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A Systematic Review of Etiology and Treatment for Hyperemesis Gravidarum

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ABSTRACT

Background: Hyperemesis gravidarum (HG) is severe nausea and repeated vomiting that prevents oral intake of food and leads to dehydration, ketoacidosis and nutritional deficiencies that may need hospitalization. **Methods:** This systematic review focused on full-text English literature published between 2014 and 2024 using the PRISMA 2020 guidelines. Editorials and review pieces published in the same journal as the submission without a DOI were not accepted. The literature was compiled using Medline, Science Direct, Scopus and Embase, among other online venues. **Result:** Five publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles. **Conclusion:** Several pharmaceuticals are currently in use, but there is no evidence regarding which is preferable, when to commence treatment, or what dosage or administration route is most beneficial.

Keyword: Hyperemesis gravidarum, nausea, vomiting, pregnant.

INTRODUCTION

Nausea and vomiting are common in early pregnancy (NVP); approximately 80% of all pregnant women are affected to some degree. When NVP is severe or protracted, the condition is often referred to as hyperemesis gravidarum (HG), affecting up to 3.6% of pregnancies. Women with HG may become dehydrated, lose weight or require hospital admission. After HG, women more often report anxiety, depression and posttraumatic stress disorder, reflecting the detrimental effect of HG on maternal wellbeing and quality of life. HG may increase the chance of preterm birth and small for gestational age, and there is evidence suggesting adverse long term outcomes among offspring and mothers.[1,2]

Hyperemesis gravidarum (HG) is a severe and debilitating condition characterized by persistent and excessive nausea and vomiting during pregnancy (NVP), often leading to significant maternal and fetal morbidity. This literature review aims to provide a scientifically comprehensive overview of HG within the context of the emergency room (ER) setting. This review aims to enhance understanding and improve the management of HG cases presented to the ER by synthesizing current knowledge and evidence-based practices.[3,4]

Hyperemesis gravidarum refers to intractable vomiting during pregnancy, leading to weight loss and volume depletion, resulting in ketonuria and/or ketonemia. There is no consensus on specific diagnostic criteria, but it generally refers to the severe end of the spectrum regarding nausea and vomiting in pregnancy. It occurs in approximately two percent of all pregnancies in the United States. It can significantly impact the quality of life of women and their families and, unfortunately, may be very challenging to treat.(Jennings)(Nurmi)

The etiology of hyperemesis gravidarum is largely unknown, but several theories exist (see pathophysiology). There are, however, risk factors associated with the development of hyperemesis during pregnancy. Increased placental mass in the setting of a molar or multiple gestations has been associated with a higher risk of hyperemesis gravidarum. Additionally, women who experience nausea and vomiting outside of pregnancy due to the consumption of estrogen-containing medications, exposure to motion, or have a history of migraines are at higher risk of experiencing nausea and vomiting during pregnancy. Some studies also suggest a higher risk of hyperemesis in women with first-degree relatives, for instance, if her mother or sister experienced hyperemesis gravidarum.[5,6]

Up to 80% of all pregnant women experience some form of nausea and vomiting during their pregnancy.The *International Statistical Classification of Disease and Related Health Problems, Tenth Revision*, defines hyperemesis gravidarum (HG) as persistent and excessive vomiting starting before the end of the 22nd week of gestation and further subdivides the condition into mild and severe, with severe being associated with metabolic disturbances such as carbohydrate depletion, dehydration, or electrolyte imbalance. HG is a diagnosis of exclusion, characterized by prolonged

and severe nausea and vomiting, dehydration, large ketonuria, and more than 5% body weight loss. Affecting approximately 0.3%–2.0% of pregnancies, HG is the commonest indication for admission to hospital in the first half of pregnancy and is second only to preterm labor as a cause of hospitalization during pregnancy.[7]

