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Hyperemesis gravidarum: a literature review

Hiperémesis gravídica: una revisión bibliográfica

Fabricio Sánchez-Velásquez[1]

[1]Universidad Católica de Cuenca, Av. de las Américas y Humboldt, Campus Humboldt, Cuenca, Ecuador.

Correspondence: fabriciosanchez1967@gmail.com

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ABSTRACT

Background: Pregnancy is a time of physiological changes that lead to the development of various symptoms, the most common of which are nausea and vomiting; these are present in 70-80% of all pregnant women. They usually appear between the second and fourth week of gestation, and spread up to 22 weeks. Hyperemesis gravidarum consists of repeated vomiting at least one to four times a day, associated with constitutional changes in weight. **Objective:** to update the community on diagnostic and therapeutic advances in hyperemesis gravidarum. **Methods:** we used articles of great scientific relevance, validated and published in the last 5 years in different databases such as: Pubmed, Scopus or Web of Science, in English and Spanish, that address the diagnosis and treatment of hyperemesis gravidarum. **Results:** the review of the methods of diagnosis of HG referred to in the scientific literature leads to the conclusion that to date no universal system for classifying the disease has been adopted.

Keywords: hyperemesis gravidarum, pregnancy, diagnosis, treatment.

RESUMEN

Antecedentes: el embarazo es una etapa en la que existen cambios fisiológicos que conllevan a desarrollar varios síntomas, entre los más comunes las náuseas y el vómito; estos están presentes en el 70 al 80% de todas las embarazadas. Suelen aparecer entre la segunda y cuarta semana de gestación, y se difunden hasta las 22 semanas. La hiperémesis gravídica consiste en vómitos que se repiten por lo menos de una a cuatro veces al día, y que se asocian a cambios constitucionales en el peso. **Objetivo:** actualizar a la comunidad sobre los avances diagnósticos y terapéuticos de la hiperémesis gravídica. **Método:** se utilizaron artículos con gran relevancia científica, validados y publicados en los últimos 5 años en las diferentes bases de datos como: Pubmed, Scopus o Web of Science, en idioma inglés y español, que aborden el diagnóstico y tratamiento de hiperémesis gravídica. **Resultados:** la revisión de los métodos de diagnóstico de la HG referidos en la literatura científica permite concluir que hasta el día de hoy no se ha adoptado un sistema universal para clasificar la enfermedad.

Palabras clave: hiperémesis gravídica, embarazo, diagnóstico, tratamiento.

INTRODUCTION

Nausea and vomiting are common problems in most pregnant women. They occur in 70%-75% of pregnancies (Popa et al., 2021) and appear in the first weeks after fertilization and can last until week 20. It has been determined that, in 0.3 to 10% of pregnant women, the symptoms are attenuated, which is called pernicious vomiting of pregnancy or –as it is currently known– hyperemesis gravidarum (hereinafter HG) (Liu et al., 2022).

HG is characterized by homeostatic alteration, which causes nausea and uncontrollable vomiting on more than three occasions; these manifestations are associated with weight loss of up to 3 kilograms, dehydration, alkalosis and ketoanuria. It is considered one of the most common causes of hospitalization (Jennings et al., 2021). Its etiology is unknown. Triggering factors for this entity are of genetic, hormonal and psychological origin; however, they are associated with other factors such as: the location of the corpus luteum, Helicobacter Pylori infection, embryo gender, metabolic states and history of estrogen-based contraceptive use (Austin et al., 2019).

Its detection is essential for maternal-fetal well-being; however, as it presents a multifactorial etiology, its identification is based on the application of exclusion criteria. In general, it is necessary to confirm the presence of extreme nausea and vomiting during pregnancy; therefore, it is important to carry out an adequate clinical history and a complete physical examination to reach a diagnosis. In addition, laboratory tests complement the diagnosis. The use of imaging studies may be considered to discharge other alternative pathologies (Jennings et al., 2021).

The management of HG is multifactorial and will depend on the severity of the disease. It is generally based on non-pharmacological support measures, nutritional support, psychological and pharmaceutical therapy. These actions seek to improve the quality of life of the pregnant woman, as well as guide the pregnancy to a successful and uncomplicated term (London et al., 2017).

HG is a frequent indication for admission to the hospital ward during the first 20 weeks of gestation. It does not have a unique clinical definition and criteria regarding the guidelines on nausea and vomiting, which makes its analysis difficult; this leads to multiple complications that harm maternal and fetal well-being.

