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Gastroenterol Clin North Am. Author manuscript; available in PMC 2013 June 09.

Published in final edited form as:
Gastroenterol Clin North Am. 2011 June ; 40(2): 309–vii. doi:10.1016/j.gtc.2011.03.009.

Nausea and Vomiting of Pregnancy

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Introduction

Nausea and vomiting are common experiences in pregnancy, affecting 70–80% of all pregnant women. Although most women with nausea and vomiting of pregnancy (NVP) have symptoms limited to the first trimester, a small percentage of women have a prolonged course with symptoms extending until delivery. Women with severe nausea and vomiting during pregnancy may have hyperemesis gravidarum (HG), an entity distinct from NVP, which if left untreated may lead to significant maternal and fetal morbidity.

Various metabolic and neuromuscular factors have been implicated in the pathogenesis of NVP and HG; however, their exact cause is unknown. Consequently, treatment of NVP and HG can be difficult as neither the optimal targets for treatment nor the full effects of potential treatments on the developing fetus are known. This article reviews the epidemiology, pathology, diagnosis, outcomes, and treatment of NVP and HG.

Epidemiology

It is estimated that 70–80% of pregnant women experience NVP [1]. In the United States and Canada this translates to approximately 4,000,000 and 350,000 women who are affected each year, respectively [2].

NVP is found more often in Western countries and urban populations and is rare among Africans, Native Americans, Eskimos, and most Asian populations [3]. Only a few studies have examined the racial distribution of NVP in a given population. One such study from Canada of 367 women found that Asians and blacks were less likely to report symptoms of NVP than Caucasians. Sociodemograhic factors did not account for the racial/ethnic variation in disease prevalence, suggesting that genetic and/or cultural factors may be at play [4].

HG is rare in comparison to NVP, occurring in 0.3–2% of all pregnancies [5]. The incidence appears to vary with ethnicity [6] and ranges between 3 and 20 per 1,000 pregnancies [7]. It is more commonly diagnosed in women in India, Pakistan, Asian, New Zealanders compared to European, American Indian, and Eskimo populations [8].

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Risk Factors

Data from the Collaborative Perinatal Project, one of the largest studies to date of pregnant women, found NVP to be more common in younger women, primigravidas, women with less than 12 years of education, non-smokers, and obese women [9]. Increased risk of NVP in the first trimester has also been reported in women with multiple gestation compared to women with singleton pregnancies (87% vs. 73%, $p<0.01$) [10].

NVP has been associated with low income levels and part-time employment status [11]). Housewives have also been found to be at increased risk while women with white collar occupations appear to be protected [12]. Whether employment status is a true risk factor for NVP or a confounder, however, remains unclear as affected women may cease employment because of their symptoms. Similarly, their decision to not work outside the home may be due to multiparity and the need to care for other children [13].

Maternal genetics also appear to serve as risk factors for NVP. Data from a large Norwegian twin population show higher use of nausea medication in pregnancy among female monozygotic twins compared to female dizygotic twins [14]. In addition, higher levels of nausea have been found in women who had mothers who experienced trouble with nausea in their pregnancy [15]. A personal history of NVP has also been shown to be a risk factor for NVP in subsequent pregnancies [15]; however, this finding has not been consistent across studies [16]

Other risk factors for NVP include a personal history of motion sickness, due possibly to a common vestibular mechanism [17] and history of migraine headaches [18]. Women who have a history of nausea when taking estrogen-containing oral contraceptives also appear to be at an increased risk for NVP [19].

Location of the corpus luteum may also serve as risk factor for NVP. Ultrasound studies have shown that pregnant women experience more nausea and vomiting when the corpus luteum is present in the right ovary [20]. This may be due to differences in venous drainage between the left and right ovary and a higher concentration of sex steroids when the corpus luteum is on the right side [21].

A higher daily intake of total fat, especially saturated fat, prior to pregnancy increases the risk of hospitalization for NVP [22]. Smoking before pregnancy and vitamin use before and/or in early pregnancy are associated with a decreased risk for NVP [23]. Maternal alcohol consumption prior to conception has also been found to be protective for NVP [24].