According to the Hyperemesis Education and Research Foundation, conservative estimates indicate that HG can cost a minimum of $200 million annually in in-house hospitalizations in the United States. Taking into account other factors such as emergency department treatments, potential complications of severe HG, and the fact that up to 35% of women with paid employment will lose time from work through nausea, the actual cost of HG to the economy is significantly higher. In a related economic analysis, Piwko et al projected that the United States spends nearly $2 billion in costs attributed to pregnancy-related nausea and vomiting; 60% of this expenditure is a result of direct costs (eg, drugs, hospital admission), and 40% is a result of indirect costs (eg, time lost from work).[7]

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards were scrupulously followed by the work's author. The purpose of this was to make sure the study satisfied all the requirements. The chosen technique was carefully designed to ensure the accuracy and dependability of the investigation's findings.

Criteria for Eligibility

This study does a thorough evaluation of the last 10 years worth of literature on the etiology and treatment for hyperemesis gravidarum. This study intends to improve and provide light on patient treatment procedures through a thorough examination of data. The primary goal of this paper is to highlight the significance of the noteworthy topics that have been identified across the literature.

To ensure the quality of the included information in this study, strict inclusion and exclusion criteria are applied. To be eligible for inclusion, papers must have been published in the English language between 2014 and 2024. Editorials, submissions without a DOI, previously published reviews, and duplicate journal entries are some of the exclusion criteria.

Search Strategy

The keywords used for this research is “Etiology and treatment for hyperemesis gravidarum”. The Boolean MeSH keywords inputted on databases for this research are: *((*"Emesis"*[MeSH Subheading] OR* "Hyperemesis"*[All Fields] OR* "Gravida*” [All Fields]) AND (*"Hyperemesis gravidarum"*[All Fields] OR* "Etiology"*[All Fields]) AND (*"Treatment"*[All Fields]) OR (*"Outcome”* [All Fields]))*

Data retrieval

The writers thoroughly evaluated the abstract and title of each manuscript before beginning this systematic review in order to assess each one's significance. Just articles that met the inclusion criteria and aligned with the article's objectives were selected for further examination.

Ultimately, a definitive result was obtained from a consistent pattern found over several analyses. Only full-text, English-language submissions were acceptable. Content that satisfied all pre-established inclusion criteria and directly related to the study's subject matter was included after the most stringent screening procedure. Studies that failed to satisfy these requirements were frequently ignored, and their conclusions were not taken into consideration. A thorough analysis was conducted on a plethora of information discovered throughout the research process, including titles, authors, publication dates, locations, study methodologies, and parameters.

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Quality Assessment and Data Synthesis

The research that was reported in the titles and abstracts of each article was independently assessed by the authors in order to determine which papers needed additional investigation. Going over each document that satisfied the pre-established requirements to be included in the review was the following stage. The selection of an article for inclusion in the review was based on the evaluation procedure's results. By accelerating the selection of articles for further evaluation, this criterion was able to accomplish the goal of facilitating a thorough analysis of previous research and the factors that qualified them for the review.