This constitutes a problem, since mothers diagnosed with HG need immediate attention; hence the importance of this research work, whose purpose is to provide updated scientific evidence regarding the diagnosis and treatment of HG to health professionals, so that they can guarantee adequate care for this group of patients. In addition, this review will serve as a reference material for future colleagues, providing them with both general and specific information on the subject. Furthermore, based on the results of this study, health professionals will be able to identify the current state of research on HG, as well as the gaps and limitations that exist around the object of study. This constitutes a starting point for

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further investigation into the subject, the main benefits of which will be for pregnant women and their families.

THEORETICAL FRAMEWORK

HG is a common condition during pregnancy, characterized by persistent and intense nausea and vomiting; it may or may not be associated with the presence of metabolic disorders, with a prevalence of 0.3% to 2% (Groleau et al., 2019). It generally occurs before 22 weeks of gestation. It has a fundamental effect on the quality of life of this group of patients, as it is related to perinatal side effects (van Vliet, 2018).

It is of unknown etiology, however, several theories have been associated with its presence, in which the following are involved: 1) Gastrointestinal factors such as the association of Helicobacter Pylori, although there is controversy regarding this. Several studies indicate that there may be a correlation between this infection and HG, so more research studies are needed. 2) Psychological factors, such as stress, depression, anxiety, mood disorders, which may be closely related to this condition. 3) Genetic factors, which include two types of proteins: with a family inheritance of up to 3 times in those users whose mother or sister had this condition (Dean et al., 2019); or in which high levels of hormones related to pregnancy are found: human chorionic gonadotropin (HCG), progesterone, estrogens, placental growth hormone, leptin and adrenal corticals. In those women with a high level of HCG and estrogens, nausea and vomiting are more intense compared to pregnancy, where such figures are normal (Ahmed et al., 2021).

Currently there is no single guideline that defines and is considered appropriate for the diagnosis of HG (London et al., 2017). It is essential, as in any disease, to start with an adequate detailed anamnesis of every woman during the gestation period. In women suspected of having HG, aspects such as the history of complications during previous pregnancies, estimated gestational age, onset, frequency and severity of nausea and vomiting, use of medication and interventions performed to treat symptoms should be considered (Jennings et al., 2021).

In addition, it is essential to perform paraclinical tests, complete blood count, complete biochemistry, and renal function tests, in order to evaluate the possible complications that the user presents; for example, hemoconcentration and electrolyte alterations indicate a context of dehydration and, therefore, acute renal failure. Imaging studies can be useful for the evaluation or confirmation of alternative diagnoses (Jennings et al., 2021).

An identification system has been generated that serves as support to categorize HG, such as the “PUQE (Unique Quantification of Emesis and Nausea During Pregnancy)” scoring index; However, its diagnosis is still carried out through the clinical method of exclusion (London et al., 2017). A score of 6 or better is considered a mild condition, 7-12 is moderate, and 13 or better is considered severe (Liu et al., 2022).

Current studies on this disorder have basically focused on treatment. There is a wide range of research on its management, from supportive alternatives to pharmacological measures (London et al., 2017).

It is important to tell patients with characteristic symptoms that they should avoid certain odors, foods, or activities that they consider could aggravate their condition (Abramowitz et al., 2017). Complementary measures are recommended as initial therapy, such as providing adequate rehydration and, depending on their requirement, electrolyte replacement (London et al., 2017). The use of ginger supplements (one 250 mg capsule orally every 6 hours a day) has been shown to be effective in reducing nausea and vomiting (Jennings et al., 2021). The use of this therapy is very simple and effective, as it relieves nausea and vomiting in pregnant women, stimulates gastrointestinal movement and gastric secretions, and inhibits the development of H. Pylori (Liu et al., 2022).

The presence of nausea and vomiting is caused by different mechanisms that are unknown; therefore, the combination of oral antiemetic medications has been shown to have a promising effect in controlling the condition, improving the quality of life. However, if the symptoms are not controlled, hospitalization of the pregnant patient should be considered (Liu et al., 2022).

According to the guidelines established by the American College of Obstetrics and Gynecology (ACOG), non-pharmacological treatment will be started; but in the event that patients continue to present significant symptoms, the combination of pyridoxine (vitamin B6) and doxylamine is recommended, two first-line drugs, cost-effective, easy to obtain and safe for both the mother and the fetus. The combination of both drugs is the only one considered by the FDA for the therapy of nausea and vomiting during the period of pregnancy (Abramowitz et al., 2017). The dose can be from 10-20 mg and from four to 12 hours a day, respectively. Drugs recommended as second line are dimenhydrinate, diphenhydramine, prochlorperazine and promethazine (Liu et al., 2022).

