Hyperemesis Gravidarum

Strategies to Improve Outcomes

Kimber Wakefield MacGibbon, BSN, RN

ABSTRACT

Hyperemesis gravidarum (HG) is a debilitating and potentially life-threatening pregnancy disease marked by weight loss, malnutrition, and dehydration attributed to unrelenting nausea and/or vomiting; HG increases the risk of adverse outcomes for the mother and child(ren). The complexity of HG affects every aspect of a woman's life during and after pregnancy. Without methodical intervention by knowledgeable and proactive clinicians, life-threatening complications may develop. Effectively managing HG requires an understanding of both physical and psychosocial stressors, recognition of potential risks and complications, and proactive assessment and treatment strategies using innovative clinical tools.

Key words: antiemetic, enteral nutrition, genetics, granisetron, HELP score, hyperemesis gravidarum, intravenous, malnutrition, nausea, neurodevelopmental disorder, ondansetron, parenteral nutrition, pregnancy, premature delivery, total parenteral nutrition, vomiting, vomiting center, Wernicke's encephalopathy, Zofran

Nausea and vomiting of pregnancy (NVP) affects at least 70% of women globally, whereas severe NVP, or hyperemesis gravidarum (HG), reportedly affects 0.5% to 14% of women across all ethnicities and socioeconomic levels.[1-3] Because of inconsistent diagnostic criteria, the actual incidence is unknown yet significant, given that 18% of women take antiemetics for NVP.[1,4] In addition, some women choose therapeutic termination before being diagnosed or hospitalized.[5] HG is the leading cause of hospitalization in early pregnancy and second only to premature labor as the most common cause of hospitalization throughout all of pregnancy.[6]

The onset of HG typically occurs between 4 and 6 weeks, peaks around 10 and 13 weeks, and resolves by midpregnancy in half of women; however, HG persists until delivery in nearly 22%.[7-9] Nausea lasts all day in most women and causes debility and malnutrition because of its severity and poor response to medications. Emesis may be episodic and triggered by stimuli such as motion, smells, or the thought of food.[8-10] Unlike emesis attributed to food poisoning, emesis because of HG rarely brings relief, and the emetic impulse may be so forceful and continuous that oral intake is impossible. Some women lose consciousness and bladder function. Severe cases may experience extensive dental damage, organ damage, encephalopathy, esophageal rupture, pneumomediastinum, and retinal hemorrhage.[11-14] Poor intake causes debility and profound fatigue, which impairs self-care that often continues postpartum.[8,10,14]

About 80% of women lose weight, use medications, and have HG every pregnancy, whereas 67% receive intravenous (IV) treatment and only 39% are hospitalized.[15] Recurrence rates exceed 70%, although women proactively manage symptoms to avoid the traumatic experience of hosptialization.[16-20] About 30% of women report that their symptoms in future pregnancies are the same, 26% say symptoms are worse, and 44% report better pregnancies.[15] Maternal quality of life is severely altered by HG; thus, proactive and compassionate intervention is imperative.[10,21,22]

CLINICAL CHARACTERISTICS

NVP is a spectrum from mild or morning sickness, to severe, or HG. In between are women suffering with symptoms not

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The author of this article has no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's website (http://journals.lww.com/journalofinfusionnursing).

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DOI: 10.1097/NAN.0000000000000363

requiring hospitalization or nutritional intervention. They continue some daily activities and maintain marginal intake and hydration, so they are often dismissed until symptoms are severe. Objective signs and symptoms of moderate NVP are challenging to distinguish, yet aggressive intervention may help prevent progression (Figure 1).

HG typically presents with nausea, vomiting, retching, weight loss, hyperolfaction, ptyalism, abdominal pain, debility, gastroesophageal reflux, gastroparesis, electrolyte deficiency, malnutrition, and dehydration.[23,24] About 25% of women lose 15% or more of their preconception weight and are much more likely to have prolonged symptoms, gallbladder and liver dysfunction, and retinal hemorrhage.[8] Although significant weight loss and ketonuria are common, they are not reliable diagnostic criteria for HG.[25] Proactive antiemetics may reduce weight loss and patient distress.

DIFFERENTIAL DIAGNOSIS

When a patient presents with NVP, determining possible causes requires consideration of the timing. Nausea and vomiting beginning after 9 weeks' gestation or refractory to medications requires an in-depth workup. Other conditions such as infections, hepatic and renal dysfunction, intestinal obstruction, peptic ulcers, gastroenteritis, thyrotoxicosis, gallbladder disease, and intracranial lesions should be evaluated.[23,26] Careful history-taking is paramount, because HG has a multifactorial etiology. In addition, some disorders may develop secondary to dehydration and medications, worsening symptomatology, so close monitoring is crucial until symptoms resolve (Table 1).[27,28]

TABLE 1

Differential Diagnosis

Gastrointestinal Gastroenteritis Gastroparesis Intestinal obstruction Peptic ulcer disease *Helicobacter pylori* Pancreatitis Appendicitis	Genitourinary Pyelonephritis Uremia Ovarian torsion Kidney stones Uterine leiomyoma	Metabolic and Endocrine Diabetic ketoacidosis Porphyria Addison's disease Thyroid disease
Miscellaneous Drug toxicity Infection	Neurologic Pseudotumor cerebri Migraines CNS tumor	PG Complications Acute fatty liver Preeclampsia

Abbreviations: CNS, central nervous system; PG, pregnancy.

RISK FACTORS

The risk factors for HG include multiple gestation, younger age, first pregnancy, extreme high or low body weight, history of motion sickness, allergies, premenstrual syndrome, migraines, thyroid disease, high-fat diet, vegetarian/lactose-free diet, and gastrointestinal (GI) disorders.[7,14,26,29-33] Incidence increases slightly if mothers are carrying a child that is female or has Down syndrome.[30] However, the predominant risk factor is a previous HG pregnancy or a family member with HG. A woman has a 17-fold increased risk if her sister has HG and a 27-fold risk if her mother had it with both daughters.[34] Some studies find HG risk decreases in those with higher body mass index (BMI), advanced age, and in those who smoke tobacco, which could be attributed to reduced olfactory sensation or decreased expression of placental proteins.[29,35-37] Newer research finds genetic evidence that overexpression of the GDF15 risk allele is linked to recurrent HG.[16]

Multiple studies confirm that HG is not associated with pre-existing psychiatric diagnoses, including anxiety, depression, bipolar disorder, or eating disorders.[17,38-41] Rather, psychological sequelae are the result of prolonged symptoms, malnutrition, medications, and/or hospitalization and may improve dramatically with resolution of HG. Psychological support may lessen psychological sequelae, but a clinician's focus should be on alleviating the misery of NVP.

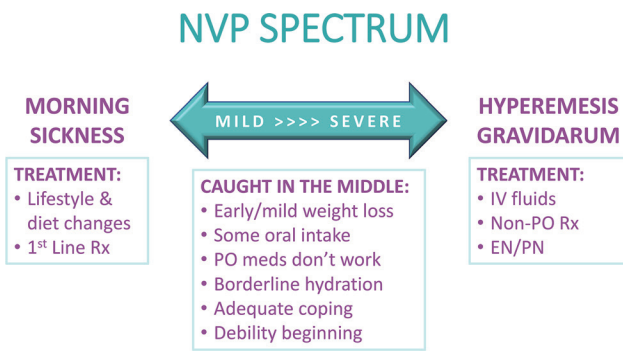

Figure 1 NVP spectrum. *Abbreviations: EN, enteral nutrition; IV, intravenous; PN, parenteral nutrition; PO, oral or by mouth; Rx, prescription medication.*

CONTRIBUTING FACTORS

HG is complicated by secondary factors that may worsen symptoms but alone are not the cause of HG. For example, gallbladder dysfunction may worsen HG, but a cholecystectomy does not cure HG. *Helicobacter pylori* (*H. pylori*), present in about half of the world's population, may be more prevalent in HG, possibly activated by changes in gut motility and gastric emptying, poor nutrition, and the hormonal and immunological changes of pregnancy.[28,42-44] However, positive *H. pylori* tests do not reliably predict the occurrence and severity of HG, its complications, or outcomes, and treating *H. pylori* may not resolve NVP.[43,45-47]

Sensory sensitivity increases symptoms and reduces quality of life and intake.[48,49] The scent of cleaning products, toiletries, high-odor foods (eg, garlic, fermented products, fish), and even normal body smells can trigger nausea and vomiting. Dysgeusia develops in response to hormones, inadequate dental hygiene, acid irritation to tongue, low protein intake, vitamin deficiencies, and dysosmia.[50,51] Gastroesophageal reflux disease (GERD), repetitive emesis, and gastroparesis further alter taste and smell sensations.[48] The senses are so dysfunctional and hypersensitive during HG that nausea and food aversions to usually appealing foods cause significant weight loss. Consequently, women often have a limited diet with frequently changing food tolerances, predisposing them to significant nutritional deficiencies, which may worsen symptoms.[52] These women necessarily avoid social situations and isolate themselves to cope with overwhelming stimuli. Identification and effective management of these contributing factors are important to reducing morbidity and improving treatment response (Table 2).