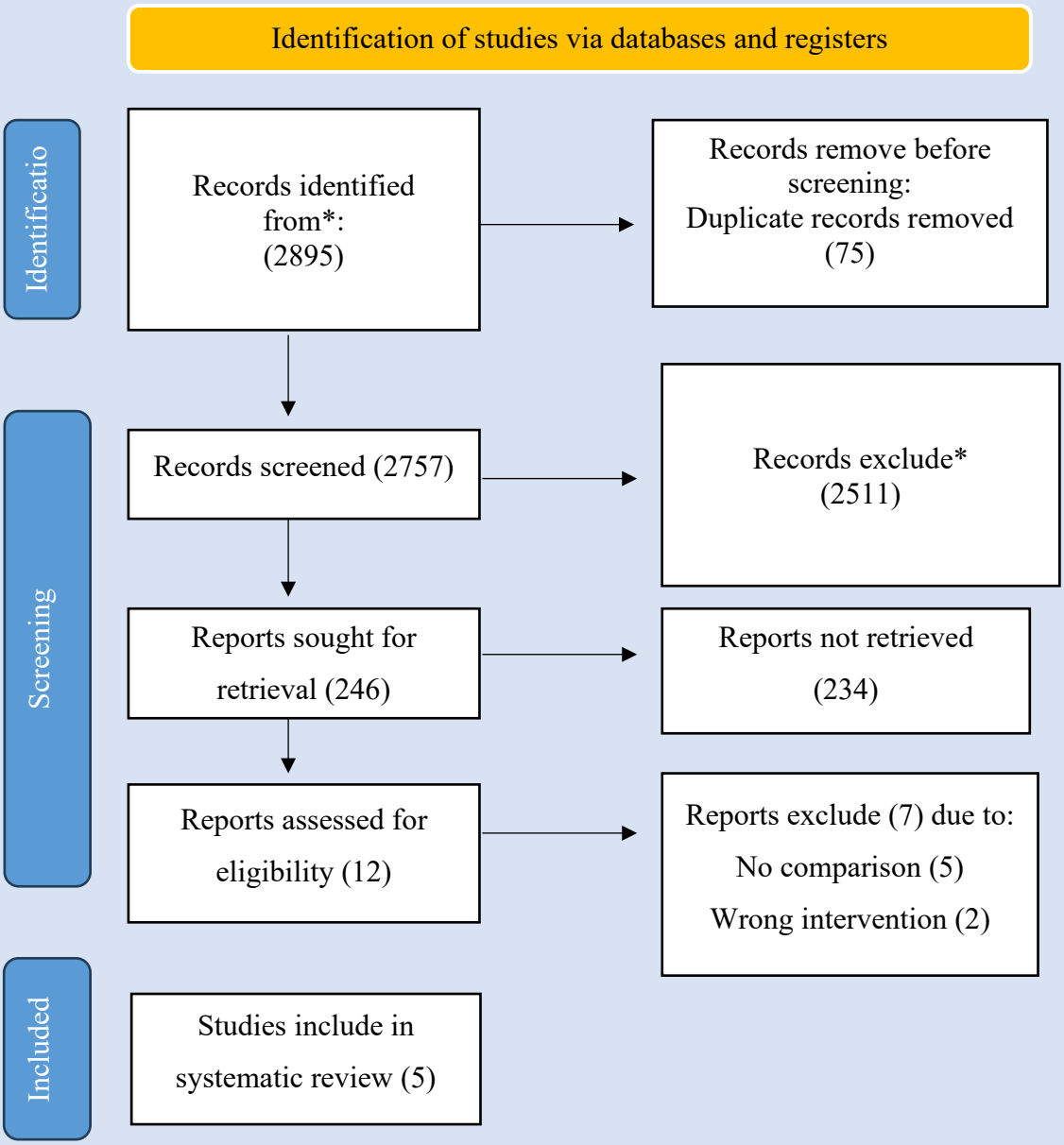


Figure 1. Article search flow chart

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RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered 2895 publications. A thorough three-level screening strategy was used to identify only five papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 1 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 1. The literature included in this study

Author	Origin	Method	Sample Size	Result
Adane, KD et al., 2023[8]	Ethiopia	This is hospital-based cross-sectional study of 355 pregnant mothers in Akesta general hospital in northeast Ethiopia from September 1/2018- to August 30 /2020. A simple random sampling technique was used to select the patient card from the whole admission of pregnant women cards during the study period.	355	A total of 355 pregnant women were involved in this study, with a response rate of 100%. Majority of the pregnant women 282 (79.4%) live in the rural area. More than three fourth 270 (76.1%) of the pregnant women were within the age group of 20–35 years, with a mean age of 26 years ± 5.8 SD. The majority of the respondents 348 (98%) of the pregnant women were married while 13(3.7%) had secondary education and above. The odds of hyperemesis gravidarum were 10.9 times higher among women who had previous history of HG compared with women who had no previous history of HG AOR (95%CI) = 10.9[2.46, 48.44]. The odds of hyperemesis gravidarum were 4.32 times higher among women who had previous history of UTI compared with women who had no previous history of UTI AOR (95%CI) = 4.32[1.58, 11.86]. The odds of hyperemesis gravidarum