Risk factors for HG are similar to those of NVP. They include multiple gestations, trophoblastic disease, HG in prior pregnancy, fetal abnormalities such as triploidy, trisomy 21, and hydrops fetalis, and nulliparity [25]. Family history of HG is also a risk factor with approximately 28% of women reporting a history of HG in their mothers and 19% reporting their sisters had similar symptoms [26]. Additional risk factors include married or partnered status and age greater than 30. Cigarette smoking may be protective [27].

Maternal body mass index has been evaluated as a risk factor for HG with inconclusive results. In a study by Depue et al, obesity increased the risk for HG by 50% [28]. Work by Cedergren et al. however, found that a low body mass index (<20 kg/m2) was associated with a 40% higher risk of HG and that obesity decreased the risk of hospitalization for HG [29]. A more recent study of 33,647 women in Norway found that being either underweight or overweight increased the risk for HG, but only in non-smokers [30]. It is postulated that underweight women with low body mass indices have low pre-pregnant estrogen levels and thus may have an exaggerated response during the first trimester when estrogen levels surge

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[31]. In contrast, in obese women fat deposits may neutralize placental factors thought to contribute to the pathogenesis of [29].

With regards to fetal gender, an association between HG and female gender of the fetus has been found in several studies. Using data from the Swedish Medical Birth Registry, Kallen et al. found HG to be over-represented in the 3068 pregnancies when the infant was a girl [32]. Similarly, in a study of pregnant women hospitalized with HG in the first trimester the odds of having a female infant was 50% higher in cases compared to healthy pregnant controls (OR 1.5, 95% CI 1.4, 1.7) [33].

Pathogenesis

Metabolic and hormonal factors

Although the exact pathogenesis of NVP and HG unknown, it is widely accepted that gestational vomiting results from various metabolic and endocrine factors, many of placental origin. The most implicated factor is human chorionic gonadatropin (hCG). This link between hCG and NVP is based largely on the temporal relationship between the peak of NVP and the peak of hCG production, both of which occur between 12 and 14 weeks gestation. In addition, nausea and vomiting are often worse in pregnant women with conditions associated with elevated hCG levels such as molar pregnancies, multiple gestations, and Down's syndrome [13]. Higher urinary hCG [34] and serum hCG levels have also been found in women with NVP compared to those who are asymptomatic [35]. Furthermore, a study by Goodwin et al. found that concentrations of hCG correlated positively with the severity of nausea and vomiting in women with HG [36].

Despite the multitude of studies linking hCG to NVP and HG, others have found no relationship between serum hCG in pregnant women during the first trimester and the frequency or intensity of nausea and vomiting. In a study by Soules et al., even in a subset of women with molar pregnancies in whom levels of hCG in women were 5 to 10 times higher than in controls, no correlation was found [37]. Furthermore, studies have found high levels of hCG to be associated with fetal growth retardation and preterm delivery [38] whereas NVP appears to be protective for preterm delivery making it unlikely for hCG to be the sole contributor to the pathogenesis of NVP.

It is postulated that varying biologic forms (i.e. isoforms) of hCG may explain the variability between hCG levels and nausea and vomiting in normal and sick populations [39]. Each hCG isoform has a unique half-life and potency at the luteinizing hormone and thyroid-stimulating hormone (TSH) receptor. Isoforms without the carboxy-terminal portion have shorter half-lives but are more powerful stimulants of the luteinizing hormone and TSH receptors. In contrast, hyperglycosylated hCG has a longer half-life and longer duration of action [40]. These different isoforms of hCG are likely the result of genetic factors or long-term environmental changes which may thus explain the differences in HG incidence found in different populations. In addition to isoform variation, hCG receptor mutations may also explain some of the variability in the relationship between NVP and hCG [39].

The ovarian hormones, estrogen and progesterone, have also been implicated in the pathogenesis of NVP and HG. It is known that some women experience nausea when taking oral contraceptives. Furthermore, states of high estrogen concentration such as low parity and high maternal body mass index have been associated with a higher incidence of HG [28]. Estrogen is thought to contribute to HG by stimulating the production of nitric oxide via nitrogen oxidase synthetase, which in turn relaxes smooth muscle slowing gastric intestinal transit time and gastric emptying.