In addition, in those women whose symptoms cannot be controlled with the medication described above and who do not present signs of severity, the administration of ondasetron or metoclopramide is recommended, although considering the risk-benefit. Research on the safety and efficacy of these two drugs found that, for the most part, they were associated with effects on newborns (Abramowitz et al., 2017).

Currently, the study of gabapentin as an inhibitor of symptoms in HG has been implemented, which gave good results in patients whose oral antiemetics did not cause clinical improvement. At the moment, the exact risk-benefit level of this drug is not known, but different studies already apply it as a treatment regimen for this condition (Guttuso et al. 2021).

The use of corticosteroids in this disease has also had a great impact on in- and out-of-hospital management. The efficacy of its use was determined, mainly in the first trimester of pregnancy, as long as the therapeutic regimens have not caused improvement and the patient is previously informed of the risk (Asmat et al., 2020).

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Surgical treatment for HG is still limited; however, there are techniques already implemented since 1997, such as the percutaneous endoscopic jejunostomy tube, which is one of the surgical procedures with good results. On the other hand, in several case reports in which this technique was applied, especially in patients with severe or refractory HG, both pharmacological and non-pharmacological therapeutic methods did not cause improvement. Currently, these procedures are still under study, due to the complications triggered by surgical intervention in pregnant patients (Kruchko et al., 2020).

For those patients diagnosed with HG and who present severe dehydration or ketonuria, the use of intravenous fluids is recommended. Basically, sodium chloride or Ringer's lactate is used; in turn, and according to previous research, the administration of dextrose has shown improvement in symptoms, as long as the patient does not have comorbidities related to its components. Likewise, parenteral nutrition and vitamin and mineral supplementation are of great support for the correction of the electrolyte imbalance that this group of patients could experience (Liu et al., 2022).

Various pregnancy-related complications may occur: severe dehydration, malnutrition, anemia, Wernicke's encephalopathy due to vitamin B1 deficiency, acute kidney failure, seizures, altered state of consciousness, ataxia, liver disease, pancreatitis, cardiovascular disorders, coagulopathies, stroke, deep vein thrombosis, pulmonary embolism, depression, and stress. Complications related to the newborn include low birth weight or prematurity. Complications that are considered life-threatening are rare; the most frequent are: hydroelectrolytic imbalance, vitamin K deficiency, and Wernicke's disease (Popa et al., 2021).

METHODS

This research consisted of a bibliographic review of the medical literature on the diagnosis and treatment used in HG. The information was collected through the analysis of different scientific articles published in the last 5 years in different databases (Pubmed, Web of Science, Scopus and Medigraphic).

First, a question was posed that facilitated the collection of important and precise data for the documentation; later, and through the search equation strategy using the MeSh tool, the following terms were established for an adequate review: “Hyperemesis Gravidarum” [MeSh] and “Diagnosis”; “Hyperemesis Gravidarum” [MeSh] and “Treatment”. As a limitation, it was established that the published articles be from the last 5 years, both in Spanish and English.

Each title and summary of the selected articles was read in order to identify those that have a precise focus on the established topic.

DISCUSSION

Based on the literature review, the most important findings are discussed; these are classified into four dimensions: (1) risk factors involved in the development of HG; (2) methods of diagnosis of HG; (3) maternal-fetal complications arising from HG; and (4) therapeutic techniques applied in HG.

Risk factors

There are many risk factors related to HG; however, it was recurrent, in the scientific literature reviewed, to point out that an adequate methodology and clinical research design are still required to report these associations (Tayfur et al., 2017). For the present analysis, the risk factors were categorized into:

Personal factors

Many studies agreed that HG is more common among young mothers. In addition, the young age of pregnant women also carries a risk of disease duration extending beyond 27 weeks of gestation (Austin et al., 2019). The decreased risk of HG incidence with age may be explained by the subsequent treatment of high estrogen levels by the production of sex hormone-binding globulin during subsequent menstrual cycles (Lu et al., 2021). Low socioeconomic status is considered a risk factor for HG (Beyazit et al., 2017). However, sociodemographic factors do not explain racial/ethnic variation in HG prevalence, but rather these variations between societies are due to other cultural, genetic, or diet-related factors (Austin et al., 2019). Low socioeconomic status is also an important risk factor for H. pylori infection; This is because crowded populations have a higher risk of transmission and higher prevalence rates of this pathogen, which spreads between people through the fecal-oral or oral-oral route and contaminated water is a possible environmental reservoir (Koot et al., 2020; London et al., 2017).

