DOI: 10.1097/JPN.0000000000000075

CE Continuing Education
J Perinat Neonat Nurs • Volume 29 Number 1, 12–22 • Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Hyperemesis Gravidarum

A Holistic Overview and Approach to Clinical Assessment and Management

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ABSTRACT

Hyperemesis gravidarum (HG) is a rare and severe form of nausea and vomiting of pregnancy associated with significant costs and psychosocial impacts. The etiology of HG remains largely unknown, although maternal genetics and placental factors are suspected. Prompt recognition and treatment of HG are essential to minimize associated maternal and fetal morbidity. Diagnosis is made on the basis of typical presentation, with exclusion of other causes of severe nausea and vomiting of pregnancy. Validated clinical tools are available to assess severity of symptoms and guide plans of care. Evidence to guide management of HG is limited, but many nonpharmacologic and pharmacologic interventions are available with published guidelines to inform implementation. Care of the woman with HG requires compassion and acknowledgement of individual needs and responses to interventions.

Key Words: hyperemesis gravidarum, morning sickness, nausea and vomiting of pregnancy

Nausea and vomiting is very common in pregnancy, with rates as high as 91%.[1] Hyperemesis gravidarum (HG) is a fairly rare and extreme form of nausea and vomiting of pregnancy,[2–4] with distinct features and outcomes. A recent meta-analysis found that its prevalence in pregnancy to be between 0.3% and 3.6%, with an average of 1.1%.[1] Hyperemesis gravidarum is a clinical diagnosis based on typical presentation and exclusion of other causes of nausea and vomiting in the pregnant woman.[4] A universal definition has yet to be established, although it is classically defined by persistent nausea and vomiting, signs of dehydration, ketonuria, and weight loss of 5% or more of prepregnancy weight.[5] Onset of symptoms typically occurs between 6 and 8 weeks' gestation and peaks by 12 weeks.[5] Most women experience relief of symptoms by 20 weeks' gestation.[5] However, 10%[6] to 20%[7] of affected women experience symptoms throughout pregnancy and symptoms may even persist postpartum.[7]

Despite a low overall prevalence, the impact on women, families, and society is substantial. Poursharif and colleagues[6] found that more than 80% of women with HG reported negative psychosocial effects, including socioeconomic burdens, relationship difficulties, and psychological sequelae. Furthermore, the severity of symptoms of nausea and vomiting is correlated with decreased quality of life (QOL).[8,9] In one study, affected women were 3 to 6 times more likely to have a of low health-related quality of life (HRQOL) than women with normal nausea and vomiting of pregnancy, although both groups were more likely to have low HRQOL than asymptomatic women.[10] To offer perspective, Lacasse et al[8] report that HRQOL of women with moderate to severe nausea and vomiting of pregnancy was similar to HRQOL of women with breast cancer and myocardial infarction.

Hyperemesis gravidarum is the most common indication for hospitalization during the first half of pregnancy and is second only to preterm labor in pregnancy-related hospitalizations.[6,11] There were more than 22 000 HG-related hospitalizations in the United States in 2009 and more than 160 000 emergency department visits for the condition in 2008.[12] The cost

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Disclosure: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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Submitted for publication: June 19, 2014; accepted for publication: September 18, 2014.

of each of these hospital admission is estimated at $5932,[13] with total inpatient costs estimated at $250 million in 2009.[12] Although significant, these estimates do not include the costs of outpatient services or indirect costs[6] such as missed days of work and decreased productivity.[14] In addition, women must pay costs associated with lifestyle modifications, prescribed therapies, and complementary and alternative therapies, making HG a major financial burden on affected women and the healthcare system.

RISK FACTORS

Both pregnancy and prepregnancy factors have been associated with HG. Reported pregnancy-specific risk factors include gestational trophoblastic disease,[15] female fetal sex,[16–20] and multifetal pregnancy.[17,19] In addition, Roseboom and colleagues[16] found that affected women more often conceived with assisted reproductive technologies than unaffected women.

Prepregnancy variables that have been associated with HG include younger maternal age,[16,17] nulliparity,[17] prepregnancy body mass index less than 18.5 kg/m^2[17,21] and greater than 25 kg/m^2,[17,22] and lower socioeconomic status.[16] Medical histories of HG[17,23,24] and gestational trophoblastic disease[17] have also been associated with HG. Associated comorbidities include psychiatric illness,[16,17] migraines,[25] asthma,[17] preexisting diabetes,[16,17] hyperthyroid disorders, and gastrointestinal disorders.[17] In addition, there is growing evidence that *Helicobacter pylori* infection is a factor in the development of severe nausea and vomiting of pregnancy, although a causal relationship has not been established.[26] Furthermore, a maternal family history of HG is associated with diagnosis, implying a genetic or epigenetic component.[27,28] In a recent survey of 395 affected women, allergies and restrictive diets (eg, lactose avoidance, vegetarian) were associated with a longer duration of symptoms (>27 weeks), suggesting that these factors may affect the symptom duration.[29] Conversely, maternal age of more than 30 years and smoking are associated with a decreased risk of severe nausea and vomiting of pregnancy.[17,22]

