Chapter 16
Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum

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I Have Heard the Terms, "Morning Sickness," "Nausea and Vomiting of Pregnancy," and "Hyperemesis Gravidarum." What Do They All Mean? How Do They Differ? Which One Do I Have?

Nausea and vomiting of pregnancy (NVP) is one of the most common GI disorders of pregnancy, affecting 70–80% of pregnant women [1]. It is characterized by nausea and vomiting which typically begin within 4 weeks of the last menstrual period, peaks between 10 and 16 weeks gestation, and resolves after 20 weeks gestation [2]. NVP is often erroneously referred to as "morning sickness" as NVP is limited to the morning in less than 2% of women and more commonly persists throughout the day [2]. Women with severe symptoms may have hyperemesis gravidarum (HG), a condition associated with fluid, electrolyte and acid-base imbalance, nutritional deficiency, and weight loss [3]. HG is much less common than NVP, affecting only 0.3–3.6% of all pregnancies worldwide [4]. While there are no strict criteria for HG, it is commonly defined as the occurrence of greater than three episodes of vomiting per day with accompanying ketones in the urine and weight loss of more than 3 kg or 5% of body weight [5].

Although NVP and HG exist on a continuum and share the classic symptoms of nausea and vomiting, they are distinct conditions and pose different risks to mother and fetus. It is important that pregnant women who are nauseous and vomiting be accurately classified as having NVP or HG so their treatments can be tailored to their disease severity and maternal and fetal outcomes can be optimized.

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How Did I Get This?

Multiple risk factors have been identified for the development of NVP and HG. These include history of HG in a prior pregnancy, multiple gestations, female gender of the fetus, history of psychiatric illness, high and low prepregnancy body mass index, young age, black or Asian ethnicity, and Type I diabetes [6–9]. Interestingly, smoking has been associated with a decreased risk of HG [10].

The exact cause of NVP and HG has not been determined; however, several factors have been proposed to contribute to their development including genetics, psychological factors, hormones, infection with *Helicobacter pylori*, and altered gastrointestinal tract motility. With regard to genetic factors, history of NVP in a woman's mother or sister has been long noted to be a risk factor for NVP [11, 12]. Furthermore, a twin study found that monozygotic twins had twofold increased risk of having NVP compared to dizygotic twins [13]. Two potential candidate genes, GDF15 and IGFBP7, both of which have roles in early pregnancy, have been associated with HG [14].

It has been noted by numerous investigators that psychiatric disturbances are common in women with NVP and HG, and many have queried whether depression and anxiety may contribute to their development [15–17]. Furthermore, HG has been hypothesized to be some to be a psychosomatic illness or a conversion disorder underlying a subconscious wish for an abortion [18]. HG has also been linked with abnormal personality traits and with unhealthy bonds between the pregnant woman and her mother [19]. Depression, anxiety, and other psychiatric disorders associated with HG are more likely to be secondary to HG rather than contributing factors [20, 21].

With regard to hormonal factors, beta human chorionic gonadotropin (β-hCG) has been most strongly implicated in the pathogenesis of NVP as serum concentrations of β-hCG and the symptoms of NVP peak at the same time. Furthermore, conditions associated with a higher risk for HG including multiple gestations, Down's syndrome, carrying a female fetus, and molar pregnancy are also characterized by higher β-hCG levels [22]. It is hypothesized that hCG levels may directly affect nausea centers in the brain or may indirectly induce symptoms by leading to increases in other hormones (e.g., thyroid hormones, estradiol) which affect nausea [23]. It should be noted, however, that some studies have not found high level of β-hCG in affected women [3, 24, 25].

Other hormones which have been implicated in the development of NVP and HG include progesterone, estrogen, thyroid hormones, and leptin; however, studies evaluating their role in these conditions have not been conclusive [26–31]. It is thought that the ovarian hormones progesterone and estrogen may cause nausea and vomiting by affecting gastric smooth muscle and impairing gastric motility [32]. Thyroid hormones have also been implicated due to the shared alpha subunit between thyroid-stimulating hormone (TSH) and β-hCG and which allow β-hCG to cross-react with the TSH receptor and stimulate free thyroxine (T4) production [33]. Thyroid hormone abnormalities (typically high-free T4 and low TSH levels)

have been found in 30–60% of women with HG; however, despite these laboratory abnormalities, women with HG are generally euthyroid and nearly always return to normal TSH levels by 20 weeks gestation without intervention [33–37]. Lastly, leptin is a hunger regulatory hormone that has recently been shown to be secreted by the placenta [38]. Lower levels of leptin have been reported in a small study of women with HG compared to controls; however, other studies have not shown this association [31, 39].