				were 4.12 times higher among women who had previous history of gastrointestinal disease compared with women who had no history of gastrointestinal disease AOR (95% CI) = 4.12[1.40, 12.65]
Boelig, RC et al., 2016[9]	USA	Randomized controlled trials of any intervention for hyperemesis gravidarum. Quasi-randomized trials and trials using a cross-over design were not eligible for inclusion. We excluded trials on nausea and vomiting of pregnancy that were not specifically studying the more severe condition of hyperemesis gravidarum.	2052	Twenty-five trials (involving 2052 women) met the inclusion criteria but the majority of 18 different comparisons described in the review include data from single studies with small numbers of participants. The comparisons covered a range of interventions including acupressure /acupuncture, outpatient care, intravenous fluids, and various pharmaceutical interventions. The methodological quality of included studies was mixed. For selected important comparisons and outcomes, we graded the quality of the evidence and created 'Summary of findings' tables. For most outcomes the evidence was graded as low or very low quality mainly due to the imprecision of effect estimates. Comparisons included in the 'Summary of findings' tables are described below, the remaining comparisons are described in detail in the main text. No primary outcome data were available when

				acupuncture was compared with placebo, There was no clear evidence of differences between groups for anxiodepressive symptoms (risk ratio (RR) 1.01, 95% confidence interval (CI) 0.73 to 1.40; one study, 36 women, *very low-quality evidence*), spontaneous abortion (RR 0.48, 95% CI 0.05 to 5.03; one study, 57 women, *low-quality evidence*), preterm birth (RR 0.12, 95% CI 0.01 to 2.26; one study, 36 women, *low-quality evidence*), or perinatal death (RR 0.57, 95% CI 0.04 to 8.30; one study, 36 women, *low-quality evidence*).
Robson, S et al., 2021[10]	UK	This was a multicentre, double-dummy, randomised, double-blinded, dummy-controlled 2 × 2 factorial trial (with an internal pilot phase), with qualitative and health economic evaluations.	592	Of the 592 patients screened, 122 were considered eligible and 33 were recruited into the internal pilot (metoclopramide and dummy ondansetron, $n = 8$; ondansetron and dummy metoclopramide, $n = 8$; metoclopramide and ondansetron, $n = 8$; double dummy, $n = 9$). Owing to slow recruitment, the trial did not progress beyond the pilot. Fifteen out of 30 evaluable participants experienced treatment failure. No statistical analyses were performed. The main reason for ineligibility was prior

				treatment with trial drugs, reflecting an unpredicted change in prescribing practice at several points along the care pathway. The qualitative evaluation identified the requirements of the study protocol, in relation to guidelines on anti-sickness drugs, and the diversity of pathways to care as key hurdles to recruitment while the role of research staff was a key enabler. No important adverse events or side effects were reported.
Havnen, GC et al., 2019[11]	Norway	A cross-sectional study based on a structured telephone interview and an online questionnaire. Participants were recruited by social media and by the Norwegian patient's organization for HG.	107	The study included 107 women. Maternal morbidity was profound; about 3/4 of participants were hospitalized due to HG, and the majority showed clinical signs of dehydration (79%), ketonuria (75%), and >5% weight loss (84%). Antiemetics were used by >90% and frequently prescribed "as needed". Metoclopramide (71%) and meclozine (51%) were most commonly used. Participants described HG as having severe psychosocial consequences and profound impact on daily activities. Almost two out of five reported thoughts of elective abortion, and 8 women had at least one elective pregnancy termination due to HG. Overall, 20 women (19%) changed GPs due to