ETIOLOGY

Although no conclusive pathogenesis has been determined, some theories are favored more than others. In general, the cause is thought to be multifactorial,[30] with the placenta playing a large role in the disorder.[31] Several placental hormones have been explored as causal components including human chorionic gonadotropin (hCG), estrogen, progesterone, human growth hormone, prolactin, and leptin.[30] Of these, hCG is most often implicated as a cause.[30,32]

The peak occurrence of HG is at the time of highest hCG levels. In addition, the association of HG with conditions associated with increased placental mass and elevated hCG levels such as multifetal and molar pregnancies supports this theory.[30] It is thought that hCG may stimulate upper gastrointestinal secretory processes or that the structural similarity between hCG and thyroid-stimulating hormone may cause excessive thyroid stimulation, leading to overwhelming nausea and vomiting.[30] The latter is supported by findings of declining thyroid-stimulating hormone levels mirroring elevations in hCG levels during early pregnancy and the high prevalence of excessive thyroid stimulation in women with HG.[30] Found in as many as two-thirds of afflicted women,[30] this excessive thyroid stimulation is often referred to as gestational transient thyrotoxicosis and is characterized by elevated free T4 and suppressed thyroid-stimulating hormone levels during the first half of pregnancy without evidence of autoimmune disease.[33] Other causes of hyperthyroidism in pregnancy, such as Graves disease, are not typically associated with severe nausea and vomiting,[4,30] emphasizing the role of hCG rather than solely the state of hyperthyroidism.[4]

However, research has failed to conclusively link elevated hCG levels to HG. Proposed explanations for this include dissimilar research methods, as the sensitivity of hCG assays varies, and the existence of hCG isomers. It is theorized that the type of hCG, rather than simply the amount, may play a role in the development of nausea and vomiting of pregnancy.[30] In addition, there is individual variation in sensitivity to hCG.[4] While hCG is a likely cause of nausea and vomiting of pregnancy, hCG alone cannot be responsible for all cases of HG, as symptoms often persist beyond the first trimester after hCG levels have peaked.[30]

Another factor commonly theorized to play a role in the development of HG is estrogen. Support for this hypothesis stems from estrogen-related gastrointestinal changes in pregnancy, including delayed gastric emptying and increased intestinal transit time.[30] In addition, nausea is a well-known side effect of estrogen therapies.[4,30] Nevertheless, while some studies have found a link between elevated estrogen levels and HG,[4,30] others have not.[30] With the lack of conclusive evidence, the etiology of this condition remains elusive.

OUTCOMES

Maternal outcomes

Typical nausea and vomiting of pregnancy may serve to protect the mother and the fetus from food-borne pathogens and is associated with decreased rates

of miscarriage when compared with women without these symptoms.[34] While HG has a similar relationship with miscarriage,[15] the severe symptoms are beyond normal[34] and are associated with substantial maternal morbidity.[35] In severe cases, the fetus may be immediately affected or suffer from long-term health effects.[35]

Once associated with substantial maternal mortality, advances in healthcare, especially intravenous fluid therapy, have dramatically decreased the risk of death from HG[35]; yet, significant maternal morbidity persists.[35] In addition to the disruption that the symptoms of nausea and vomiting have on the daily lives of women, HG can result in dehydration, electrolyte and metabolic imbalance, nutritional impairment, and weight loss.[36] In a survey of 819 affected women, 26.1% had lost more than 15% of prepregnancy weight. In the same study, women also reported such severe effects as retinal hemorrhage, hematemesis, anemia, hypotension, gallbladder dysfunction, liver dysfunction, and renal failure.[7] Other complications include hyponatremia, central pontine myelinolysis, vitamin B_6 (pyridoxine) and vitamin B_{12} (cyanocobalamin) deficiency, Mallory-Weiss tears, and venous thromboembolism.[37] Retinal detachment, esophageal rupture, pneumomediastinum, and splenic avulsion have been reported as well.[2] One of the most serious complications is Wernickes encephalopathy. Caused by thiamine deficiency, it can lead to permanent neurologic dysfunction and death.[2]