Infection with *Helicobacter pylori* (*H. pylori*) may contribute to the development of HG. Two meta-analysis have found higher rates of *H. pylori* infection in women with HG compared to controls [40, 41], and several small case reports have reported that treatment of *H. pylori* improved symptoms [42, 43]. What has confounded determining causality between *H. pylori* and HG is the mode of diagnosing *H. pylori* as many studies use serum IgG antibodies as a marker of infection despite the fact that seropositivity for the *H. pylori* IgG is not a direct marker for active infection and may reflect cleared infection.

Abnormalities in gastric emptying and lower esophageal sphincter (LES) resting pressure have been proposed to be mechanisms for the development of NVP and HG; however, as in studies evaluating hormonal causes, results have been mixed. In one study by Koch et al. which evaluated the gastric myoelectric activity in pregnant women, with and without nausea gastric dysrhythmias were demonstrated in all nauseated women, while normal 3-ccylce per minute patterns were seen in all of the women with minimal to no nausea [44]. However, other studies of gastric transit have not found abnormalities in women with HG compared to controls [29]. Lower resting LES pressure and reduced percentage of transmitted contractions in the esophagus have been found during pregnancy [45]. This likely accounts for the high prevalence of gastroesophageal reflux disease (GERD) during pregnancy [46–48]. Although decreased LES pressure is most likely to produce heartburn, GERD may also manifest as including nausea and vomiting [49].

How Do You Diagnose NVP and HG?

NVP and HG are clinical diagnoses which are characterized by the development of nausea and vomiting, typically in the early first trimester [2]. Some women may also experience ptyalism (i.e., excess salivation) or GERD symptoms such as heartburn and non-cardiac chest pain [50]. The onset of nausea and vomiting more than 8 weeks after the last menstrual period is atypical for NVP and should prompt investigation for other conditions which can cause nausea and vomiting in pregnancy (see Table 16.1) [50, 51].

Most women with NVP have normal vital signs and a benign physical exam. Women with HG, however, may show signs of dehydration and be orthostatic. HG may also lead to muscle wasting and weakness, peripheral neuropathies due to vitamin B6 and B12 deficiencies, mental status changes, and cognitive malfunction [52].

Table 16.1 Differential diagnosis of NVP and HG

Gastrointestinal conditions	Gastroenteritis Gastroparesis Achalasia Biliary tract disease Hepatitis Intestinal obstruction Peptic ulcer disease Pancreatitis Appendicitis
Genitourinary tract conditions	Pyelonephritis Uremia Ovarian torsion Nephrolithiasis Degenerating uterine leiomyoma
Metabolic conditions	Diabetic ketoacidosis Porphyria Addison's disease Hyperthyroidism Hyperparathyroidism
Pregnancy-unique conditions	Acute fatty liver of pregnancy Preeclampsia
Other	Drug toxicity or intolerance Psychologic conditions

Adapted from Goodwin TM. Hyperemesis Gravidarm. Obstet Gynecol Clinics 2008;3:401–17

A complete physical exam should always be done to rule out peritonitis and evaluate for other causes of nausea and vomiting.

No specific laboratory or radiographic studies are needed for the diagnosis of NVP. Tests which may be helpful in ruling out other causes of nausea and vomiting in a pregnant woman include a white blood cell count, liver function tests, fasting serum glucose, and TSH. Women with suspected HG laboratory studies should undergo laboratory testing to evaluate the severity of the disease. Labs to consider include a serum blood urea nitrogen, creatinine, and hematocrit which may all be elevated due to volume depletion. Urinalysis should also be obtained to assess specific gravity and evaluate for ketones. Additionally, electrolytes should be checked to assess for deficiencies in sodium and potassium levels and to check acid-base status as should prealbumin, vitamin B1 (thiamin), iron, calcium, and folate as deficiencies are possible [53–55].

Liver function tests are commonly abnormal in women with HG [51]. Specific abnormalities include mild hyperbilirubinemia (bilirubin <4 mg per deciliter), elevations in alkaline phosphatase to twice the upper limit of normal, and elevated alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels [56] with the latter being most common. The transaminase elevation is usually modest and within two to three times the upper limit of normal [57]. Liver test abnormalities typically resolve once vomiting subsides. Serum amylase and lipase levels are less commonly elevated compared to liver function tests; however, elevations in these enzymes occur in 10–15% of women [30].

What Can I Do to Feel Better?