HISTORY OF HG

For centuries, toxemia, neurosis, and hormones were presumed to be the etiology of HG.[53] Theories focused on hormones such as β-chorionic gonadotropin, thyroid-stimulating hormone, progesterone, and estradiol, which change during pregnancy.[25,26,32,54-57] However, research does not find consistent support for these theories.

Around 1900, when Freudian theory dominated, female disorders without a known cause were assumed to be psychological. Thus, the presumed etiology of HG was changed from a toxemia of pregnancy to one of maternal role conflict, frigidity, hysteria, and attention-seeking behaviors.[23,41,58] HG was a leading cause of maternal death until the introduction of IV therapy in the 1940s, and women were often treated poorly and intentionally given painful subcutaneous hydration to discourage their behavior.[53]

Although psychological etiologies have been disproved, the myths persist, and women are still admitted involuntarily to psychiatric wards, refused treatment, and told it is in their heads.[59,60] Research studies with problematic methodology continue to perpetuate this myth by evaluating the psychiatric health of women currently suffering from severe NVP and concluding that they have mental illness, despite other studies finding a return to previous mental health when symptoms resolve.[41,60,61] These erroneous beliefs delay and disrupt the institution of appropriate care for HG.

TABLE 2

Contributing Factors Worsening HG

Stress/fatigue	Gastroparesis
Prenatal vitamins/iron	Heightened gag reflex
Excessive salivation	*Helicobacter pylori*
Vestibular sensitivity	Dysgeusia
Gall bladder dysfunction	Dysosmia
Hormone sensitivity	Malnutrition
GERD	Dehydration

Abbreviations: GERD, gastroesophageal reflux disease, HG, hyperemesis gravidarum.

PATHOPHYSIOLOGY

The etiology of HG is evolving with the understanding of emetic physiology and discoveries of genetic factors, inflammatory markers, and hormonal abnormalities associated with HG. Emetic pathways with physiological triggers of the vomiting center in the medulla oblongata have been identified, and familiarity with how the brain receives these stimuli is useful in determining appropriate treatment for HG.[62] The chemoreceptor trigger zone in the medulla oblongata is located outside of the blood–brain barrier, so it is highly sensitive to signals from its many receptors that predominantly interact with dopamine, serotonin, and histamine. Triggers to the vomiting center come from peripheral nerve pathways, vestibular stimulation, the vagus nerve, enterochromaffin cells in the GI tract, and other mechanoreceptors and chemoreceptors in the gut, stomach, and liver.[63] Interestingly, enterochromaffin cells also produce more than 90% of the body's serotonin and have been suggested to affect a variety of pathophysiological states common to HG, such as GI dysmotility, nausea, and visceral hypersensitivity.[64-67]

Newer genetic studies link HG to cyclic vomiting syndrome because of an association with the ryanodine receptor gene, *RYR2*, which is expressed in the vomiting center and involved in thyroid function.[68,69] Also associated are the placental genes *IGFBP7* and *GDF15*.[16,70-72] Serum protein concentrations of these genes are significantly elevated at 12 weeks' gestation in women hospitalized for HG compared with women reporting normal NVP. Women with high levels of *IGFBP7* are more likely to have prolonged HG symptoms, possibly because *IGFBP7* causes aversions to normally attractive food, even during starvation.[70] *GDF15* is a hormone that regulates weight and appetite, and abnormal overproduction of *GDF15* in cancer is the key driver of cachexia, a major cause of death among patients with cancer.[73] So if a woman with HG says she feels like she is dying, she probably does. Development of genetic testing for these genes may offer valuable screening tools to identify HG patients most in need of proactive care.

IMPACT OF HG

Psychosocial

More than 82% of women with HG report at least 1 negative psychosocial or economic consequence related to HG.[22] Because of symptoms, women are often isolated, causing anxiety, depression, and significant relational strain.[10] Trauma

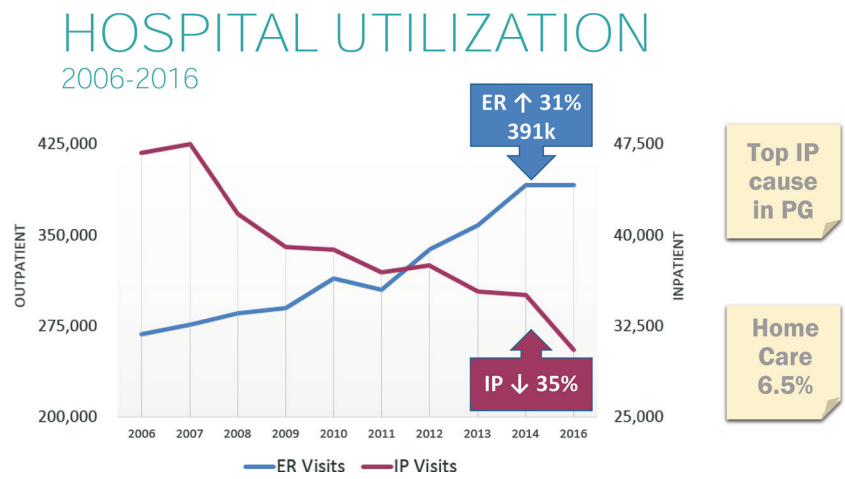

Figure 2 Hospital utilization. *Abbreviations: ER, emergency room; IP, inpatient; PG, pregnancy.*

symptoms develop after repeated episodes of continuous and forceful emesis that provoke feelings of suffocation and may cause fainting. This trauma is worsened by painful invasive procedures, fear of death, feelings of helplessness, hospitalizations, and difficult deliveries because of debility. Traumatic stress symptoms are common after HG pregnancies and are associated with an inability to breastfeed, marital problems, financial problems, and self-care difficulties, whereas full criteria posttraumatic stress disorder occurs in about 20%.[74,75] Consequently, 76% reduce the number of pregnancies or forego future pregnancies entirely.[22,76]

According to Lacroix et al,[9] NVP is comparable in severity to the nausea and vomiting associated with moderate cancer chemotherapy, which greatly diminishes quality of life. In fact, many patients with cancer consider delaying or stopping treatment because of nausea and vomiting, although it may reduce their life expectancy. Thus, it is not surprising that about 75% of women consider termination, and around 15% will seek therapeutic termination to end their suffering.[5,76,77] Of those, 66.7% report terminating because of an inability to care for family or self, 40.0% because of an inability to work, and 51.0% because they fear death.[5] Women reporting that their clinician was uncaring or unaware of their symptom severity were nearly twice as likely to report these psychological sequelae and 3 times more likely to terminate.[5]

Financial

The financial stress of HG is great, as women may miss weeks to months of employment. Most women are unable to work most or all of their pregnancies and may lose their job or be unable to return.[74,77] Beyond the potential income loss by mothers, their partners may also miss work. Additionally, there are expenses for child care and household help, as well as medical care during and after pregnancy.

There are more than 400 000 emergency department and inpatient visits for patients with HG annually in the United States, yet more than half of women with HG are not hospitalized.[15,78] Thus, including terminated and/or undiagnosed pregnancies, the actual number of patients with HG could be a half million women annually.