Hyperemesis gravidarum is also associated with significant psychological morbidity. In a prospective cohort study, affected women had higher average scores on the short-form State Trait Anxiety Inventory, Perceived Stress Scale, and Edinburgh Postnatal Depression Scale, implying elevated anxiety, stress, and depression when compared with unaffected women.[38] Of note, stress and depression scores improved with cessation of nausea and vomiting. However, anxiety scores remained elevated more than 5 weeks after cessation of vomiting.[38] A recent case-control study using the Depression, Anxiety and Stress Scale found that elevated levels of anxiety, stress, and depression in affected women fell below levels reported in controls in the third trimester of pregnancy when many women no longer experience symptoms,[39] suggesting that symptom control and resolution may ameliorate psychological distress. However, symptoms that continue into the postpartum period,[6] posttraumatic stress,[29,40] and breast-feeding and self-care difficulties have also been reported.[40] In addition, women have expressed suicidal ideations due to symptoms, demonstrating the enormity of the effects on psychological well-being. The burden can be so great that 15% of women with a history of HG reported terminating at least one pregnancy due to symptoms.[41]

During and after the experience, many women decide to modify their plans for current or future pregnancy. Seventy-six percent of women with a history of the condition reported changing their reproductive plans, many expressing a fear of pregnancy.[6] Thus, while symptoms are self-limiting, they have long-term influence on women.

Offspring outcomes

While most of the effects of HG are maternal, the fetus is at risk for poor outcomes as well. However, research is inconclusive in part due to variation in the definitions of the condition.[42] Dodds and colleagues[43] found that the offspring of affected women with weight gain of less than 7 kg (15.4 lb) were more likely to be small for gestational age, have low birth weight (<2500 g), and be born preterm (<37 weeks gestation) compared with women with normal pregnancies. However, affected women who had a pregnancy weight gain of 7 kg or more had risks equal to unaffected women,[43] suggesting that low weight gain may be the driving force behind perinatal outcomes rather than nausea and vomiting itself.[43] Since women with HG have more than double the risk of having a pregnancy weight gain of less than 7 kg,[43] this population is at increased risk for low birth weight, small for gestational age, and prematurity.

This is supported by a recent meta-analysis by Veenendaal and colleagues,[42] which found that HG was associated with low birth weight, small for gestational age, and preterm delivery. There was not an association with perinatal death, or Apgar score of less than 7 at 5 minutes. Data are limited regarding the effect on congenital anomalies. Pooled data from 3 studies included in the meta-analysis demonstrate similar rates of congenital anomalies in women with HG compared with women without. However, other studies have reported an association between the condition and specific anomalies including undescended testicles, hip dysplasia, trisomy 21, and central nervous system and skeletal anomalies. In contrast, one study found lower rates of oral clefts in offspring affected by hyperemesis than those without.[42]

Little is known about risks for offspring beyond the perinatal period. At the time Veenendaal and colleagues[42] conducted their meta-analysis, no studies had been published specifically investigating the long-term outcomes of children whose gestations were complicated by HG. In a survey since then, affected women more often reported having infants with irritability and colic than unaffected women.[29] In addition, in a survey of adult children whose mothers had HG, emotional and behavioral disorders were significantly more frequent than adults whose mothers had

uncomplicated gestations.[29] Investigating offspring of women with HG, Ayyavoo and colleagues[44] found decreased insulin sensitivity and increased fasting glucose values, which could mean these individuals are at risk for metabolic disease due to epigenetic changes. Further epigenetic research may find more health-related implications.

COMPREHENSIVE AND HOLISTIC ASSESSMENT

Essential to the assessment and care of pregnant women presenting with severe nausea and vomiting are compassion and appreciation for the burden of the condition on the whole woman. Women's perception of their healthcare providers' beliefs about their illness and their providers' humanistic qualities play a critical role in how women perceive the quality of their healthcare.[45] In a survey of affected women, more than a quarter reported having providers who were uncaring or who did not understand the severity of their symptoms.[6] These women were twice as likely to experience psychological sequelae and also more likely to change providers.[6] In another survey, women who had terminated pregnancies due to symptoms were 3 times as likely to report having providers who were uncaring or not understanding.[41] In addition to highlighting the magnitude of the maternal burden of the condition, these findings underscore the importance of caring and supportive healthcare providers.