Dietary Modifications

Women who are able to tolerate oral intake should consume small frequent meals that are high in protein, bland in flavor, and low in odor [58–61]. Small frequent meals can help prevent hypoglycemia and gastric over-distention [62].

Women with HG should be encouraged to eat any pregnancy-safe food or beverage they can tolerate. If hospitalization is required to manage HG, the diet order should be regular as tolerated. A focus on adequate calories, as opposed to proper macronutrient distribution, is advised. A dietitian should elicit the patient's food choices to identify types of foods preferred and tolerated which will help drive further dietary suggestions.

Dietary advice for women with NVP and HG is summarized in Table 16.2.

Complementary and Alternative Medicine

Women with mild symptoms may respond to treatment with ginger, acupressure, or acupuncture. Ginger has been found to improve mild to moderate nausea and vomiting compared to placebo across several studies and meta-analyses [63–68]. Although its exact effects are not known, ginger may reduce nausea via antagonistic effects on serotonergic 5-HT3 and cholinergic receptors and/or by improving GI tract motility and increasing bile and gastric acid secretion [63, 69–71]. It can be taken in various forms including fresh, candies, teas, and capsule and syrups. The dose of ginger found to be effective in a crossover study of women with HG was 1 g/day [66]. With regard to acupressure, stimulation of the median nerve at the Pericardium 6 (known as P6 or Neiguan) acupuncture point by placing pressure on the ventral aspect of the wrist has been shown to decrease symptoms in several studies of NVP as well as in a systematic review of 26 trials which included a variety of conditions which cause

Table 16.2 Dietary recommendations for NVP and HG

Eat small meals every 2–3 h (about 1–1.5 cups)
Choose bland foods like toast, rice, baked chicken
Avoid high-fat/greasy foods
Choose low-fat high-protein foods like lean meats, eggs, and beans
Separate liquids and solids. Drink liquids 20–30 min before or after eating
Avoid foods with strong odors like fish and cauliflower
Explore different food characteristics such as salty versus sweet, hot versus cold, and crunchy versus soft or combinations that may be complementary
Try ginger (tea, lollipops, capsules)
To reduce bitter or metallic taste, try candies and colder fluids

Adapted from: Austin K, Wilson K, Saha S. Hyperemesis Gravidarum. Nutr Clin Prac 2018; 0:1–16

nausea and vomiting (e.g., chemotherapy, postoperative state, pregnancy) [72–74]. Acupuncture has been rigorous than acupressure in women with NV; however, small studies have suggested that traditional and P6 treatments may be beneficial [75].

Pharmacotherapy

Pharmacologic treatments include vitamin B6 (pyridoxine) alone or in combination with doxylamine, antihistamines, metoclopramide, and ondansetron. Randomized controlled trials have shown that vitamin B6 taken at doses of 10–25 mg every 8 h reduces symptoms among women with NVP [76, 77]. Vitamin B6 has also been found to be effective when used in conjunction with doxylamine. The combined formulation of vitamin B6 and doxylamine, Diclegis (Duchesney, Bryn Mawr, PA), is currently the only FDA-approved medication for NVP [58, 78]. Antihistamines are thought to reduce nausea and vomiting by indirectly affecting the vestibular system and decreasing stimulation of the vomiting center and/or by inhibition of muscarinic receptors [79]. First- and second-generation histamine antagonists such as dimenhydrinate, diphenhydramine, hydroxyzine, and meclizine have long been used for treatment of NVP, and many studies have found them to be effective [80]. Their safety was also recently established in systematic review of 37 studies which found no increased risk for spontaneous abortions, prematurity, stillbirth, or low birthrate when used for a variety of indications during pregnancy including seasonal allergies, asthma, and NVP [81].

Dopamine antagonists used in the treatment of NVP and HG include metoclopramide and several phenothiazine derivatives (e.g., promethazine, prochloroperazine, and chlorpromazine). Metoclopramide is thought to improve nausea and vomiting by antagonizing D2 receptors in the chemoreceptor trigger zone within the central nervous system and at higher doses by antagonizing 5-HT3 receptors [82]. Phenothiazinee derivatives work as D2 antagonists and have antihistamine activity by blocking H1 receptors [83, 84]. While case reports have suggested an association between phenothiazines and birth defects, multiple prospective cohort, retrospective cohort, case-control, and record linkage studies have been reassuring [85]. When used continuously into the third trimester, newborns should be monitored for withdrawal, including extrapyramidal effects [86]. Metoclopramide has not been associated with an increased risk for major congenital malformations, low birth weight, preterm delivery, or perinatal death [87–89]. It does, however, carry an FDA-issued black box warning due to the risk of tardive dyskinesia with high cumulative doses. To minimize this risk, it is generally recommended that metoclopramide use be limited to less than 12 weeks.