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Jarnfelt et al. reported a significant association between emesis gravidarum and a history of intolerance to oral contraceptives [40]. Using a more quantitative approach, Depue et al found mean levels of total estradiol to be 26% higher and mean levels of sex hormone binding-globulin binding capacity to be 37% higher in patients with HG than in control subjects after adjusting for gestational age [28]. It is important to note, however, that like the relationship between hCG and NVP the relationship between estrogen levels and NVP has been inconsistent across studies [35]. A review of 17 studies showed a positive association between NVP and estrogen in only 5 studies [41]. Furthermore, estrogen levels peak in the third trimester of pregnancy, while HG tends to improve during late pregnancy [8].

Progesterone in combination with estrogen may also have a role in NVP. Progesterone decreases smooth muscle contractility and may alter gastric emptying and lead to increased nausea and vomiting. Using elastogastography after a standard meal, Walsh et al. showed that the same slow-wave gastric rhythm disruption found in women with NVP could be evoked in non-pregnant women by progesterone alone or in combination with estradiol in doses that reproduce levels in pregnancy [42]. Other studies, however, have not found any significant difference between progesterone levels in women with or without NVP [28].

The role of placental prostaglandin E2 (PGE2) has also been evaluated in the pathogenesis of NVP due to its effect on gastric smooth muscle [43]. hCG stimulates placental PGE2 and like hCG peaks between 9 and 12 weeks of gestation. North et al. quantified maternal serum PGE2 and found levels to be higher during periods of nausea and vomiting in 18 women in early pregnancy compared to during asymptomatic periods. They also evaluated maternal levels of interleukin-1 beta and tumor necrosis factor alpha levels and found both to be similar during symptomatic and asymptomatic periods [44].

Due to its role in chemotherapy-induced nausea and vomiting, serotonin has also been hypothesized to contribute to NVP. A study by Borgeat et al. however, did not show any difference in serotonin levels among pregnant women with HG, asymptomatic pregnant women, and nonpregnant women [45]. In addition, a randomized controlled trial comparing the serotonin 5-HT3 receptor antagonist, ondansteron to promethazine found no significant difference in symptom control [46].

Due to cross reactivity between hCG and the thyroid stimulating hormone (TSH) receptor, thyroid dysfunction has also been studied as a possible mechanism for NVP and HG development In fact, abnormal results on thyroid function are found in two thirds of women with HG [36]. This “biochemical thyrotoxicosis” is characterized by suppressed TSH and slightly elevated FT4. Despite these laboratory abnormalities, women with HG are generally euthyroid with no history of prior thyroid diseases, absent goiter and negative anti-thyroid antibodies [47]. Furthermore, studies have not found a relationship between thyroid dysfunction and the severity of symptoms [48] and almost all women with HG have normal TSH levels by 20 weeks gestation without any intervention [49].

Recently, a relationship between the hormone leptin and HG has been proposed. Increased serum leptin levels during pregnancy, possibly the result of increased total fat mass and the placenta production have been found to be significantly higher in patients with HG when compared to healthy pregnant controls [50, 51]. Leptin may contribute to HG by increasing hCG secretion by the paracrine action of the placenta or by decreasing appetite and promoting more severe nausea and vomiting. Notably, however, other prospective cohort studies have not found a similar statistically significant difference in serum leptin levels in HG between cases and controls [52, 53].

Immune system dysregulation has also been proposed to occur in women with HG. Increased concentrations of fetal cell free DNA have been found in the mothers’ serum [54]

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causing a hyperactive maternal immune response and trophoblast damage. Furthermore, the normal shift in pregnancy wherein T-helper cell types move into T-helper cell type 1 is more exaggerated in women with HG [55]. This in turn, leads to increased release of interleukin-4 is as well as tumor necrosis factor-alpha, both of which have been linked to HG [56]. Adenosine has also been found to be increased in HG, and its role is to attenuate the TNF-alpha [57]. Interleukin-6 levels have also been found to be increased with HG in a prospective trial [58] as well as increased immunoglobulin G (IgG), IgM, complement levels, and lymphocyte counts [59]. One cannot precisely define the role of these immunologic factors, however, because in starvation states, the immune system is usually suppressed, not activated; thus, perhaps the boost in immune factors seen in HG could be an attempt to limit the progression of HG [8].

Other hormones including thyroid-stimulating hormone, growth hormone, prolactin, adrenocortical-stimulating hormone, cortisol, luteinizing hormone, and follicle-stimulating hormone have also been evaluated and are not considered to contribute to the pathogenesis of NVP [60].