Hyperemesis gravidarum is a clinical diagnosis of exclusion; no formal diagnostic criteria exist. Differential diagnoses for nausea and vomiting in pregnancy are shown in Table 1. A thorough maternal history including a detailed account of the present illness and the woman's medical and family history is essential.[37]

History of present illness

Systematic assessment of the presenting illness facilitates the exclusion of other causes of nausea and vomiting in pregnancy, the identification of hallmarks of HG, symptom severity, and consequent complications, and assists in the development of an individualized plan of care. Determining the onset of symptoms is critical. Nearly all women with nausea and vomiting of pregnancy present before 9 weeks' gestation. Nausea and vomiting predating conception or presenting after 9 weeks' gestation suggests alternative diagnoses.[4] Determining the duration of symptoms is essential, as Wernicke encephalopathy has been reported as soon as 3 weeks after the onset of symptoms.[37] Evaluating associations with meals and identifying triggers may also be helpful, as sensitivity to food odors is common with HG.[47] Fever,[2,4,46] urinary tract symptoms (dysuria, urinary urgency and frequency, suprapubic and flank pain),[37] or diarrhea[37] suggests that infection is the cause of the nausea and vomiting. While mild epigastric tenderness may be reported after protracted episodes of retching or vomiting, abdominal pain warrants further investigation.[2,4,37,46] Likewise, headache is not typical but, in rare instances, could represent a manifestation of neurologic disturbance secondary to complications such as Wernicke encephalopathy or central pontine myelinolysis.[4,46] Women should specifically be asked about the presence of hematemesis, as it could indicate gastric ulceration or Mallory-Weiss tears.[37]

Table 1. **Differential diagnoses for nausea and vomiting in pregnancy**[2,4,36,46]

Neurological	Genitourinary	Gastrointestinal	Metabolic	Pregnancy associated	Drug associated
Migraines Meningeal irritation Increased intracranial pressure Pseudotumor cerebri CNS lesion/tumor Vestibular abnormalities Porphyria	Nephrolithiasis Pyelonephritis Ovarian torsion	Foodborne illness Gastroenteritis Cholelithiasis/ cholecystitis Cholangitis Pancreatitis Hepatitis Appendicitis Gastroesophageal reflux disease Peptic ulcer disease Diaphragmatic hernia Intestinal obstruction	Addison disease Diabetic ketoacidosis Thyrotoxicosis	Multifetal pregnancy Gestational trophoblastic disease Preeclampsia/ HELLP Acute fatty liver of pregnancy	Drug intolerance Drug intoxication/ withdrawal

Abbreviation: CNS, central nervous system.
[a]From Goodwin,[2] American College of Obstetricians and Gynecologists,[4] Lee and Saha,[36] and Jueckstock et al.[46]

Medical and family history

In addition to excluding other causes of nausea and vomiting in pregnancy, personal medical histories including a complete obstetric history and a family history may identify risk factors. Preexisting conditions that could contribute to nausea and vomiting may point to a different diagnosis including cholelithiasis,[4] diabetes mellitus,[4,37] or Addison disease.[37] Conversely, a personal or family history of HG supports clinical diagnosis.[28,47]

Physical examination

A head-to-toe physical examination, including vital signs and weight, provides valuable information. Bottomley and Bourne[37] recommend obtaining lying and standing blood pressures and heart rates. However, orthostatic changes may not be a sensitive indicator of the severity of dehydration.[48] Evaluation of the oral mucosa, thyroid, heart, lungs, costovertebral angle tenderness, abdomen, skin turgor, peripheral pulses, and capillary refill is typically benign but may reveal signs of dehydration such as dry mucous membranes, tachycardia, and decreased skin turgor.[36] However, ptyalism, or excessive salivation, is also common.[36] Findings such as neurologic abnormalities,[2,4] goiter,[2] abdominal pain other than mild epigastric discomfort,[2,4] organomegaly, or costovertebral angle tenderness[37] require further investigation. If appropriate for gestation age, auscultation of fetal heart tones may provide maternal reassurance of fetal status.

Laboratory tests and diagnostic imaging

Although no laboratory data and diagnostic imaging are required to make a diagnosis, both may be helpful in excluding other causes of nausea and vomiting and providing maternal reassurance. While there are no biomarkers for diagnosis or to assess severity,[49] other laboratory data can exclude other diagnoses and assess maternal response to prolonged vomiting.

Recommended preliminary laboratory values include urinalysis, complete blood cell count, renal function tests, electrolytes, and hepatic function tests.[37] Although positive serum IgG antibodies for *H pylori* are positively associated with HG, a recent systematic review and meta-analysis found that testing was not valuable.[49] Coupled with the fact that there is limited evidence to support eradication of *H pylori* as part of a treatment strategy,[49] routinely drawing IgG antibodies for *H pylori* is unnecessary. Similarly, although gestational transient thyrotoxicosis is strongly associated with HG, it requires no treatment.[33] Unless goiter or manifestations of thyroid disease (anxiety, exophthalmos, palpitations, tremor, heat intolerance) are present, thyroid function tests are likely of little clinical value. However, it has been suggested that evidence of gestational transient thyrotoxicosis may support HG diagnosis.[2] In addition, drawing blood/serum thiamine levels is not helpful in determining deficiency, as little is carried in the serum.[37]