Use of hospital care is changing for patients with HG. The number of emergency care visits is steadily increasing, whereas inpatient visits are declining as patients are moved toward outpatient management. Specifically, inpatient visits since 2006 have dropped 35%, emergency visits increased by 31%, and home health visits increased nearly 5%. Inpatient and emergency costs are estimated to be more than $500,000,000 per year and exclude costs for outpatient visits, home health, pharmaceuticals, and other services. Early aggressive care may help reduce severe symptoms and costly interventions (Figure 2).

Maternal Complications

HG has serious adverse effects on nearly every aspect of a woman's life. When women's symptoms are dismissed, more severe symptoms can develop, and women may be reluctant to seek treatment. This is counterproductive, because delayed treatment may lead to refractory symptoms and an increased risk of complications.[7] Women with severe HG may experience retinal damage, pneumothorax, liver and gallbladder dysfunction, esophageal tears, organ rupture or failure, sepsis, and many complications of poor nutrition, including cardiac and neurologic damage.[8,79,80]

Mortality still occurs because of malnutrition, esophageal rupture, sepsis, and suicide. Women with prolonged symptoms are more likely to experience hematemesis, fainting, depression, GERD, anxiety, and excessive saliva.[7,80] They are also more likely to report postpartum issues, such as trauma, motion sickness, muscle weakness, and anxiety.[14] Prolonged immobility may result in severe muscle atrophy, depression, and thrombosis, in addition to sensory processing disorder in the child.[81,82] Thromboembolism risk is also increased because of pregnancy-related changes and use of IV catheters.[83]

There is a misperception that HG affects women only during pregnancy, yet women may experience psychological sequelae, GI dysfunction, and food aversions long after

delivery.[7,14,84-86] Because of malnutrition, acid erosion, immune changes, dry mouth, and other physiological changes, many women have severe dental damage requiring numerous root canals or even dentures.[51] Other research suggests a link to future immune disorders, including rheumatoid arthritis and thyroid cancer, a risk that increases with subsequent hyperemetic pregnancies.[7,8,15,25,87-90]

Fetal and Child Complications

Offspring are not immune from the impact of HG. Contrary to longstanding assumptions, infants do not get adequate nutrition and many have restricted growth or low birth weights.[91] About 1 in 3 HG pregnancies do not result in a live birth.[5,92] Babies have a 3- to 4-fold increased risk of preterm birth, neurodevelopmental delay, immune disorders (eg, allergies, chronic infections), autism, and emotional/behavioral disorders.[8,91,93,94] Fejzo et al[8,13] found the risk of neurodevelopmental disorders increased to 9.3% in those with weight loss exceeding 15.0% of their preconception weight.

In addition, children born to mothers with prolonged symptoms and/or excessive weight loss (>15%) were significantly more likely to experience premature birth, low birth weight, intrauterine growth restriction, irritability or severe colic, neurodevelopmental disorders, autism, sensory processing disorders, sleep difficulties, and social delays.[7,8,94,95] Fetal damage can occur from early deficiencies, such as vitamin K deficiency, which may result in facial and limb anomalies, or intracranial hemorrhage even when maternal coagulation is normal.[96,97] Research also finds that female children born after early prenatal malnutrition are more likely to deliver children with low birth weights (Table 3).[95]

Thus, in pregnancies with severe or persistent symptoms, it is critical that IV vitamins are administered. Vitamin-deficient mothers who breastfeed increase the risk of serious complications in their newborns.[98] These offspring may also experience long-term adverse health conditions, such as metabolic syndrome, obesity, coronary disease, breast cancer, chronic obstructive pulmonary disease, and neurobehavioral and psychiatric disorders.[13,22,91,93,94,99-101]

TABLE 3

Adverse Fetal Outcomes

Autism	Premature birth
Intrauterine growth restriction	Fetal/neonatal death
Immune dysfunction	Neurodevelopmental disorders
Irritability/severe colic	Behavioral disorders
Sleep difficulties	Low birth weight
Delayed social development	Delayed speech/language development
Adult cardiac/metabolic disorders	Sensory processing disorders

The totality of the social, emotional, and financial costs of managing these complications cannot be measured (Figure 3).[102] Proactive care to aggressively prevent excessive weight loss may improve maternal and fetal outcomes.

ASSESSMENT TOOLS

HG is difficult to assess because of the subjective nature of many symptoms, such as nausea. It is important to not only look at symptoms but also the impact of NVP. Women's tolerance and coping capacity vary. Thus, determining the need for treatment may be unclear, leading to delayed intervention. Accurate assessment is key but has been limited by the available tools.

HYPEREMESIS EDUCATION AND RESEARCH FOUNDATION RESOURCES

The Hyperemesis Education and Research (HER) Foundation (www.hyperemesis.org/tools) is a 501(c)3 nonprofit based in Clackamas, Oregon. Founded in 2003, HER has collaborated with the University of California, Los Angles (UCLA) and the University of Southern California on dozens of research studies, including the first genetic studies on HG. HER has created numerous resources for clinicians, including HG treatment protocols, standardized assessment tools, educational brochures, a treatment algorithm, and an HG care app.

The HER Foundation assessment packet includes HG-specific prenatal and visit assessment intake forms with a clinician care planning checklist (Figure S1, Supplemental Digital Content; http://links.lww.com/JIN/A97) and a severity screening tool called the HyperEmesis Level Prediction Score (HELP Score; Figure 4). The HELP Score quantifies severity with more complex symptomology. Using patient-friendly language, the HELP Score evaluates the severity of nausea, vomiting, and retching, plus 5 key clinical indicators, hydration, treatment effectiveness and tolerance, psychosocial functioning, oral intake, and overall progress. The HELP Score includes 10 questions plus 2 data points scored from 0 (normal) to 5 (severe). All questions except weight loss are based on the previous 24 hours. Once totaled, the score can be trended to monitor treatment response and symptom severity.

HG CARE APP

In addition to these assessment tools, the HER Foundation designed an HG app that was codeveloped with UCLA (Figure 5). The HG Care app not only allows tracking of symptoms and treatments (eg, medications, dressing changes) but also alerts patients when abnormal changes are entered, such as low urine output. The app calculates the HELP Score and trends data into meaningful reports that can be shared with clinicians to improve communication about

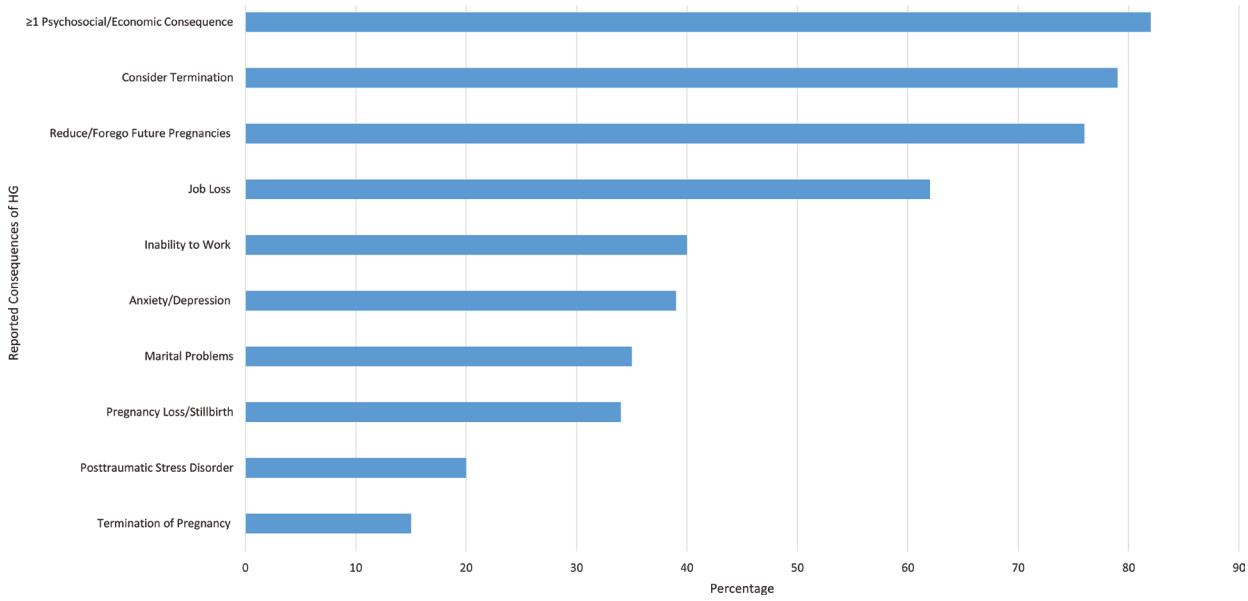

Figure 3 Psychosocial impact of hyperemesis gravidarum. [a]Data from Poursharif et al,[5] Tan et al,[41] Christodoulou-Smith et al,[74] and Power et al.[102]

HELP (HyperEmesis Level Prediction) SCORE

Name: _____ Date: _____ Gestational Age: _____ SCORE: _____

TODAY'S Weight: _____ LAST WEEK'S Weight: _____ Change: _____% PREVIOUS SCORE: _____

Meds: ☐ Ondansetron ☐ Granisetron ☐ Diclegis ☐ Promethazine ☐ Metoclopramide ☐_____

Mark ONE box in EACH ROW that most accurately describes your experience over the last: _____ day(s).