On the other hand, the diet of pregnant women during the 12 months prior to conception has been studied, finding that those with certain dietary habits are at risk of HG; this is the case for different populations, for example, Asian and Indian (Tian et al., 2017). Asian women are at higher risk of HG because they are lactose intolerant and have diets low or deficient in dairy products. The Indian population, which is more commonly vegan, is more likely to have HG.

Obstetric factors

The incidence of HG was found to be higher in multiple pregnancies, molar disease, and Down syndrome (Lu et al., 2021). Nulliparous women are at higher risk because they have higher serum and urinary estrogen levels than multiparous women, and those women in their first pregnancies have higher estrogen levels in the first trimester than in subsequent pregnancies (Lu et al., 2021). In multiple pregnancies, the incidence of HG was found to be higher in male and male twins and in male and female twins. All female twins have a lower incidence, which was unexpected due to higher maternal estrogen levels (Abramowitz et al., 2017; Austin et al., 2019; Jennings and Mahdy, 2022; Tayfur et al., 2017).

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RESULTS

Table 2

Summary table of the findings of the bibliographic review

Authors	Risk factors	Diagnostic methods	Maternal-fetal complications	Applied therapeutic techniques
Nurmi et al. (2020)	Underweight Overweight Older age	Classification of Diseases (ICD)	NS	NS
London et al. (2017)	*H. pylori*	Objective measure of acute starvation (usually large ketonuria on urinalysis)	**Maternal:** lethargy, confusion, hyporeflexia, ataxia, oculomotor symptoms including nystagmus and ophthalmoplagia. Deaths associated with Wernicke's encephalopathy.	Hydration. Prenatal vitamins Pharmacological methods Alternative medicine: acupuncture
Tayfur et al. (2017)	Multiple pregnancy Hyperthyroidism Molar pregnancy Gastrointestinal disorders Female offspring Gestational trophoblastic neoplasia Diabetes Psychiatric disorders	Calculation of the platelet to lymphocyte ratio and platelet count.	NS	Antihistamines (H1 receptor antagonists).
Mitchell-Jones et al. (2017)	NS	NS	**Maternal:** NVP experienced by up to 91% of women.	Therapeutic intervention for physical and psychological morbidity.
Abramowitz et al. (2017)	African American, Indian, or Pakistani ancestry Primiparous women Multiple gestations Gestational trophoblastic disease Sister or mother who had HG	Pregnancy Single Emesis Quantification Score (PUQE) Rhodes Index Assessment of comorbid conditions: reflux Obstetric ultrasound.	**Maternal:** increased blood urea nitrogen and hematocrit, and in 15% to 25% of cases, hyponatremia, hypokalemia, and hypochloremia. Between 15% and 50% of patients have elevated serum aminotransferases and total bilirubin.	Combination of doxylamine and pyridoxine Ondansetron or dopamine antagonists such as metoclopramide or promethazine Mirtazapine
Kjeldgaard et al. (2017a)	Women with a history of depression.	NS	**Mothers:** Symptoms of emotional distress	NS
Kjeldgaard et al. (2017b)	Genetic components Endocrine factors Helicobacter pylori infection	NS	NS	Treatment focused on relieving somatic discomfort and ensuring the health of mother and child
Beyazit et al. (2017)	Physiological, biological, and sociocultural factors High levels of human chorionic gonadotropin Gastrointestinal dysfunction Liver dysfunction Metabolic disorders Lipid disorders Helicobacter pylori infection Genetic susceptibility	· Review of mean platelet volume (MPV), platelet distribution width (PDW), neutrophil to lymphocyte ratio (NLR), red blood cell distribution width (RDW), and platelet to lymphocyte ratio (PLR).	NS	NS

