and vomiting in pregnancy.⁷² Temporary discontinuation may be helpful in controlling nausea and vomiting in pregnancy and is not expected to have deleterious effects on the fetus.⁷³ Patients with prolonged discontinuation of iron supplementation may require intravenous iron supplementation.

Management of comorbidities

Conditions such as diabetes, epilepsy, HIV, autoimmune disorders, and psychiatric disorders, or any condition requiring regular oral medication, can be severely affected by comorbid hyperemesis gravidarum. Inability to keep down medication or maintain oral intake can lead to deterioration of these comorbidities. Pregnant people with a history of bariatric surgery may have pre-existing nutritional deficiencies and compromised absorption of oral medication or vitamins, but also need to be urgently assessed for bowel obstruction caused by intestinal herniation if they present with vomiting and abdominal discomfort.^{74,75}

Can hyperemesis gravidarum be prevented?

People with a history of hyperemesis gravidarum in a previous pregnancy are at higher than baseline risk of recurrence. Recurrence rates vary from 15% to 86%, with lower recurrence rates reported in registry studies, which tend to rely on hospital admission for identification of hyperemesis gravidarum, and higher recurrence rates reported in cohort studies which rely on maternal report of symptoms, impact of symptoms, and need for treatment.^{6,7} A single randomized trial has shown that starting doxylamine succinate and pyridoxine hydrochloride preemptively once pregnancy is confirmed may reduce the overall severity and duration of nausea and vomiting in pregnancy.⁷⁶

Conclusion

Hyperemesis gravidarum increases the risk of unfavourable health outcomes for pregnant people and their offspring. Treatments are aimed at the alleviation of symptoms, but their impact on improved perinatal outcomes is less clear. Many unanswered questions about the prevention and management of hyperemesis gravidarum remain. In 2021, a prioritized list of questions deemed important to patients and providers was published.⁷⁷ Understanding the causes of hyperemesis gravidarum and developing more effective treatments were highlighted priorities, along with a greater understanding of the effects of hyperemesis gravidarum and its treatments on both pregnant people and their babies.

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Competing interests: Iris Grooten and Rebecca Painter are expert members for the development of the Dutch guideline on hyperemesis gravidarum and the thyroid in pregnancy, respectively. Rebecca Painter reports funding from ZonMw, participation on a data safety monitoring board for the CRISTAL study, an advisory position with Stichting ZEHG, and a board position with NVOG. No other competing interests were declared.

This article was solicited and has been peer reviewed.

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Contributors: All of the authors contributed to the conception and design of the work, drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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