My nausea level most of the time:	0	1 (Mild)	2	3 (Moderate)	4	5 (Severe)
I average __ vomiting episodes/day:	0	1-2	3-5	6-8	9-12	13 or more
I retch/dry heave __ episodes daily:	0	1-2	3-5	6-8	9-12	13 or more
I am urinating/voiding:	Same	More often, IV fluids; light or dark color	Slightly less often, and normal color	Once every 8 hours; slightly dark yellow	Less than every 8 hours or darker	Rarely; dark, blood; foul smell
Nausea/vomiting severity 1 hour *after* meds OR after food/drink if no meds:	0 or No Meds	1 (Mild)	2	3 (Moderate)	4	5 (Severe)
Average number of hours I'm unable to work adequately at my job and/or at home due to being sick has been:	0	1-2 (hours are slightly less)	3-4 (can work part time)	5-7 (can only do a little work)	8-10 (can't care for family)	11+ (can't care for myself)
I have been coping with the nausea, vomiting and retching:	Nor-mal	Tired but mood is ok	Slightly less than normal	It's tolerable but difficult	Struggling: moody, emotional	Poorly: irritable depressed
Total amount I have been able to eat/drink AND keep it down: *Medium water bottle/large cup = 2 cups/500mL.*	Same; no weight loss	Total of about 3 meals & 6+ cups fluid	Total of about 2 meals & some fluid	1 meal & few cups fluid; only fluid or only food	Very little, <1 meal/minimal fluids; frequent IV	Nothing goes or stays down, or daily **IV/TPN/NG**
My anti-nausea/vomiting meds stay down/are tolerated:	No meds	Always	Nearly always	Sometimes	Rarely	Never/**IV/SQ** (subQ pump)
My symptoms compared to last week:	Great	Better	About Same	Worse	Much Worse	So Much Worse!!!
Weight loss over last 7 days: ___%	0%	1%	2%	3%	4%	5%
Number of Rx's for nausea/vomiting*	0	1	2	3	4	5+
	0 pts	**1 pt/answer**	**2 pts/answer**	**3 pts/answer**	**4 pts/answer**	**5 pts/answer**
TOTAL each column = (#answers in column) x (# points for each answer)	0	____	____	____	____	____
TOTAL for ALL columns: _____	**None/Mild ≤ 19**			**Moderate 20-32**		**Severe 33-60**

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Weight Loss % = (Amount lost ÷ Pre-pregnancy weight) x 100
(Weight loss calculation optional for home use)
* Number of Rx's = Number of Rx medications for HG (not doses)

Figure 4 HELP Score. ©The HER Foundation. Reprinted with permission. *Abbreviations: HELP, HyperEmesis Level Prediction Score; IV, intravenous; Pt, point; Rx, prescription medication; SQ/Subcutaneous, subcutaneous; TPN, total parenteral nutrition.*

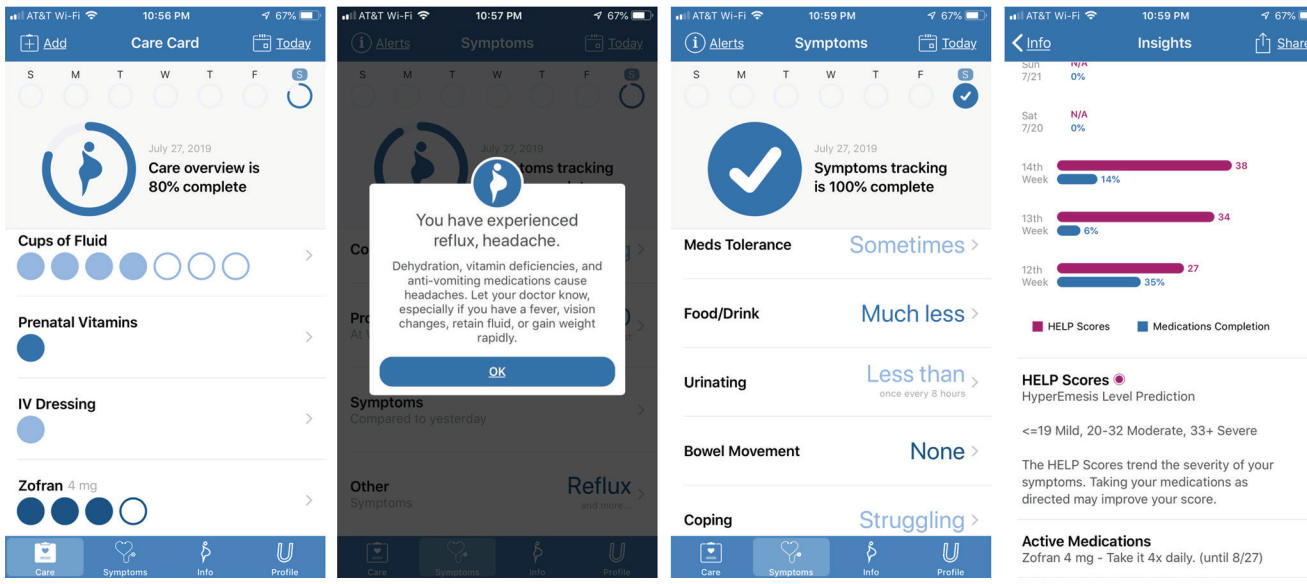

Figure 5 HG Care App. ©The HER Foundation. Reprinted with permission. *Abbreviations: HG, hyperemesis gravidarum; IV, intravenous; N/A, not applicable.*

symptoms and treatment. In a pilot study, symptom severity was found to be accurately scored by the app, and patient–provider communication was improved by use of the app.[103]

TREATMENT

Treatment of HG requires a combination of medical interventions, lifestyle changes, dietary changes, adjunctive care, and patient education, which should be used early, because NVP is more difficult and costly to manage over time.[104] Proactive treatment may reduce symptom severity, thus treatment should begin at the onset of symptoms, limiting food and/or fluid intake.

The primary management goals are to reduce symptoms to improve maternal health and well-being, optimize maternal/fetal outcomes, and reduce costs. This requires a focus on maintaining hydration and nutrition but also mobility. Infusion nurses are key advocates for achieving these goals (Table 4).

Medication Strategy

When planning treatment, the sequence of antiemetic administration is frequently from best-studied fetal safety and least invasive to less-documented fetal safety and more invasive. Most clinicians begin with oral medications; then when symptoms are refractory or severe, they temporarily change to intravenous therapy or injections. A more effective strategy is moving to nonoral routes, such as transdermal, subcutaneous, or rectal, at the onset of oral medication intolerance, then progressing to infusion therapy if necessary. Figure 6 shows the HER Foundation algorithm for treatment guidelines.

Other alternatives to oral medications include compounding medications into topical products and suppositories.[105] Intramuscular injections are avoided because of decreased pain tolerance and reduced muscle mass. Compassionate care should be central to all clinical decision making. Infusion nurses play an important role in ensuring that patients not only receive hydration but also transition to non-oral medications when needed (Table 5).