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Authors	Risk factors	Diagnostic methods	Maternal-fetal complications	Applied therapeutic techniques
Fejzo et al. (2017)	Genetic predisposition Being a relative of patients with HG Mutations in the thyrotropin receptor gene	NS	**Maternal:** Deaths from HG, as well as morbidity including Wernicke encephalopathy, acute renal failure, liver function abnormalities, splenic avulsion, esophageal rupture, pneumothorax, and post-traumatic stress symptoms. Fetal: 4-fold increased risk of preterm birth and 3-fold increased risk of neurodevelopmental delay in children.	NS
Grooten et al. (2017)	NS	NS	**Fetal:** poor fetal growth and increased risk of prematurity, low birth weight (OR 1.4 for birth weight <2500 g), being small for gestational age (OR 1.3).	Enteral tube feeding
Senturk et al. (2017)	Endocrine factors Gastrointestinal dysfunction Liver abnormalities Autonomic nervous dysfunction Psychosomatic factors	NS	**Maternal:** Mental health is negatively affected, psychiatric symptoms may continue even after HG is discontinued.	Treatment for anxiety
Topalahmetoğlu et al. (2017)	Low educational level Low income Poor social relations	Observation of persistent vomiting and nausea, weight loss of more than 5% of pre-pregnancy body weight, ketonuria, electrolyte abnormalities, and dehydration	**Maternal:** dehydration, electrolyte imbalance, impact on quality of life and psychological state of pregnant women. Higher relative risks of moderate depression and severe anxiety.	Determination of the psychological status of women with HG
Koot et al. (2017)	NS	HG code from the International Classification of Diseases 8 (ICD-8) of 1968-1986	**Fetal:** poor perinatal outcomes, including prematurity and low birth weight.	NS
Fossum et al. (2017)	Placental dysfunction Gastrointestinal pathology Immunological factors Endocrine and metabolic factors	NS	**Maternal:** Women exposed to HG have a reduced risk of death from cancer.	NS
Sari et al. (2022)	Increased levels of ischemia-modified albumin (IMA) in maternal serum. Ischemic intrauterine environment leading to elevated serum concentrations of IMA.	NS	**Maternal:** metabolic vomiting, carbohydrate depletion, dehydration or electrolyte imbalance, Wernicke's encephalopathy, central pontine myelinolysis, hepatic dysfunction and renal failure. **Fetal:** premature delivery, fetal and neonatal mortality.	Current treatment of HG is empirical and suboptimal
Tian et al. (2017)	Hypoglycemia Irritable bowel syndrome Panic disorder Special diet	NS	**Maternal:** physical and psychosocial problems both before and after pregnancy. **Fetal:** 4 times higher risk of premature birth and 3 times higher risk of delayed neurological development in children.	NS
Dean et al. (2018)	HG in previous pregnancy	Pregnancy Unique Quantification of Emesis-24 (PUQE) score Exclusion of other causes of nausea and vomiting Ketonuria as a marker of dehydration and/or threshold for admission, discharge, and access to intravenous fluids	**Maternal:** loss of identity, social isolation, feelings of guilt and suicidal ideation, and pressure to terminate pregnancy. **Fetal:** termination of pregnancy occurs in about 10% of cases, low birth weight, premature labor, small babies for gestational weight, small long-term cardiometabolic and neurodevelopmental effects.	Pharmacological interventions Intravenous fluid therapy Social and psychological support