Some abnormal laboratory values are expected with HG. On urinalysis, elevated specific gravity as well as ketonuria may be present. Associated with catabolism, ketonuria may indicate poor tolerance of oral intake.[49] However, it has not been correlated with severity of nausea and vomiting.[49] Complete blood cell counts may demonstrate elevated hematocrit or anemia.[37] However, total white blood cell counts greater than 15 000[46] and thrombocytopenia suggest an alternate diagnosis.[2] Liver function test abnormalities are very common[36,37] and include mild hyperbilirubinemia (<4 mg/dL), elevated alkaline phosphatase (up to twice the normal limit), and elevated alanine aminotransferase and aspartate aminotransferase levels (up to 2-3 times the normal limit).[36] These elevations typically resolve rapidly with cessation of vomiting.[36] Laboratory values exceeding expected variations or those that do not resolve with treatment raise suspicion for other hepatic pathology, at which time hepatitis titers and abdominal ultrasonography may be considered.[37] Although not necessarily recommended on initial evaluation, elevations in amylase and lipase levels may also be noted (up to 5 times normal levels). Levels associated with acute pancreatitis are significantly higher, with amylase levels typically 5 to 10 times normal levels.[2] Renal function and blood urea nitrogen (BUN) levels may be low or elevated. Although sometimes present with HG, elevated blood urea nitrogen or creatinine levels can also indicate renal failure.[37] Expected variations in electrolytes include hyponatremia, hypokalemia, and hypochloremic metabolic acidosis.[2]

The value of diagnostic imaging to the evaluation of nausea and vomiting in pregnancy is dependent on the clinical scenario. Obstetric ultrasonography is recommended if gestational trophoblastic disease and multiple gestations have not previously been ruled out.[2,46] However, with the widespread use of early obstetric ultrasonography, such data may be available when women present with symptoms. Other imaging results may be obtained as clinically indicated.[47] For example, upper gastrointestinal endoscopy may be necessary in women with profuse hematemesis.[37]

Clinical assessment of the severity of HG

Once other sources of nausea and vomiting have been ruled out, clinical assessment tools may be helpful in quantifying the severity and impact of symptoms. The

Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) index, a 3-item self-administered questionnaire that characterizes the severity of nausea and vomiting of pregnancy is available in 3 forms (PUQE, PUQE-24, and modified PUQE), which vary by the time frame that symptoms are evaluated (last 12 hours, last 24 hours, and since the beginning of pregnancy).[50] All are validated and brief and may be chosen as appropriate to the clinical situation.[50–52]

In addition the to various PUQE indices, the Hyperemesis Impact of Symptoms Questionnaire is a 10-item self-administered questionnaire.[53] It was designed and validated to holistically assess the physical and psychosocial impact of HG.[53] Since it includes questions about activities of daily living and psychosocial stress, it may aid in the creation of a holistic and compassionate plan of care.[53]

TREATMENT

Lifestyle modification

Treatment is largely supportive, with the goal of managing symptoms of nausea and vomiting, correcting dehydration and electrolyte disturbances, preventing complications, and maximizing QOL. Recognizing HG as a severe manifestation of symptoms of nausea and vomiting of pregnancy, management is typically guided by the same recommendations and algorithms presented for the treatment of nausea and vomiting of pregnancy. The most recent Cochrane review evaluating treatments of nausea and vomiting of pregnancy concluded that there is insufficient data to recommend any single intervention over another.[54] The authors point out that this does not mean that treatments are not effective but that there is a lack of quality evidence to guide use.[54]

Management of symptoms of nausea and vomiting includes dietary and lifestyle modifications, complementary and alternative therapies, and pharmacologic therapies. Initial management depends on the severity of symptoms and hydration status at the time of presentation. Hospitalization is not required for all affected women but should be considered for women who have not responded to outpatient treatment and are unable to maintain hydration by oral intake.[4]

Little evidence is available to support dietary modifications; however, many women find them useful.[55] Recommendations typically include eating dry crackers before getting out of bed,[32] eating small and frequent meals,[56] and avoiding fatty and spicy foods.[5] Separating foods and fluids by 20 to 30 minutes and consuming fluids frequently in small amounts may also help.[56] Since protein-predominant meals are associated with symptom relief, women may benefit from eating a high-protein meal 45 minutes before getting out of bed.[32] Not practical for all women, this strategy might also be used for daytime meals. If the smell of hot foods is bothersome, women may try cold foods.[36] Ice chips, popsicles, and electrolyte-enhanced beverages may also be recommended.[56] Most importantly, women may be encouraged to eat what they are able to.[56]