Subcutaneous Medication and Fluid Administration

A few medications come in transdermal form, such as granisetron. However, when these are ineffective, infusion therapy is necessary. Before beginning home infusion therapy, a trial of continuous subcutaneous medications (eg, ondansetron, metoclopramide) may be beneficial. Subcutaneous medications are less invasive and restrictive than IV medications, eliminate the peaks and troughs of

TABLE 4

Keys to Preventing HG Complications

1. Intervene early if the patient has a history of HG or if symptom onset is early and rapid.
2. Address and prevent worsening psychosocial stress (eg, take leave of absence).
3. Increase mobility to prevent DVT, atrophy, depression, and fetal sensory processing disorder.
4. Educate that medication risks may be significantly less than risks of severe symptoms.

Abbreviations: DVT, deep vein thrombosis; HG, hyperemesis gravidarum.

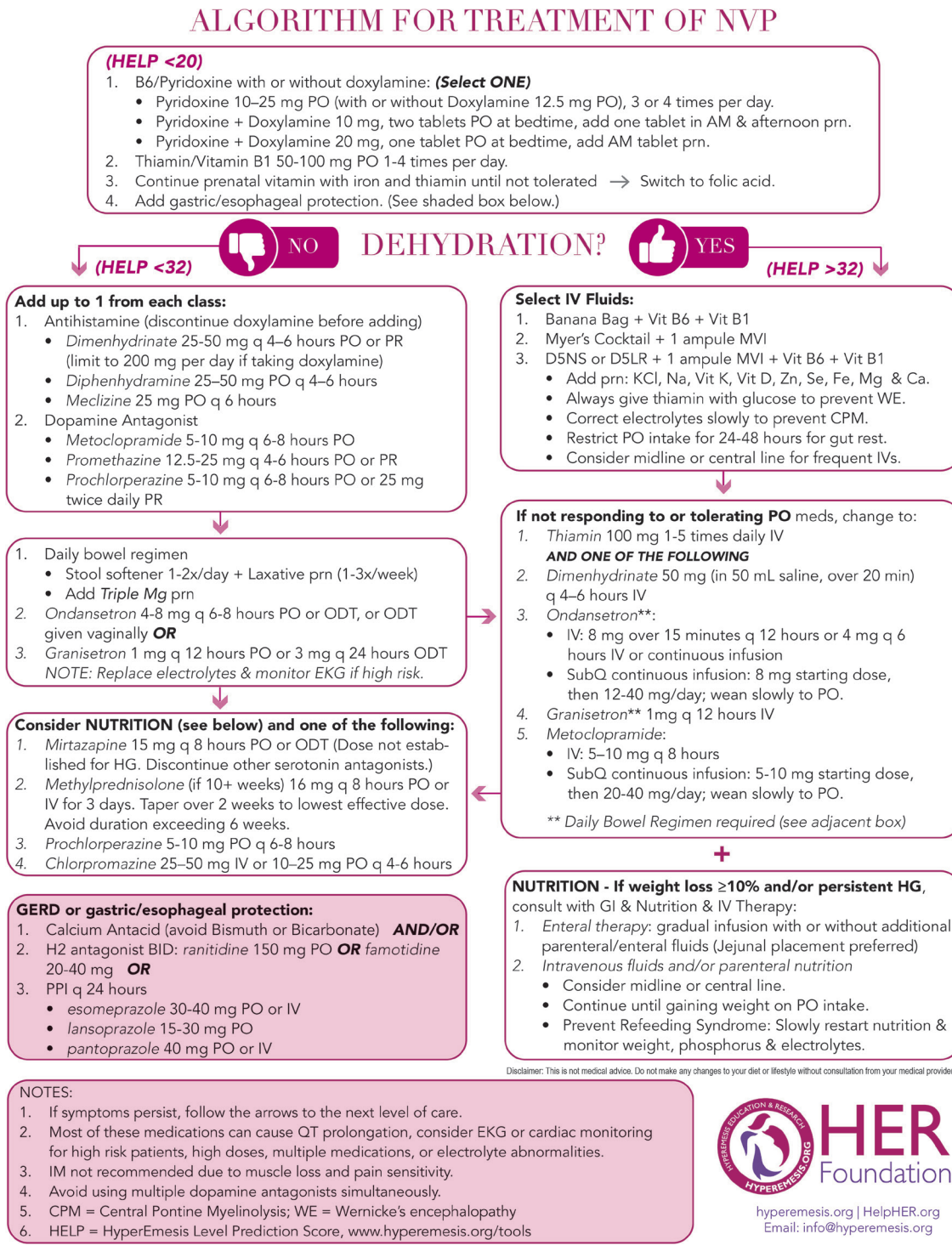

Figure 6 Algorithm for treatment of NVP. ©The HER Foundation. Reprinted with permission. *Abbreviations: AM, morning; BID, twice per day; Ca, calcium; CPM, central pontine myelinolysis; D5LR, 5% dextrose with lactated Ringer's; D5NS, 5% dextrose with 0.9% sodium chloride; EKG, electrocardiogram; Fe, iron; GI, gastrointestinal; H2, histamine H2 receptor; IM, intramuscular; IV, intravenous; KCl, potassium chloride; Min, minutes; Mg, magnesium; MVI, multivitamin infusion; Na, sodium; NVP, nausea vomiting of pregnancy; ODT, oral dissolving tablet; PO, oral/by mouth; PPI, proton pump inhibitor; PR, rectal; prn, as needed; q, every; QT, QT interval; Se, selenium; Vit D, vitamin D; Vit K, vitamin K; Vit, vitamin; Zn, zinc.*

oral therapy, circumvent inconsistent oral tolerance, and provide consistent bioavailability. Subcutaneous antiemetics may be effective in reducing symptoms within a few days and decreasing hospital stays.[106] Slow transition from subcutaneous to oral medications can be attempted after a few weeks of stabilization and improvement in symptoms. Additional therapies such as IV fluids and acid-reducing medications may still be needed.

TABLE 5

Compassionate Care

1. Listen to the patient with compassion and empathy.
2. Take her complaints seriously and help her cope.
3. Provide warmed blankets and a quiet, odor-free room.
4. Warm IV fluids to avoid discomfort and shivering.
5. Use local anesthesia for catheter insertion and utilize skilled personnel.
6. Avoid IM injections due to atrophy and pain sensitivity.
7. Order a PT consult to minimize atrophy and increase mobility.

Abbreviations: IM, intramuscular; IV, intravenous; PT, physical therapy.

IV Hydration

Dehydration is a nearly universal challenge for patients with HG. IV fluids are one of the most effective treatments for HG, and patients report improved medication effectiveness and intake after rehydration.[91] Typical hydration includes 0.9% sodium chloride or 5% dextrose with electrolytes, folic acid, multivitamins, and extra B vitamins. Patients requiring hydration more than weekly should be evaluated for non-oral medications and home infusion therapy.

Deciding the best option for rehydration requires an evaluation of the patient's history, current medical condition, and severity of symptoms. In first-trimester patients with a history of prolonged HG in a previous pregnancy, begin scheduled or home infusion therapy at the onset of dehydration. Patients further along in pregnancy with intermittent dehydration may benefit from more aggressive medications, such as steroids, in addition to IV fluids.

Longer dwelling catheters are considered when weight loss exceeds 10% or a patient requires repeated hydration, total parenteral nutrition (PN), or IV antiemetic therapy. Patients with HG reporting severe vein scarring, distress over repeated insertions, and avoidance of needed IV therapy because of pain and lack of compassionate care will likely benefit. The American College of Obstetrics and Gynecology recommends enteral feedings before placing central vascular access devices (CVADs) because of reported complication rates up to 66% in patients with HG.[104] Usage of expert clinicians, extra comfort measures, and practical selection of vascular access devices are important for the best outcomes in this population. Device options include a midline catheter, peripherally inserted central catheter (PICC), or a CVAD. Midline catheters are appropriate for patients with expected infusion therapy duration of a few weeks to a month and allow IV medication administration. Midline catheters pose less risk of sepsis and are useful for fluid and vitamin administration in the home; however, total complication rates may not be lower, and dwell time is less than CVADs.[107] A PICC offers more options, such as nutritional therapy and extended dwell time. CVADs are reserved for those with expected infusion therapy lasting months or those with difficult IV access.