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Authors	Risk factors	Diagnostic methods	Maternal-fetal complications	Applied therapeutic techniques
Jennings y Mahdy (2022)	Increased placental mass in a molar or multiple gestation Mother or sister experienced HG	Check for ketonuria Complete blood count Electrolyte assessment Thyroid, lipase, and liver function tests Radiographic studies Obstetric ultrasounds Magnetic resonance imaging (MRI)	**Maternal:** vitamin deficiency, dehydration and malnutrition, Wernicke's encephalopathy, esophageal rupture and pneumothorax, electrolyte abnormalities such as hypokalemia, higher rates of depression and anxiety during pregnancy.	Switch prenatal vitamins to folic acid supplements. Antihistamines and dopamine antagonists. Administer intravenous fluid boluses or continuous infusions of normal saline.
Yeh et al. (2018)	Psychological predisposition Evolutionary adaptation Hormonal stimulation	Clinical diagnosis of exclusion	**Maternal:** persistent vomiting, weight loss of more than 5%, ketonuria, electrolyte abnormalities (hypokalemia), and dehydration (high urine specific gravity).	Early intervention and treatment of nausea and vomiting to prevent progression to hyperemesis gravidarum.
Austin et al. (2019)	HG in previous pregnancies Multiple pregnancies Psychiatric illnesses High and low BMI before pregnancy Young age Diabetes	Laboratory studies Urinalysis to reveal ketonuria Electrolyte analysis to show hypochloremic metabolic alkalosis or metabolic acidosis with severe volume contraction	**Maternal:** weight loss, dehydration, micronutrient deficiency and muscle weakness, Mallory-Weiss tears, esophageal rupture, Wernicke encephalopathy, central pontine myelinolysis, retinal hemorrhage, spontaneous pneumomediastinum, and vasospasm of cerebral arteries. **Fetal:** fetal growth retardation, preeclampsia, SGA, earlier delivery and lower birth weight.	Use of transdermal clonidine. Rescue antiemetic therapy.
Sridharan y Sivaramakrishnan (2018)	Young primiparous women Non-Caucasian women	NS	NS	Acupuncture, acupressure and methylprednisolone.
Yan et al. (2020)	Young primiparous women Non-Caucasian race Non-smokers	NS	**Fetal:** prematurity, small for gestational age, nervous system delay, and autism spectrum disorder in offspring.	External treatment of traditional Chinese medicine (TCM): acupuncture, acupressure, etc.
Ostenfeld et al. (2020)	NS	NS	**Maternal:** dehydration, electrolyte imbalances, weight loss and hospitalization, lower quality of life and elective termination of pregnancy.	Ondansetron. Mirtazapine.
Žigrai et al. (2020)	Hyperthyroidism	NS	**Maternal:** Wernicke's encephalopathy	Symptomatic treatment according to local protocol. Antihypertensive treatment. Subsequent treatment with thiamine.
Kruchko et al. (2020)	Combination of hormonal changes Liver dysfunction Metabolic disorders Lipid disorders	NS	**Maternal:** nausea and vomiting, associated hypovolemia, dehydration, metabolic abnormalities, weight loss, muscle weakness, Boerhaave's syndrome and vitamin deficiency encephalopathy.	Gastric feeding. Rarely, post-pyloric feeding. Placement of PEG-J tube.
Meinich et al. (2020)	Maternal weight gain Failure to regain pre-pregnancy weight by week 13 to 18 Having a low pre-pregnancy BMI	NS	**Maternal:** dehydration, weight loss and fluid and electrolyte disturbances, reduced quality of life for the woman, Wernicke's encephalopathy. **Fetal:** increased risk of premature birth.	Individualized nutritional treatment that recognizes differences in pre-pregnancy BMI and severity of first trimester weight loss.
Koot et al. (2020)	Maternal endocrine function Abnormal growth of the placenta Pre-existing Helicobacter pylori infection.	Prolonged vomiting, altered electrolyte balance, dehydration and ketonuria.	NS	Measurement of urinary ketones. Treatment with intravenous dehydration therapy.
Lu et al. (2021)	High levels of chorionic gonadotropin High levels of estrogen Vitamin B deficiency Down syndrome. Hypofunction of the adrenal cortex	NS	**Maternal:** hospitalization at the beginning of pregnancy, physical and mental disorders, affects the postpartum period and has an impact on quality of life.	Correction of electrolyte disturbances. Vitamin supplements Serotonin receptor antagonists Treatment of Helicobacter pylori Vitamin B6

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Medical factors

First, hyperthyroidism should be mentioned: pregnant women with a medical history of hyperthyroidism were found to be more prone to HG in pregnancy (Lu et al., 2021; Žigrai et al. 2020).

On the other hand, pregnant women with a medical history of depression, anxiety, or any mood disorder are more prone to HG in pregnancy (Kjeldgaard et al., 2017a; Kjeldgaard et al., 2017b). Furthermore, marital stress and conflict have been associated with an increased risk of HG. A significantly high incidence of depression and anxiety occurs in women with HG, especially with a long duration of the disease, making it difficult to explain the causal relationship between HG and mental health problems (Senturk et al., 2017; Tayfur et al., 2017).

In turn, there is a correlation between changes in hormonal levels during pregnancy, especially high progesterone level and relaxation of the upper esophageal sphincter; this may play a role in the pathogenesis of pregnancy dyspepsia. Pregnant women with a medical history of peptic ulcer are more susceptible to hospitalization due to HG (Yeh et al., 2018). Recently, Helicobacter pylori infection has been established as a possible cause of HG (Yeh et al., 2018). However, it is necessary to ask whether a higher incidence of nausea and vomiting may lead to the elevated levels of H. pylori found in these pregnant patients, due to the loss of acid and the creation of a basic environment that favors the growth of H. pylori. Another possible explanation is that a shift in intracellular and extracellular volume occurs at the beginning of pregnancy as a consequence of the increase in steroid hormones, and these translate into a change in pH that could favor H. pylori infection. In this case, although an association between HG and H. pylori infection is suggested, considerable heterogeneity between studies causes limitations (London et al., 2017).