Helicobacter pylori

An increased incidence of infection with *Helicobacter pylori (H. pylori)* has been observed in women with HG and is now considered to play a role in its pathogenesis. Frigo et al. found that 90.5% of women with HG were *H. plyori* IgG positive, compared to 46.5% of controls [61]. Bagis et al. used the gold standard of testing, histologic exam of the mucosal biopsy, and found that 95% of HG patients tested positive for *H. pylori* compared with 50% in the control group. They also found higher *H. pylori* densities in the gastric antrum and corpus in HG patients, suggesting a possible relationship between *H. pylori* density and the severity of symptoms [62].

A systematic review from 2007 evaluating 14 case-control trials from 1966 to 2007 found a significant association between maternal *H.pylori* infection and HG in 10 studies. Odds ratios in the studies varied from 0.55 to 109.33 [63]. Similarly, an updated systematic review and meta-analysis from 2009 of 25 studies found a pooled odds ratio of 3.32 (95 % confidence interval: 2.25–4.90) for *H. pylori* infection in women with HG [64]. Notably, high heterogeneity among studies was found in both reviews.

Infection with *H. pylori* in pregnancy may occur due to steroid-hormone induced changes in gastric pH [65] and/or increased susceptibility due to changes in humoral and cell-mediated immunity [66]. However, there is no clear evidence that pregnancy predisposes to *de novo H. pylori* infection. On the contrary, it has been suggested that *H. pylori* may exacerbate hormone-induced changes in the nerve and electric functioning of the stomach and thereby increase the risk for infected women to be at the more severe end of the spectrum of nausea and vomiting [67].

While the association between *H. pylori* and HG is intriguing, it is important to note that infection does not necessarily correlate with symptoms. In fact, most infected women are asymptomatic [8]. In a study by Weyermann et al, 23% of 898 postpartum mothers were positive for *H. pylori* by 13C-Urea breath test; however, positivity did not correlate with symptoms of nausea, vomiting, or reflux symptoms during pregnancy [68]. Similarly Wu et al found 69% of pregnant women to be seropositive for *H. pylori* compared to 50% in the general population, however, did not find any correlation between antibody status and gastrointestinal symptoms [69].

Why *H pylori* cannot be precisely linked to NVP and HG has been attributed to several factors. First, most studies used antibody testing to assess for infection. However, serologic

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testing for *H. pylori* cannot distinguish between active infection and past infection [70] and active versus past infection may produce different effects on symptoms. Second, most studies have not assessed and/or accounted for *H. pylori* strain. Cytotoxin-associated gene A (CagA) protein is a marker for increased peptic ulcers and linked to a more aggressive strain of *H pylori* [71]. Only a single study included in the 2009 meta-analysis assessed for CagA pathogenicity. In this study by Xia et al, CagA positivity was more prevalent in patients with HG [72].

Treatment eradicates *H. pylori* in the majority of patients, however, currently there are no guidelines for the evaluation or treatment of *H. pylori* during pregnancy as the subsequent alleviation of symptoms of HG has not widely been studied. Case reports and cases series suggest that treatment and eradication of *H. pylori* can decrease nausea and vomiting in pregnancy and should be considered in patients with intractable symptoms [73]. Larger studies, however, are needed to determine if and when treatment should be initiated during pregnancy given the concerns of drug safety. Presently, experts recommend that after pregnancy and lactation have been completed, patients should be treated with triple therapy for two weeks [74].

Gastrointestinal Dysmotility

Alterations in lower esophageal sphincter (LES) resting pressure and esophageal peristalsis have been linked to NVP. Although these changes are more typically associated with heartburn in pregnancy, gastroesophageal reflux disease (GERD) in may produce atypical symptoms such as nausea [75] and contribute to NVP. Estrogen and progesterone are the likely mediators of esophageal dysmotility in pregnancy wherein estrogen serves as a primer and progesterone causes LES relaxation [76].

Changes in gastric rhythmic activity may contribute to NVP. Normal gastric myoelectric activity results in slow wave propagation from the proximal body to the distal antrum at a rate of 3 cycles per minute (cpm). Rhythm disturbance, either increased or decreased slow wave propagation, is associated with nausea [74]. Using elastogastrography (EGG), Koch et al. demonstrated that individuals with normal slow wave activity were less likely to complain of nausea during pregnancy [77]. In contrast, individuals with higher or slower rates were more likely to complain of nausea. Similarly, Riezzo et al. found that pregnant women without symptoms of nausea and vomiting at the time of EGG recordings have normal 3-cpm myoelectrical activity. They also found that pregnant women with NVP had more unstable EGG activity compared with women after voluntary abortions and nonpregnant controls. They speculated that this may be due to restoration of the normal gastric slow wave pattern after abortion following normalization of estradiol and progesterone levels [78].