Serotonin antagonists such as ondansetron prevent nausea and vomiting by acting peripherally on the vagus nerve and centrally by blocking chemoreceptors in the area postrema of the brain. Randomized controlled trials support the use of ondansetron for NVP with greater symptom improvement compared to metoclopramide

and to vitamin B6-doxylamine [90–93] and better side effect profile. Multiple case reports, a nationwide historical cohort study, and a prospective comparative observational study have reported no increased risk for adverse pregnancy outcomes with ondansetron use which showed no significant differences between the rates of live births, miscarriages, stillbirths, therapeutic abortions, gestational age, or risk of major malformations among infants of mothers who had taken ondansetron compared to those who had not taken any medications during pregnancy [94, 95]. However, one study reported an increased rate of cleft palate in infants born to mothers who had taken ondansetron, and another large Danish study reported an increased risk for cardiovascular birth defects (specifically cardiac septum defects) with an odds ratio of 1.62 (1.04–2.14) but no increased risk when all major adverse birth defects were pooled OR 1.11 (0.81–1.53) [96, 97].

Corticosteroids are frequently co-administered with 5-HT3 antagonists to treat chemotherapy-induced nausea and vomiting [98]. Several small, randomized controlled trials evaluated the role of corticosteroids in the treatment of HG. Two such studies comparing corticosteroids to promethazine were negative [99, 100]. A third study of women with HG admitted to the intensive care unit compared hydrocortisone to metoclopramide and found that patients treated with corticosteroids had a greater reduction in vomiting within 3 days of treatment [101]. Given these conflicting results and the potentially increased risk for oral clefts (cleft lip and cleft palate) with first trimester corticosteroid use, it is recommended that corticosteroids be reserved for refractory case and that its use be minimized in the first trimester [102, 103].

Lastly, gabapentin has been shown to be beneficial in reducing chemotherapy-induced nausea and vomiting and in one small open label study to be effective in the treatment of HG [104, 105]. A larger, controlled trial is currently underway to further assess the effectiveness and safety of gabapentin in HG.

Pharmacologic treatments for HG are summarized in Table 16.3.

Intravenous Fluids

Patients with HG who cannot tolerate oral liquids or are clinically dehydrated should be treated with intravenous (IV) fluids [58]. IV hydration not only improves fluid status but also the symptoms of nausea and vomiting. Normal saline has been shown to be an effective route of rehydration in one-controlled study although 5% dextrose normal saline (D5NS) is also a reasonable alternative [106]. It is important to note, however, that Wernicke's encephalopathy may develop when dextrose-based solutions are given prior to thiamin repletion [107–110]. Thiamin deficiency can occur within 2–3 weeks of persistent vomiting; thus thiamin should be repleted intravenously before D5NS is administered [107, 111, 112]. As women with HG are also at high risk for electrolyte imbalances, serum potassium, magnesium, and phosphorus levels should be monitored and repleted as needed in the patient requiring IV rehydration [113].

Table 16.3 Pharmacologic treatments for NVP and HG

Treatment	Dose	Possible side effects	Contraindications
Ginger	250 mg up to 4 times daily	Heartburn	None
Vitamin B6 (pyridoxine)	10–25 mg 3–4 times daily	Numbness, paresthesia, unsteady gait	None
Antihistamine/B6 combination	10–12.5 mg doxylamine +10 mg B6 up to four times daily	Fatigue, epigastric pain, constipation, impaired coordination, paresthesia	None
Metoclopramide	10 mg up to 4 times daily	Fatigue, anxiety, headache, dizziness, depression, galactorrhea, extrapyramidal symptoms, dystonia	Hypertension, seizure disorder, Parkinson's disease, history of tardive dyskinesia, depression
Phenothiazine derivatives (promethazine, Compazine, Thorazine)	10–25 mg up to 3 times daily	Tissue damage, seizures, respiratory depression, hallucinations, sedation, extrapyramidal symptoms, dry mouth	Respiratory depression, seizure disorder
Ondansetron	Up to 24 mg/day in 3–4 divided doses	Headache, constipation, urinary retention, dizziness, possible increased risk for birth defects	Congenital long QT interval
Corticosteroids	Hydrocortisone 100 mg twice daily IV, converted to prednisone 40 mg and taper to lowest effective dose	Possible increased risk for oral clefts,	Corticosteroids
Clonidine	5 mg patch	Hypotension, headache, sedation, contact dermatitis, dizziness, constipation	Recent myocardial infarction, depression, hemodynamic instability, renal impairment
Gabapentin	300–900 mg up to three times daily	Fatigue, depression with abrupt withdrawal	Renal impairment, depression