Lifestyle modifications include identifying triggers, avoiding noxious stimuli, and increasing rest.[5] Women whose symptoms are exacerbated by prenatal vitamins may benefit from switching to a multivitamin without iron[4] or to a folic acid supplement until symptoms improve.[56] In addition, women with ptyalism may be advised not to swallow excess saliva, as it can exacerbate symptoms.[56]

Complementary and alternative therapies

Many women are interested in using complementary and alternative therapies that are available without a prescription.[57] Common therapies for the treatment of nausea and vomiting of pregnancy include acupressure, acupuncture, and ginger (*Zingiber officinale*).[5] Acupressure is a modality of traditional Chinese medicine in which pressure is applied to various points on the body to relieve illness or induce relaxation.[58] Although evidence is mixed, the most recent Cochrane review of therapies used to treat nausea and vomiting of pregnancy found some evidence of effectiveness for both auricular acupressure and acupressure at the P6 point,[54] located midline and approximately 3 cm from the crease on the inside of the wrist.[57] Acupressure at the P6 point may be accomplished manually or with wristbands, available with and without electrical stimulation.[57] Acupuncture is similar to acupressure in that is assumes the body has various points that can be stimulated to facilitate healing or relaxation but involves the insertion of fine needles into the skin.[58] While a few individual studies support acupuncture as a treatment,[5] a meta-analysis did not demonstrate significant benefit.[54]

Ginger can be used to treat nausea and vomiting. It is available fresh, crystallized, and in many other forms including liquid extracts, syrups, teas, sodas, candies, and capsules.[59] Both small-scale individual studies and a Cochrane review have demonstrated the effectiveness of ginger in treating nausea and vomiting.[5,54] The full safety profile of ginger is not known, but it has been used without demonstrable adverse outcomes.[54] The dose typically recommended is 1000 mg daily, in single or divided doses.[59] As ginger is available in a variety of forms with varying potencies, women may be advised to find the form and dose that fit their needs.

Many complementary and alternative therapies state that they alleviate nausea and vomiting. However, there

is often little evidence to assess the effectiveness or the risks of their use, making it difficult to provide women clear information regarding risks and benefits. Women may be cautioned that any product absorbed into the bloodstream through ingestion or skin application may have adverse fetal effects during a critical point in development.

Pharmacologic therapies

Pharmacologic treatments include vitamin B_6 (pyridoxine), antihistamines (dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, meclizine), dopamine antagonists (droperidol, metoclopramide, trimethobenzamide), phenothiazines (prochlorperazine, promethazine), 5-hydroxytryptamine$_3$ receptor antagonists (ondansetron), and glucocorticoids.[31] (See Table 2).

Although verified as current in 2009,[62] the most recent American College of Obstetricians and Gynecologists (ACOG) guidelines for nausea and vomiting of pregnancy were published in 2004.[4] These guidelines recommend vitamin B_6 monotherapy (10-25 mg, 3-4 times per day) as first-line pharmacologic therapy and add doxylamine (12.5 mg, 3-4 times per day; half a tablet of Unisom SleepTabs) if symptoms do not improve.[4]

At that time, the single-drug combination of pyridoxine and doxylamine was not available in the United States. However, this treatment has recently returned to the US market. Previously available as Bendectin (doxylamine succinate/pyridoxine hydrochloride), the drug was removed from the US market in 1983 because of unfounded fears of teratogenicity.[60] In April 2013, the single-drug combination of pyridoxine and doxylamine was reintroduced as Diclegis (doxylamine succinate/pyridoxine hydrochloride).[60] Although more costly than over-the-counter preparations, Diclegis has delayed-release effects and is a single tablet.[60] Available in Canada as Diclectin (doxylamine succinate/pyridoxine hydrochloride) for many years, it is first-line treatment of pregnancy-related nausea and vomiting in Canadian treatment algorithms.[63] Similar to other therapies, high-quality evidence substantiating its effectiveness is limited, but what is available is promising.[60] Furthermore, the combination of pyridoxine and doxylamine has been studied more than any other drug used in pregnancy and evidence suggests that it can be used without the risk of congenital malformations.[60]

No formal changes have been made to ACOG guidelines to reflect the new availability of Diclegis. However, considering that guidelines from the Society of Obstetricians and Gynecologists of Canada (SOGC)[63] incorporate the availability of a delayed-release pyridoxine and doxylamine combination drug and the similarity of SOGC and ACOG guidelines on this topic, it is reasonable to incorporate Diclegis into practice.