Advocating for patients can avoid the dehydration–rehydration cycle by encouraging aggressive medications and home or scheduled IV therapy. In addition, although laboratory results may show normal electrolytes because of a hemoconcentrated state, electrolyte replenishment should be considered for all patients with emesis and limited intake, especially those receiving antiemetics and/or those at risk of cardiac arrhythmias.

Electrolyte levels, like sodium, also influence uptake of important nutrients like thiamin. Patients with short-term memory loss, confusion, neuropathy, muscle weakness, spasms, seizures, cardiac symptoms, and decreased consciousness should be closely evaluated for electrolyte deficiencies.[108] Severe deficiencies can cause brain swelling, life-threatening arrhythmias, and other complications. Methodical replacement and rehydration are imperative to avoid development of osmotic demyelination syndromes, such as central pontine myelinolysis.[79,109-112]

Nutritional Interventions

Optimizing medical therapy to allow adequate oral intake is the goal; however, that is not always achievable in patients with HG. The risks of enteral and PN may be less than those of chronic malnutrition and dehydration, especially in women with severe or prolonged symptoms. Once weight loss exceeds 8% to 10%, less in underweight patients, nutritional intervention should be strongly considered. At a minimum, IV hydration with added vitamins should be administered on a schedule while symptoms are refractory.

Nutritional intervention must begin gradually with adequate electrolytes, vitamins, micronutrients, and careful fluid resuscitation to avoid refeeding syndrome (RS).[113] Poor nutritional intake for more than 10 days, weight loss >15%, electrolyte loss, and low serum magnesium levels, all common in HG, are highly predictive of RS risk.[114] RS results from severe electrolyte and fluid shifts that occur after reinstitution of nutrition to patients who are malnourished or metabolically stressed, particularly if there is more than 10% weight loss over 2 months.[115] Symptoms of RS may not appear for a week or more and include arrhythmias, confusion, seizures, weakness, vital sign changes, and rapid weight changes. Daily monitoring of laboratory results, such as phosphorus, magnesium, sodium, calcium, glucose, and potassium, are important over the first week of refeeding.

To avoid RS, gradual introduction starting at 25% of needed nutrition and slowly increasing to goal as tolerated at a controlled rate is imperative.[114] Once patients tolerate goal flow rates, they are discharged from the hospital. Additional IV hydration, antiemetic medication, electrolytes, and vitamin supplementation are often needed, even with maximum feeding rates. Nutritional therapy is continued until oral tolerance surpasses 1000 calories daily and symptoms do not impair intake. Simultaneous use of peripheral PN via a midline catheter or central PN via a CVAD may be beneficial until adequate flow rates are tolerated.

Enteral Nutrition

If a patient has a history of prolonged HG, is early in pregnancy, malnourished, underweight, and/or losing weight

rapidly, enteral nutrition (EN) should be considered. EN is beneficial for preventing mucosal atrophy and permeability, but absorption in patients with severe vomiting and gastric erosion is unknown. Generally, EN is contraindicated during intractable vomiting, thus antiemetics must effectively control symptoms before beginning treatment. Failure to tolerate EN for 7 days indicates the need for PN.

Research on EN success in HG is limited to smaller cohorts, making results difficult to generalize. EN is associated with longer hospital stays and similar outcomes to other nutritional interventions.[116] Nasogastric tubes are poorly tolerated by many patients because of nasal and esophageal discomfort and repeated insertions. Small bore tubes and a slow rate are preferred but still may worsen reflux and increase aspiration risk. Duodenal placement is problematic, because tubes may coil in the stomach and formula may flow back to the stomach.[117,118] Placing a nasojejunal tube may reduce the frequency of tube placements and may decrease aspiration risk. It is indicated if a patient is on bedrest or experiencing severe emesis, GERD, or gastroparesis.[119,120] Use of an infusion pump is required because of physiological response of postpyloric feeding. Start slow, increase the rate gradually as tolerated, and monitor for dehydration regularly.

For patients still experiencing emesis and expected to need nutritional therapy for more than 1 month, a gastrostomy or jejunostomy tube is more appropriate. They require surgical placement but are more likely tolerated than nasal tubes, because they bypass the hypersensitive gag reflex, minimize nasal irritation and patient discomfort, and avoid replacement for occlusion and expulsion by vomiting.[121] They may remain in place for months, and, in limited studies, appear to achieve term deliveries and weight gain.[122]

Parenteral Nutrition

PN and CVADs present challenges from risk of sepsis, pneumothorax, arterial puncture, and thrombosis to drug shortages and cost.[123-126] Infection and thrombosis are the 2 most frequent complications and likely attributed to pregnancy-associated hypercoagulability and immune suppression. Although some studies find high complication rates, other studies report reduced rates with new protocols, outpatient use, and new technology, and some report few if any infection rates.[125,127-132] Catheter type, placement techniques, and location were all significant determinants of adverse outcomes, with CVADs having more complications.[132,133] Strict adherence to aseptic protocols, using new techniques (ie, new protocols, new insertion devices, etc), frequent laboratory monitoring (eg, electrolytes, glucose), and using well-trained staff can greatly reduce complications. For patients with HG, especially those with small children, having home infusion care is less stressful than arranging scheduled IV therapy in a clinic. Successful intervention requires the family receive detailed education and an understanding of when to call for help. Specific information on the critical importance of careful maintenance is imperative.

For pregnant women, the risks of malnutrition on the fetus must also be considered. Less than 20% of women receive central PN, yet about 26% lose more than 15% of their body weight and report adverse maternal and fetal outcomes.[8,134,135] To provide nutrition and gut rest in malnourished patients, peripheral PN (PPN) or central PN are options. PPN can be given for up to 2 weeks (or less if given via a midline catheter), whereas central PN can be administered indefinitely via central lines.[120] Early central PN should be considered in patients with rapid weight loss, a low BMI, or a history of severe or prolonged HG. In obese patients with rapid weight loss, nutritional therapy, particularly micronutrient repletion, is essential, or the risk of infant mortality and growth restriction increases.[136] When nothing alleviates intractable NVP, the benefits of PN outweigh the risks of starvation. Importantly, antiemetics and supportive care are still required with PN.

COMMON MEDICATIONS

Studies find IV hydration, serotonin inhibitors, corticosteroids, and PN provide the most relief for HG symptoms, with effectiveness rates as high as 80% compared with less than 50% for other common medications, such as promethazine and metoclopramide.[92,135] To decrease risks, monitoring and correction of electrolyte and fluid imbalances are necessary.

Administering multiple medications means simultaneous action on key receptor sites triggering the vomiting center in the brain and improving symptom severity. Common medication combinations include acid reducers, antihistamines, serotonin antagonists, and dopaminergic medications, such as metoclopramide or promethazine. If a multigravida does not respond to first-line therapies, rapidly advance treatment to what was effective in the previous pregnancy to prevent the development of severe or refractory symptoms (Table 6).

First-Line Medications

Antihistamines are generally considered first-line medications for HG, but only about 20% of patients with HG find them to be effective.[91] A study by Fejzo et al[91] found that antihistamines were taken by almost 50% of patients with an adverse outcome.

TABLE 6

HG Management Strategy

1. Assess current symptoms and treatment ⇒ adjust dose/frequency/route of Rx ⇒ add Rx ⇒ change Rx.
2. If NVP persists, review comorbid conditions (eg, GERD, h-pylori) and other potential causes, especially if symptoms increase after 12 weeks.
3. If NVP persists, add IV fluids on schedule/home ⇒ enteral nutrition ⇒ parenteral nutrition.

Abbreviations: GERD, gastroesophageal reflux disease; HG, hyperemesis gravidarum; h-pylori, *Helicobacter pylori*; IV, intravenous; NVP, nausea vomiting of pregnancy; Rx, prescription medication.