				dissatisfaction with HG management.
Asrade, L et al., 2023[12]	Ethiopia	A multicenter, facility-based, unmatched case-control study was conducted on 444 pregnant women (148 cases and 296 controls) from January 1 to May 30. Women with a documented diagnosis of hyperemesis gravidarum on the patient chart were considered as cases, and women who attended antenatal care service without hyperemesis gravidarum were assigned as controls.	444	Living in urban (AOR = 2.717, 95% CI : 1.693,4.502), primigravida (AOR = 6.185, 95% CI: 3.135, 12.202), first& second trimester of pregnancy (AOR = 9.301, 95% CI: 2.877,30.067) & (AOR = 4.785, 95% CI: 1.449,15.805) respectively, family history of hyperemesis gravidarum (AOR = 2.929, 95% CI: 1.268,6.765), helicobacter pylori (AOR = 4.881, 95% CI: 2.053, 11.606) & Depression (AOR = 2.195, 95% CI: 1.004,4.797) were found to be determinants of hyperemesis gravidarum.

Adane, KD et al (2023)[8] showed the proportion of hyperemesis gravidarum at Akesta general hospital was high. The independent associated factors of HG were previous history of HG, history of gastrointestinal disease, history of abortion and history of UTI. Healthcare providers should give health education and counseling service concerning about pre pregnancy care. Before pregnancy, women should be screened and treated for UTI and gastrointestinal disease.

Boelig, RC et al (2016)[9] showed For hydrocortisone compared with metoclopramide, no data were available for primary outcomes and there was no difference in the readmission rate (RR 0.08, 95% CI 0.00 to 1.28;one study, 40 women). In a study with 80 women, compared to promethazine, those receiving prednisolone had increased nausea at 48 hours (RR 2.00, 95% CI 1.08 to 3.72; *low-quality evidence*), but not at 17 days (RR 0.81, 95% CI 0.58 to 1.15, *very low-quality evidence*). There was no clear difference in the number of episodes of emesis or subjective improvement in nausea/vomiting. There was insufficient evidence to identify differences between groups for stillbirth and neonatal death and preterm birth.

Robson, S et al (2021)[10] showed the treatment failure rate observed (50%) was higher than predicted in the sample size calculation at the design stage (10–20%). A higher proportion of women than anticipated were ineligible for the trial; the main reason was prior prescription of trial medication(s). This reflected a change in prescribing practice, often inconsistent with national antiemetic guidelines, with greater use of second-line drugs, particularly ondansetron. The qualitative study identified that the hurdles to and enablers of recruitment were both trial specific and site specific.

Havnen, GC et al (2019)[11] showed women with HG reported suboptimal management and a lack of support from healthcare professionals, despite the severe psychosocial burden of illness and the high impact on their daily activities. Greater awareness and knowledge are needed among healthcare professionals to improve care for patients with HG. Understanding patient perspectives and acknowledging the impact of the illness are important factors for optimal HG management.

Asrade, L et al (2023)[12] showed living in an urban area, primigravida woman, being in the first and second trimester, having family history of hyperemesis gravidarum, Helicobacter pylori infection, and having depression were the determinants of hyperemesis gravidarum. Primigravid women, those living in urban areas, and women who have a family history of hyperemesis gravidarum should have psychological support and early treatment initiation if they develop nausea and vomiting during pregnancy. Routing screening for Helicobacter pylori infection and mental health care for a mother with depression at the time of preconception care may decreases hyperemesis gravidarum significantly during pregnancy.