Other than Diclegis, no other pharmacologic therapies are Food and Drug Administration approved for use in nausea and vomiting of pregnancy. However, published guidelines are available to direct choice of pharmacologic therapy in both inpatient and outpatient

Table 2. Initial enteral antiemetic therapies for hyperemesis gravidarum[a]

Antihistamine/vitamin B_6	
Doxylamine/pyridoxine (10 mg/10 mg DR)	2 tablets PO at bedtime; may add tablet every morning and afternoon as needed for total of 4 tablets per day
Antihistamines	
Dimenhydrinate	25-50 mg PO every 4-6 h 50-100 mg PR every 4-6 h
Diphenhydramine	25-50 mg PO every 4-6 h
Doxylamine	12.5 mg PO 3-4 times per day; may be given with 10-25 mg of pyridoxine 3-4 times per day
Hydroxyzine	50 mg PO every 4-6 h
Meclizine	25 mg PO every 4-6 h
Dopamine antagonists	
Metoclopramide	10 mg PO every 6-8 h
Phenothiazines	
Prochlorperazine	5-10 mg PO every 6-8 h 25 mg PR every 12 h
Promethazine	12.5-25 mg PO every 4-6 h 12.5-25 mg PR every 4-6 h
Serotonin antagonists	
Ondansetron	4-8 mg PO every 6-8 h

Abbreviations: DR, delayed-release; PO, orally; PR, rectally.
[a]From Niebyl,[31] Nuangchamnong and Niebyl,[60] Angelini and LaFontaine.[61]

settings.[4,31,56,57,63] Generally, a stepwise approach to treatment is recommended.[57] However, variation in severity may require bypassing typical first-line therapies, as they are orally administered. King and Murphy[57] provide a treatment algorithm according to severity of symptoms determined by PUQE scores. In this algorithm, first-line antiemetic therapies include metoclopramide (5-10 mg every 8 hours intravenously), or ondansetron (1 mg/h intravenously × 12-24 hours or 8 mg over 15 minutes every 12 hours) or droperidol (1 mg/h intravenously) with diphenhydramine (50 mg intravenously over 30 minutes every 6 hours).[57] Treatment choices may be guided by side effects, individual tolerance, and response. The sedating effects of treatments may be used therapeutically if the woman struggles to rest. For example, promethazine is generally as effective as ondansetron and metoclopramide but is more sedating[60] (see Table 3).

The safety of these common drugs is widely accepted, implying no adverse maternal or fetal impacts,[61] but individual studies have raised safety concerns.[60] Although of little clinical consequence, being abreast of such research findings may be useful to inform conversations with concerned parents. For example, a recent study reported an increased risk of congenital heart defects when ondansetron was used in the first trimester of pregnancy. However, other studies investigating the safety of ondansetron have not found an increased risk of congenital malformations.[60] Likewise, the safety of phenothiazines was questioned by one study suggesting a possible link to congenital malformations, but other research has not demonstrated this risk.[62]

Data regarding the effectiveness of corticosteroids are conflicting and use of corticosteroids has been associated with a slight increase in oral clefts.[57] For this reason, corticosteroids are used as a last resort and not before 10 weeks' gestation when fetal organogenesis is complete.[4] When used, methylprednisolone (16 mg orally or intravenously every 8 hours for 3 days and then tapered over 2 weeks to lowest effective dose) should be used for a maximum of 6 weeks.[2]

Metoclopramide (Reglan), although not concerning regarding congenital malformations, crosses the maternal blood-brain barrier and has been associated with dystonic reactions (involuntary muscle contractions of the face and the body).[60] These symptoms resolve rapidly with the administration of diphenhydramine[57] but can be alarming. In response, metoclopramide use should be limited to 12 weeks' duration to minimize the risk of dystonic reactions.[60]

Droperidol (Inapsine) has been associated with the cardiac complication prolonged Q-T syndrome in doses greater than 25 mg.[62] Although smaller doses are used to treat HG, it should be used with caution.[62] Lacasse et al[64] have recommended the infusion of metoclopramide (1.2 mg/h) with diphenhydramine (50 mg every 6 hours) as an effective alternative to droperidol protocols.