Finally, genetic factors have also been pointed out. One of the theories that attempt to explain the etiology of HG is the presence of a genetic role. The importance of a positive family history in the development of the disease has been shown (Abramowitz et al., 2017; Beyazit et al., 2017; Fejzo et al., 2017; Jennings and Mahdy, 2022).

Diagnostic methods

All studies addressing the topic of HG diagnoses agree that there is no single definition of HG. The most commonly reported criteria for diagnosing this disease include persistent vomiting unrelated to other causes (Topalahmetoğlu et al., 2017; Koot et al., 2020), an objective measure of acute starvation (usually elevated ketonuria on urinalysis) (Austin et al., 2019; Dean et al., 2018; Jennings and Mahdy, 2022; Koot et al., 2020; Topalahmetoğlu et al., 2017), electrolyte abnormalities, and acid-base disturbances (Lu et al., 2021). Weight loss, on the other hand, is cited as a loss of at least 5% of pre-pregnancy weight (Lu et al., 2021). Serum electrolyte and acid-base abnormalities may include hypochloremic alkylosis, hypokalemia, and hyponatremia (Topalahmetoğlu et al., 2017). Hyperemesis gravidarum may also present with signs and symptoms associated with severe dehydration, such as orthostatic hypotension, tachycardia, dry skin, mood changes, and lethargy (Dean et al., 2018; Koot et al., 2020; Topalahmetoğlu et al., 2017). The literature review identified the classification system for categorizing hyperemesis gravidarum, known as the PUQE scoring index, which represents the daily number of vomiting episodes, the duration of nausea per day in hours, and the number of retching episodes per day (Abramowitz et al., 2017; Dean et al., 2018).

In this case, it is noted that a universal classification system for hyperemesis gravidarum has not yet been adopted, with clinical diagnosis of exclusion being the most effective (London et al., 2017). The differential diagnosis of patients with HG is broad and includes infections, metabolic, gastrointestinal, neurological, and iatrogenic causes (Austin et al., 2019). Common diagnoses such as gastroenteritis, cholecystitis, hepatitis and biliary tract diseases, drug abuse/misuse, migraines, and rarer causes such as diabetic ketoacidosis, intracranial lesions leading to increased intracranial pressure, and intestinal obstruction should also be considered (Jennings and Mahdy, 2022).

In turn, the following laboratory tests were identified for the initial evaluation: complete blood count and serum metabolic panels, urinalysis for ketones and specific gravity, thyroid function studies, amylase/lipase levels, and in early pregnancies, a serum beta-human chorionic gonadotropin level for evaluation of possible molar or multiple gestations (Austin et al., 2019; Franken et al., 2021; Jennings and Mahdy, 2022; Koot et al., 2020; Topalahmetoğlu, 2017). However, only a limited subset of these tests is used in daily clinical practice for a patient with an initial presentation of HG (Lu et al., 2021).

Finally, cranial computed tomography (CT) or magnetic resonance imaging (MRI) can be used for the diagnosis of Wernicke encephalopathy, which can reveal symmetric periventricular lesions in the mediodorsal nuclei of the thalamus, hypothalamus, and periaqueductal gray matter (Žigrai et al., 2020).

Maternal-fetal complications

Observations from most studies included in the present literature review demonstrated that certain complications of HG could occur in cases of inadequate therapy or even lack of medical support (Jennings et al., 2022). However, some complications occurred even after the patient received adequate therapy. The most frequent life-threatening complication of HG was Wernicke encephalopathy (Austin et al., 2019; Fejzo et al., 2017; Jennings and Mahdy, 2022; Kruchko et al., 2020; Sari et al., 2017; Žigrai et al., 2020). This condition manifests itself by confusion, gait ataxia, ophthalmoplegia, or seizures. Wernicke encephalopathy is due to a deficiency of thiamine (vitamin B1), an essential cofactor in carbohydrate metabolism. In the clinical setting of HG, this deficiency is usually caused by fluid replacement without thiamine supplementation. Most patients manifest only one or two of the above symptoms (Žigrai et al., 2020).