H2 blockers like ranitidine and famotidine may reduce nausea and help protect the gastric and esophageal mucosa. While commonly given before meals, this impairs nutrient absorption; thus, administration 2 hours after meals may be beneficial. If using twice-daily dosing, give after breakfast and at bedtime. Cimetidine is not generally given during pregnancy because of possible androgenic effects.[137]

Second-Line Medications

5HT3 antagonists (eg, ondansetron, granisetron, dolasetron, mirtazapine) are highly effective for treating NVP and can be administered as a tablet, oral dissolving tablet or film, injection, compounded preparation, transdermal patch (eg, Sancuso), subcutaneous infusion, or IV infusion. Oral dissolving tablets are sometimes given vaginally. These medications act on 5HT3 receptors triggering emetic impulses to the vomiting center in the brain and influence gut motility and peristalsis in the enteric nervous system. Serotonin medications are dose dependent, so increasing dosage can significantly reduce symptoms.[138] Monitoring should be considered when coadministering with antihistamines in patients at high risk for cardiac arrhythmias, because both medications can prolong the QT interval.[139] Serotonin syndrome is also of concern in patients given multiple serotonin agonists simultaneously. Severe constipation is common, necessitating a daily bowel regimen, such as a stool softener, 1 to 2 times daily, with periodic laxatives and triple magnesium supplement.

Phenothiazines and phenothiazine derivatives (eg, prochlorperazine, chlorpromazine, promethazine, and metoclopramide) are commonly used for nausea and vomiting, but effectiveness for NVP varies greatly, with only 30% to 37% of women finding benefit.[135] Usually given in either tablet or rectal form, these may also be compounded into a gel.[140] Prescribing multiple dopaminergics simultaneously should be avoided, and duration should be limited to prevent tardive dyskinesia.[141,142]

Promethazine, commonly prescribed for emesis, possesses antihistamine, sedative, antimotion sickness, and antiemetic effects; however, the side effects of sedation and anxiety can prevent usage. Antihistamines given concomitantly may reduce anxiety. Avoid IV infusions, because the US Food and Drug Administration (FDA) warns that promethazine injections may cause severe tissue damage.[143]

Metoclopramide may be used for HG to improve symptoms of gastroparesis due to its prokinetic effects. However, the side effects of depression, anxiety, and extrapyramidal effects often prevent usage. Prescribing smaller doses more frequently may increase tolerance. Metoclopramide is available as an injection, tablets, and oral dissolving tablets. Injectable forms can be used for continuous subcutaneous infusion but are significantly less tolerated and less effective than subcutaneous ondansetron.[106] Domperidone was previously used for gastroparesis, but possible cardiac effects resulted in the FDA withdrawing approval.[144,145]

Proton pump inhibitors given orally or intravenously will reduce gastric acid levels dramatically, protect mucosal integrity, decrease tooth erosion, and reduce the risk of esophageal damage.[146-148] These medications are especially helpful with GERD and HG persisting beyond the first trimester.

Third-Line Medications

Corticosteroid (eg, methylprednisolone) usage is limited to severe cases and, when effective, may prevent the need for infusion therapy. Response is extremely varied, but symptom improvement is usually noted within 24 to 48 hours. Corticosteroids are usually given in a burst dose followed by slow tapering over 2 to 3 weeks. A low dose may be beneficial for an extended duration in those with refractory symptoms. Often corticosteroids are more effective when combined with serotonin medications. Studies on corticosteroid teratogenicity are inconsistent and underpowered, so use is limited until 9 weeks' gestation because of the small risk of orofacial clefts.[149-151] Continued use later in pregnancy is associated with intrauterine growth restriction and smaller neonatal head circumference.[152] Prenatal steroids may affect long-term fetal health, including cognitive function, anxiety, and hypothalamic pituitary adrenal function.[152] Some studies find fewer side effects with methylprednisolone versus promethazine and lower rehospitalization rates in those receiving steroids.[153,154] Anticholinergics (eg, scopolamine patch) may be helpful in those with motion sickness or excessive salivation.[155] Chlorpromazine is not recommended in early pregnancy because of possible fetal malformations and should be reserved for severe, refractory cases of HG.

Experimental Medications

Other medications being trialed for HG include clonidine and gabapentin, but the safety and risks are unproven.[156,157] Mirtazapine has many properties, including anxiolytic, sedative, appetite-stimulating, and antiemetic, that are beneficial for HG.[23,158] The droperidol/diphenhydramine combination protocol was introduced years ago for HG; however, it caused severe anxiety and inconsistent benefit, so it is rarely used.[135,159] Marijuana, although sometimes effective for NVP, contains tetrahydrocannabinol, which does cross the placenta. Dose and timing may impact adverse outcomes reported with prenatal use, including impaired fetal growth, low birth weight, memory, attention, and behavioral problems.[160-163]

Antidepressants are sometimes prescribed because of the significant psychological impact of isolation and debility, but tolerance and response vary greatly. Usage with serotonin antagonists should be avoided because of the risk of serotonin syndrome. These medications may increase risks of preterm birth, respiratory disorders, low birth weight, and neonatal adaptation syndrome, as well as future depression, anxiety, and behavioral disorders in the offspring.[164-167]

TABLE 7

The I's of Immediate Intervention

IMMEDIATELY INTERVENE IF:

1. Inability to tolerate antiemetics
2. Intake of ≤1 meal per day
3. Inadequate UOP/ketonuria
4. Increasing weight loss (>1 lb/week)
5. Inability to cope or function
6. Increasing HELP Score

Abbreviations: HELP, HyperEmesis Level Prediction; lb, pound; UOP, urine output.

Weaning

It is a mistake to immediately or abruptly discontinue medication when a patient has a few "good days," because relapse often follows. When a patient has been stable with minimal symptoms for 2 weeks, a slow reduction in frequency or dose of each medication can be trialed. The general rule for weaning, as recommended by the HER Foundation's Rule of 2's, is to wean medications over 2 weeks each, during or after the second trimester, and 2 weeks or more without symptoms.

PATIENT EDUCATION

Women are often reluctant to try medications because of the perceived risk of fetal malformations. It is important to inform patients of the known risks of stress, malnutrition, and dehydration versus the small risk of medications. In addition, teaching patients the impact of HG and how to manage improves coping and communication.

Set realistic goals with the patient, such as keeping weight loss below 10% and planning a return to work and normal intake after midpregnancy. Also clarify treatment expectations. Misperceptions about medication effects mean women often report that medications are ineffective because they expected relief from nausea, not just vomiting. Also explain alternatives to oral administration, so patients understand that there are other options.

Because HG is multifactorial, symptoms and treatment response may vary with each pregnancy. Timing and effectiveness of treatment strongly influence symptom severity. If there is a history of HG, early or rapid symptom onset, high levels of psychosocial stress, and/or debility, early and aggressive intervention is crucial (Table 7). Preemptive antiemetics started at the onset of symptoms may reduce symptom severity and duration (Table 8).[168]

TABLE 8

Patient Education: Medications

- Medications may not give immediate or total relief.
- Treatment may be needed by SQ/TD/IV routes.
- Most medications don't significantly improve nausea.
- Adjustments will be needed as symptoms change.
- Symptoms may worsen so benefits may be unclear.
- Multiple medications may be required for relief.
- Medications may be needed until delivery.
- Risk is not necessarily greater in higher doses.
- Abrupt discontinuance may lead to relapse.

Abbreviations: IV, intravenous; SQ, subcutaneous; TD transdermal.

Lifestyle Changes

Lifestyle changes are beneficial for HG but are not a replacement for antiemetic therapy. Most importantly, women need additional rest and relief from stress, which worsen HG and pose risks to the health of her unborn child(ren).[169,170] Proactive care may also reduce the duration and, thus, the cost of medications as well. Each woman has differing thresholds for stimuli, so avoidance of triggers is an important intervention, and all family members should be educated to proactively assist in trigger avoidance as treatment (eg, stuffy rooms, odors, heat, noise, and visual or physical motion, normal body smells, cleaning chemicals).

Dietary Changes

Reduced food and fluid intake is a universal challenge with HG; however, minimizing weight loss reduces the risk of maternal complications and adverse fetal outcomes.[8,171] With the unusual, severe, and persistent food aversions, in addition to lack of appetite,[70] any calorie is a good calorie. A woman may have very specific taste and texture requests that change frequently and rapidly, so the goal is to fulfill any craving immediately. Nutritional consultation may be helpful in expanding food choices and monitoring nutritional deficiencies. As symptoms resolve, reinstitution of prenatal vitamins and additional, balanced nutritional supplementation are important to overall health and recovery (Table 9).