DISCUSSION

Hyperemesis gravidarum (HG) affects pregnant women, and is characterized by nausea, vomiting,

and an inability to tolerate oral fluids or food. Short-term consequences include dehydration, weight loss, and electrolyte imbalances. In the longer term, affected women have an increased risk of developing psychiatric disorders like depression, and avoiding any further pregnancies. Termination of pregnancy due to the disease has been described in up to 15% of women with HG. Even though maternal mortality is uncommon, severe complications like Wernicke's encephalopathy exist. Short-term consequences for the infant include being born preterm, being small for gestational age, and having a low birthweight, but there is also some evidence for negative long-term health-outcomes, such as an increased risk for sleeping problems and anxiety in adulthood. On top of the individual consequences for the woman and her child, the cost to society is enormous, with HG being the leading cause of hospitalization in early pregnancy, and often resulting in sick leave.[13,14]

Nausea and vomiting in pregnancy (NVP) affects up to 85% of all women during pregnancy, but for the majority self-management suffices. For the remainder, symptoms are more severe and the most severe form of NVP - hyperemesis gravidarum (HG) - affects 0.3-1.0% of pregnant women. There is no widely accepted point at which NVP becomes HG.[15]

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. 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. 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.[16,17]

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. 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. 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.[16]

The etiology of HG is largely unknown, but recent studies indicate a strong genetic component; it is suggested that the risk of HG in offspring increases by nearly threefold if the maternal history of

HG is present. Other genomic studies indicate an association of growth and differentiation factor 15 protein (GDF15), a known cause of cancer cachexia, with HG. While other causes of HG are not as well researched, there is evidence to show that females who have undergone artificial reproductive technology (ART) for pregnancy have a higher incidence of HG. Other suggested causes include a history of motion sickness or gastrointestinal (GI) disorders , *Helicobacter pylori* infections, and low maternal weight before pregnancy.[3,18]

Extremes in body weight in either direction are associated with an increased incidence of HG. All factors being similar, overweight females are more likely to develop hyperemesis gravidarum than their underweight counterparts. Maternal prepregnant smoking was found to be protective against HG. Among females who smoke daily or occasionally, the prevalence of HG is lower than in nonsmokers. The smoking habits of the partner are not found to have any effect. Cannabis, often used as an antiemetic, can also contribute to nausea and vomiting during pregnancy (NVP) due to its biphasic effect: If taken in acute, low doses, it has an antiemetic effect, while high doses or chronic use can cause cannabinoid hyperemesis syndrome, leading to increased intractable vomiting.[3]

The mainstay of supportive measures is to provide adequate rehydration and electrolyte repletion. Current initial management recommendations include changing the patient to NPO status, providing immediate fluid resuscitation with boluses of normal saline or lactate ringers solution. Continuous hydration should then be maintained with a solution containing 5% dextrose. Studies have shown faster improvement of nausea symptoms with dextrose-containing fluids. Additionally, serum electrolytes especially magnesium, phosphate, potassium should be repleted and sodium levels should be monitored. To prevent Wernicke's encephalopathy, 100 mg of thymine should be administered at initiation of rehydration. In cases of prolonged hospitalization without improvement in symptoms, parenteral nutrition may be indicated.[19]

Non - pharmaceutical approaches to treating N/V include herbs, such as ginger and chamomile, acupuncture, and massage. Capsules of ginger decreased episodes of N/V within 1 week compared to placebo tablets. A systematic review and meta-analysis found that ginger reduced nausea but not vomiting when compared to placebo. Treatment with acupuncture was associated with decreased severity of N/V compared to placebo in one study. However, three other studies have not confirmed improvement associated with acupuncture compared to placebo. Compared to placebo, pyridoxine or vitamin B6 supplementation reduced nausea but not vomiting. Vitamin B6 supplementation resulted in similar reductions in nausea and vomiting compared to ginger and acupuncture. The mechanism of therapeutic effect is unclear and no correlation between vitamin B6 level and severity of nausea was observed. Vitamin B6 has minimal side effects and is not associated with fetal malformations.[20]

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CONCLUSION

Several pharmaceuticals are currently in use, but there is no evidence regarding which is preferable, when to commence treatment, or what dosage or administration route is most beneficial. These questions have been highly prioritized by HG patients. It is also unclear whether initial fasting, infusions with dextrose, or total parenteral nutrition have any positive effects for the patients.

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