In turn, cardiac complications in women with HG have been found to be rare but can be severe (Dean et al., 2018). They mostly refer to ventricular arrhythmias, which are caused by prolongation of the QTc interval due to electrolyte imbalance (hypokalemia, hypomagnesemia, hypocalcemia) and are triggered by repeated episodes of vomiting (Abramowitz et al., 2017; Jennings and Mahdy, 2022; Kruchko et al., 2020; Yeh et al., 2018). Among the most commonly identified fetal complications, the following

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should be mentioned: a 4-fold increased risk of preterm birth and a 3-fold increased risk of neurodevelopmental delay in children (Fejzo et al., 2017), poor fetal growth (24), fetal and neonatal mortality (Sari et al., 2022), small long-term cardiometabolic and neurodevelopmental effects (Dean et al., 2018), preeclampsia (Austin et al., 2019), nervous system delay and autism spectrum disorder in offspring (Yan et al., 2020). Another positive association described between HG and negative fetal outcomes is an increased prevalence of psychiatric disorders, mainly anxiety, depression, and bipolar disorder, in adults who were exposed to HG while in utero (London et al., 2017). However, no other studies have been published to date in support or dispute of these data.

Therapeutic techniques applied

The literature review found that there are few studies examining psychotherapy treatment for HG, including randomized trials (Mitchell-Jones et al., 2017). However, there are several case studies reporting that psychological support from family and medical staff reduces HG symptoms (Dean et al, 2018; Mitchell-Jones et al., 2017).

Among the pharmacological therapies identified, the use of antihistamines (H1 antagonists) should be highlighted, including doxylamine used in combination with pyridoxine, meclizine, dimenhydrinate and diphenhydramine; none of which are associated with fetal malformations (Jennings and Mahdy, 2022; Tayfur et al., 2017). In the case of ondansetron, a serotonin antagonist acting at the 5-HT3 receptor, it is the most frequently prescribed drug for the treatment of nausea and vomiting during pregnancy and its use is increasing rapidly. It is effective in reducing nausea and vomiting during pregnancy, and significantly more effective than combined treatment with pyridoxine and doxylamine in reducing nausea and vomiting. However, its side effects include headache, fatigue, constipation and, rarely, serotonin syndrome (Abramowitz et al., 2017; Jennings and Mahdy, 2022; Ostenfeld et al., 2020).

Dopamine antagonists, such as metoclopramide, promethazine and droperidol, have also been identified as having been used to treat HG (Abramowitz et al., 2017; Jennings and Mahdy, 2022). For example, metoclopramide is more effective in reducing nausea and vomiting than other dopamine antagonists (Abramowitz et al., 2017; Jennings and Mahdy, 2022). Therapeutic options for refractory cases include transdermal clonidine to reduce symptoms in women who cannot tolerate oral therapies (Yeh et al., 2018).

For women who do not respond to any of the previous treatments and who continue to lose weight, it is recommended that they receive support with enteral or parenteral nutrition in addition to any medications that provide symptom improvement (Meinich and Trovich, 2020). Some women refuse pharmacological treatments due to concerns about the risk of birth defects associated with medications taken during early pregnancy (Abramowitz et al., 2017). In the case of the antidepressant drug mirtazapine, it is used to treat patients receiving cancer treatment with a rapid onset of efficacy for nausea (day 1) and sleep (within the first 5 days). Its pharmacological profile of actions is similar to other medications used to treat HG (Abramowitz et al., 2017; Ostenfeld et al., 2020).

CONCLUSIONS

Risk factors for the development of HG have been identified. First, it was found that HG is common in young mothers. In turn, an association was found between low socioeconomic status and HG. Dietary factors are common in Asians, who are mostly lactose intolerant. Molar pregnancy, multiple pregnancies, fetus with Down syndrome and primary pregnancy are common obstetric factors for HG. Mood and anxiety disorders are associated with the disease, but a causal relationship has not yet been established. In particular, H. pylori infection is among the common risk factors. A strong positive family history of HG in patients highlights the genetic predisposition of these patients.

A review of the diagnostic methods for HG reported in the scientific literature allows us to conclude that to date no universal system has been adopted to classify the disease. This leads to health professionals not having a systematic, coherent guide accepted by the entire scientific community for determining the presence of HG among pregnant or gestating women. Given this situation, it is advisable to propose studies that establish the greater or lesser suitability of the different methods.

Regarding potentially fatal complications, these are extremely rare in HG. The most frequent serious complications are Wernicke's encephalopathy, electrolyte imbalance and vitamin K deficiency. The low mortality rate of patients with HG in recent years is explained by the high efficiency of modern therapy, where current guidelines can address the precise management of each complication.

From the description of the current therapeutic techniques applied in HG, it can be concluded that there is little evidence to support the superiority of one intervention over another in the treatment of HG; hence, a study comparing the side effect profiles, safety, economic costs and benefits of the treatments to inform selection is essential. Comparative evaluations of current treatments and expansion of therapies for severe or refractory HG, which has been associated with requests for termination of desired pregnancies, should be undertaken.

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