In 2008, Goodwin et al[135] reported that an astonishing 67% of women with HG in the United States and as many as 90% of women with HG in the United Kingdom were not prescribed vitamins such as pyridoxine and thiamine during the critical period of fetal development when HG presents. Because prenatal multivitamins rarely are tolerated when NVP is present, women are susceptible to numerous

TABLE 9

Patient Education: Intake Strategies

Cold, low-odor foods	⇒ Reduce olfactory triggers
Decrease fats	⇒ Reduce gastroparesis
Frequent small amounts of food/fluid	⇒ Avoid distention
Alternate liquids/solids	⇒ Prevent fullness
High protein meals	⇒ Improve gastric emptying
Cold, clear, carbonated, and/or sour fluids	⇒ Increase palatability

vitamin deficiencies. Taking prenatal multivitamins with a snack at bedtime may increase tolerance in less-severe NVP. Sometimes an iron-free prenatal formula or a single nutrient like vitamins B6 and B1 is better tolerated. Alternate forms such as transdermal or sublingual may be available; however, absorption is unknown, although promising, in B vitamins.[172]

Alternative/Adjunctive Care

Alternative medical treatments are ineffective alone as treatment of HG; however, some may improve associated symptoms or augment antiemetics.[173] Therapies might include homeopathic remedies like Cocculus Indicus for motion sickness, acupressure/acupuncture, hypnosis, and osteopathic manipulation, which may be helpful in realigning ribs displaced by emesis and impinging on the vagus nerve.[174,175]

NUTRITIONAL DEFICIENCIES

Adequate nutrition is a universal challenge in women with HG, and early supplementation is uncommon, although it reduces NVP.[176] Although it is well-established that mother and child suffer from malnutrition, few patients with HG receive nutritional therapy.[78,91,135,177] In one study of prolonged hyperemesis, only 10% of women received PN and reported higher rates of numerous symptoms, including low blood pressure, muscle weakness, and psychological distress.[7]

Regardless of BMI, clinicians must replace water-soluble vitamins such as thiamin within 2 weeks of restricted intake to avoid potentially life-threatening complications. Some vitamin deficiencies mimic HG, which may explain why symptoms improve significantly with nutritional intervention.

Key Nutrients

Nutrients specifically recommended for patients with HG include vitamin K, iron, folic acid, pyridoxine, and thiamin. If these are not tolerated orally because of severe or prolonged symptoms, IV replacement is critical until oral intake is adequate. Many deficiencies, including zinc and vitamin D, contribute to preterm birth and abnormal fetal growth and development.[120]

Vitamin K deficiency manifests as maternal peritoneal or mucocutaneous bleeding or epistaxis.[178,179] Foods high in vitamin K, like leafy greens and fermented foods, are poorly tolerated during HG. Replacement with IV or subcutaneous vitamin K is recommended.[180]

Iron deficiency is common and increases the risk of intrauterine growth restriction and prematurity.[181] Anemia may become severe and persist in patients with HG who are intolerant of oral supplementation, thus necessitating iron infusions.[182] Important B vitamins include folic acid, which is most critical during conception and early pregnancy, and pyridoxine, which may improve nausea (Table 10).

TABLE 10

Best Practices for HG Management

1. Encourage healthy preconception BMI.
2. Prescribe early PO and/or IV vitamins.
3. Proactively treat even mild symptoms.
4. Rehydrate before severely dehydrated.
5. Treat marginal electrolyte deficiency.
6. Give antiemetics on schedule vs prn.
7. Offer non-oral antiemetics before severe.
8. Prevent medication side effects.
9. Monitor laboratory results (eg, thyroid, h-pylori, CMP).
10. Begin nutrition for weight loss >10%.
11. Wean antiemetics very slowly.
12. Watch for complications or relapse.
13. Screen postpartum (PTSD/PPD).
14. Utilize technology (HG Care app).
15. Refer for support (hyperemesis.org).

Abbreviations: BMI, body mass index; CMP, comprehensive metabolic panel; HG, hyperemesis gravidarum; h-pylori, *Helicobacter pylori*; IV, intravenous; PO, oral/by mouth; PPD, postpartum depression; prn, as needed; PTSD, posttraumatic stress disorder.

Thiamin

Thiamin, or vitamin B1, is predominantly sourced from food and supplements and critical to glucose metabolism. In women with limited diets and high carbohydrate intake, thiamin deficiency (TD) occurs within 2 weeks. Malnutrition then reduces thiamin absorption by about 70%.[183] TD may be exacerbated by medications such as IV glucose, diuretics, antacids, or antibiotics, as well as nutrient and electrolyte deficiencies, including hypomagnesia, hyponatremia, protein malnutrition, and anemia.[79]

TD exacerbates HG symptoms such as depression, irritability, weakness, headache, dizziness, insomnia, myalgia, atrophy, anorexia, nausea, vomiting, weight loss, muscle wasting, constipation, memory loss, pain sensitivity, and mood lability.[184] As it progresses, a patient may experience confusion, memory loss, peripheral neuropathy, and cardiac symptoms, which signal the need for aggressive intervention to prevent heart failure and death. TD increases preeclampsia risk and affects the infant by increasing the risk of fetal loss, impaired brain development, neuromotor immaturity, cranial malformations, and growth restriction. If a mother with TD breastfeeds, her baby has an increased risk of sudden infant death syndrome, behavioral changes, autism, delayed language development, and decreased visual alertness.[79,98]

TD prevention includes daily oral doses of 50 mg of thiamin if tolerated and/or 100 mg IV.[185] Because of poor absorption in HG and the unique metabolism of thiamin, administer multiple doses per day, and give intravenously for rapid correction.[79] Although anaphylaxis is rare, IV

thiamin should be infused over 30 minutes.[183] Laboratory analysis is often unavailable and unreliable.[79] If deficiency is suspected, treat for 6 weeks with 50 mg orally 1 to 5 times per day, but preferably with 100 mg IV daily. Minimum doses of 250 mg are crucial for patients with prolonged HG, especially in late pregnancy, when fetal brain growth is rapid. Obstetrical texts in the 1940s emphasized the need for thiamin with glucose in patients with HG, yet it is still not consistently implemented.[53,185] Vitamin B1 is nontoxic and should be given proactively to all patients with HG.

Wernicke's Encephalopathy

Wernicke's encephalopathy (WE) is an acute neurologic condition that is usually caused by TD and can be life-threatening or permanently disabling if not aggressively treated. WE may occur as early as 4 weeks gestation after just 2 weeks of vomiting.[186]

The gradual or episodic onset characteristic of WE attributed to HG manifests with nonspecific symptoms such as headaches; anorexia; irritability; abdominal discomfort; weakness; changes in speech, vision, or gait; and confabulation.[79] Nearly all patients with WE have mental status changes like dizziness, drowsiness, apathy, and cognitive impairment.[187] This can be difficult to recognize in dehydrated patients receiving sedating antiemetics.

WE then progresses to neuromuscular signs like myoclonus and seizures, elevated liver function tests, and MRI findings of brain lesions.[184] Without immediate and aggressive intervention, WE may progress to cardiac and respiratory failure and will lead to death in about 20% of diagnosed patients. Survivors may develop Korsakoff's psychosis, which manifests as severe short-term memory loss, disorientation, and confabulation. Fetal loss (50%) and persistent cognitive impairment (65%) are common, and only about one quarter of patients have resolution of WE symptoms.[185,188] If WE is suspected, immediate IV thiamin up to 1500 mg per day is critical, especially if neurologic or cardiac sequelae is present.[185] Improvement may be noted within 24 hours; HG protocols should recommend infusing thiamin 100 to 500 mg/d for up to 6 weeks to replenish stores.[79]

CONCLUSION

Proactive, knowledgeable, and compassionate care can alleviate suffering and reduce complications for patients with HG. Treating both the symptoms and the underlying nutritional deficiencies exacerbating HG will improve both treatment response and outcomes. Using standardized management tools (www.hyperemesis.org/tools), the HG Care app, and the HELP Score to monitor severity and progress will improve recognition of changes impacting treatment and outcomes. Improved understanding of HG means that infusion nurses are better able to provide effective treatments, guidance, and support. Excellence in caring for these patients offers an opportunity to impact the future health of both mother and child(ren).

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