Adapted from Austin K, Wilson K, Saha S. Hyperemesis Gravidarum. Nutr Clin Prac 2018; 0:1–16

Enteral and Parenteral Nutrition

Nutrition support should be initiated in women with HG who continue to lose weight and are unresponsive to pharmacological and non-pharmacological treatments. The decision to start enteral nutrition (EN) or parenteral nutrition (PN) must be individualized and take into account the patient's gestational age, comorbidities, and preferences as well as institutional resources and expertise. In most cases, EN is preferred over PN given the increased health risks with PN during pregnancy. EN

is also more cost-effective and less intensive than PN. Nasogastric or nasoenteric tubes are preferred for an anticipated duration of 4–6 weeks, whereas longer-term needs require gastrostomy or jejunostomy placement. While gastric feedings hold a higher risk of aspiration, jejunostomy tube placement typically involves exposure to radiation, and tube dislodgement with retraction into the stomach is common. There are no studies comparing gastric to intestinal feedings, nor polymeric to elemental formulas, in the treatment of HG. Antiemetics should be co-administered with nutritional support to minimize symptoms, risk of aspiration, and tube dislodgement from retching.

PN should be reserved for those with ongoing weight loss who have failed a trial of EN or have contraindications given the increased risks associated with centrally placed catheters in pregnant women which include bacteremia/sepsis and venous thrombosis [114, 115].

What Is the Impact of NVP and HG on My Fetus and on My Own Health? What Are the Societal Costs?

NVP is associated with a favorable outcome for the fetus. In a prospective study of 16,398 women, no difference was found in congenital abnormalities between those with and without NVP [116]. A meta-analysis of 11 studies found a decreased risk of miscarriage (common odds ratio = 0.36, 95% CI 0.32–0.42) and no consistent associations with perinatal mortality [117] in women with NVP. Moreover, women without NVP have been found to deliver earlier compared to women with NVP [118]. NVP, however, causes substantial psychosocial morbidity in the mother. NVP impairs employment, performance of household duties, and parenting [119]. It is also associated depression, consideration of termination of pregnancy, and impaired relationships with partners.

HG, in comparison, is associated with both adverse maternal and fetal outcomes. In a study of over 150,000 singleton pregnancies, women with HG had increased rates of low pregnancy weight gain (<7 kg), low birth weight (LBW) babies, small for gestational age (SGA) babies, preterm birth, and poor 5-min Apgar scores [120].

Common maternal complications include weight loss, dehydration, micronutrient deficiency, and muscle weakness. More severe, albeit rare, complications include Mallory-Weiss tears, esophageal rupture, Wernicke's encephalopathy with or without Korsakoff's psychosis, central pontine myelinolysis due to rapid correction of severe hyponatremia, retinal hemorrhage, spontaneous pneumomediastinum [121], and vasospasm of the cerebral arteries [122]. HG may also lead to psychological problems and result in termination of an otherwise wanted pregnancy and decreased likelihood to attempt a repeat pregnancy [123].

Some studies have found no increased risk for adverse fetal outcomes in women with HG [124]. However, many have found an association between HG and fetal growth retardation, preeclampsia, and SGA [125]. In a retrospective study of 3068 women, HG was associated with earlier delivery and lower birth weight [126].

Similarly, Dodds et al. found higher rates of LBW, preterm birth, and fetal death in women with HG who gained less than 7 kg overall during pregnancy [120].

Various congenital malformations have been observed more in women with HG [126]. These include Down's syndrome, hip dysplasia, undescended testes, skeletal malformations, central nervous system defects, and skin abnormalities. Fetal coagulopathy and chondrodysplasia have been reported from vitamin K deficiency [127] with third trimester fetal intracranial hemorrhage [128].

It is also worth noting that NVP is one of the most common indications for hospitalization throughout pregnancy and that HG is the most common cause of hospitalization in the first half of pregnancy, accounting for over 59,000 hospitalizations annually [129, 130]. Apart from requiring hospitalization, HG leads to extra doctors' visits and emergency room visits throughout pregnancy [131]. Conservative estimates put the total economic burden posed by NVP in 2012 to be over 1.7 billion dollars annually in the United States, with over 1 billion dollars in direct costs [132]. Indirect costs which include lost time from work and caregiver time are also substantial and difficult to fully estimate in cost models.

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