In addition to antiemetic drugs, pharmacologic therapy may include agents to control comorbid heartburn or reflux. Treatment of heartburn and reflux has been associated with improved symptoms and QOL.[36] Antacids containing aluminum or calcium may be tried first, followed by histamine (H_2) blockers and proton pump inhibitors.[56] However, antacids containing magnesium and bicarbonate are not appropriate in pregnancy related to adverse fetal effects.[36]

Table 3. Initial parenteral antiemetic and fluid therapies for hyperemesis gravidarum[a]

Antiemetic therapy
Metoclopramide (1.2 mg/h or 5-10 mg IV every 8 h) ± diphenhydramine (50 mg IV over 30 min every 6 h)
or
Droperidol (1 mg/h IV) + diphenhydramine (50 mg IV over 30 min every 6 h)
or
Ondansetron (1 mg/h IV × 12-24 h or 8 mg over 15 min every 12 h)
Fluid therapy
Normal saline (0.9% sodium chloride) ± thiamine, 100 mg IV or IM daily ± Potassium chloride, 40 mEq/L of normal saline with maximum dose of 10 mEq/ h titrated to maternal potassium levels

Abbreviations: IM, intramuscularly; IV, intravenously.
[a]From Bottomley and Bourne,[37] King and Murphy,[57] and Lacasse et al.[64]

Intravenous therapies

Women who are dehydrated and unable to tolerate oral fluids require intravenous fluid therapy.[57] Normal saline (0.9% sodium chloride) is preferred even in cases of significant ketonuria[65] and hyponatremia,[37] as dextrose solutions increase the chance of precipitating Wernicke encephalopathy and more concentrated solutions of saline increase the risk of central pontine myelinolysis.[37] Furthermore, a recent randomized control trial found no advantage to using dextrose solutions compared with normal saline.[65] To prevent Wernicke encephalopathy, thiamine should be added to intravenous infusions for any woman with persistent vomiting for 3 weeks.[37] Supplementation may be initiated with 100 mg intravenously or intramuscularly daily and transitioned to 50 mg orally daily as tolerated until she can resume oral intake.[37] In cases of hypokalemia, potassium chloride can be added to infusions.[57] Supplementation of 40 mEq/L of normal saline, with maximum dose of 10 mEq/h is recommended with subsequent titration

based on maternal serum potassium levels (maximum dose 200 mEq/d).[37]

Enteral and parental nutrition

Nutritional support may be necessary for women unable to maintain their weight despite nonpharmacologic and pharmacologic efforts.[36] In severe cases, nasogastric, percutaneous endoscopic gastrostomy, or jejunostomy tubes can be used.[36] Women unable to tolerate enteral feeding may be candidates for parenteral nutrition.[36] However, peripherally inserted central catheters used to deliver parental nutrition have high rates of complications including infection and thrombosis.[36] With a lack of conclusive evidence to suggest improvement of neonatal outcomes compared with woman receiving enteral feedings or medical management alone, the worth of parenteral nutrition is questionable.[36] For these reasons, ACOG recommends attempting enteral feedings first when nutritional supplementation is required.[4]

Psychological support

Although HG is associated with significant psychosocial morbidity, the role of psychotherapy is not well understood.[36] Women have reported seeking therapy to manage psychological sequelae.[6] Given the lack of data to guide recommendations and the gravity of psychosocial morbidity, psychological therapy is not essential but is appropriate for women who are interested and find it helpful. Online support groups are available as well.

FOLLOW-UP

Close follow-up and anticipatory guidance are essential to effective management. Many women require changes in their management plan, and frequent clinic visits are important to prevent worsening symptoms and promptly identify changes in status. A careful discussion about variation in severity and duration of symptoms is important to set realistic expectations about the trajectory of symptoms. In addition, women need specific instructions about when to call their providers. Nurses and providers may review signs of dehydration, worsening symptoms, complications (eg, hematemesis), and infection at each visit.[32] For women with severe symptoms, King and Murphy[57] recommend visits every 4 days to weekly to assess weight and signs of dehydration. Incorporating home health services may also be helpful.[57]

Comprehensive postpartum care of the woman who had HG during pregnancy includes counseling on rates of recurrence and strategies for future pregnancies, as fear of recurrence can affect future childbearing plans.[6] Reported rates of recurrence widely vary from 15%[24] to 81%,[23] but women should be encouraged to seek treatment at the very beginning of their next pregnancy. There is growing evidence that preventive antiemetic therapy in newly pregnant women with a history of HG may mitigate the severity of symptoms.[66,67] In a recent study, women with a history of severe nausea and vomiting of pregnancy who were treated with Diclectin upon recognition of pregnancy were less likely to develop HG than women treated at the onset of symptoms. Considering the likelihood of recurrence and far-reaching effects, creating a plan for future pregnancies can be beneficial. Women with a history of HG may also be encouraged to take a multivitamin when planning to become pregnant, as research suggests that it too may decrease severity of symptoms.[4]

CONCLUSIONS

Although hyperemesis occurs infrequently, it is associated with significant physical and psychosocial morbidity. Women with HG require prompt recognition and a compassionate approach to care. Many aspects of this condition remain elusive, highlighting the importance of continued interdisciplinary research and collaboration. In 2013, a Cochrane protocol was developed to investigate treatment interventions[5] and will hopefully provide direction for future management.

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