Notably, however, many studies have found no difference in gastric motility between pregnant and nonpregnant women. Using gastric scintography, no significant differences in the liquid emptying rate was found in pregnant women before voluntary abortion, 6 weeks after abortion, and in nonpregnant control women [79]. Using dye dilution methods with phenol red, Davison et al. found gastric emptying to be delayed during labor but not in the third trimester compared to nonpregnant controls [80]. Similarly, studies using paracetamol showed no gastric emptying delay in the first, second, or third trimester [81].

Alterations in gastric motility in pregnancy have been attributed to high levels of progesterone. Moreover, in late pregnancy, compression from an enlarged uterus may contribute to symptoms.

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Meal composition may also serve a pathogenic role in NVP. Jednak et al. demonstrated that protein dominant meals were associated with decreased symptoms and corrected slow wave dysrhythmias. Carbohydrate or fat dominant meals had no effect on symptoms or slow wave dysrhythmias [82].

Finally, small bowel transit time has been evaluated with regards to NVP pathogenesis. Using the lactulose hydrogen breath test, an indirect measure of small bowel transit time, Lawson et al. found transit times to be prolonged in the second and third trimester compared to the first trimester with the longest times found when progesterone levels were highest [83]. Wald et al. used similar techniques and found transit time to be prolonged in the third trimester when progesterone and estrogen levels were high in comparison to the postpartum period [84]. However, in both of these studies, delayed intestinal transit times did not correlate with NVP.

Psychosocial Factors

Early studies proposed that NVP may be a psychosomatic illness in which vomiting represents intrapsychic conflicts. Some have speculated that NVP is a manifestation of a pregnant woman's subconscious attempt to reject an unwanted pregnancy [85] as studies have found that women with NVP in the first trimester are more likely to have unplanned or undesired pregnancies [86].

HG has also been associated with psychological disturbances, namely neurotic tendencies, hysteria, rejection of femininity, rejection of pregnancy as well as depression and psychological stress related to poverty and marital conflicts [8]. Recent studies, however, have not found definite psychogenic causes of HG [87, 88]. Some, therefore, argue that sociocultural factors rather than scientific evidence have led to the labeling of HG as a psychologically based condition and that it is more likely that psychological disturbances such as depression are the result rather than the cause of HG [89].

Thus while NVP and HG are likely not the result of a conversion disorder or other psychological disorder, it is well recognized that affected women have psychological responses that become intertwined with, and possibly exacerbate, their physical symptoms.

Diagnosis and Clinical Features

History and physical exam

Despite popular use of the term "morning sickness" NVP persists throughout the day in the majority of affected women and has been found to be limited to the morning in less than 2% of women [90]. It often begins within weeks of missing menses and thus is caricatured across most cultures as the initial sign of pregnancy. Symptoms usually peak between 10 and 16 weeks gestation and usually resolve after 20 weeks. Up to 10% of women, however, continue to be symptomatic beyond 22 weeks [90].

While dehydration and orthostasis can occur in women with HG, most women with NVP have normal vital signs and a benign physical exam. A careful abdominal exam, however, should be done to rule out peritonitis and other intra-abdominal causes of nausea and vomiting.

Differential diagnosis

Given the high prevalence of NVP, nausea and vomiting in the first trimester is usually due to NVP. However, if changes in bowel habits, abdominal pain, and bilious emesis are present, appropriate investigations should be conducted to exclude other causes. The differential diagnosis for NVP includes gastroesophageal reflux disease,, peptic ulcer

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disease, small bowel obstruction, acute cholecystitis, cholelithiasis, pancreatitis, as well as appendicitis, gastroenteritis, nephrolithiasis, pyelonephritis, and hepatitis [74]

Diagnostic and laboratory tests

Other than a pregnancy test, no specific laboratory studies are recommended for the diagnosis of NVP. Other tests, however, may be helpful in excluding other causes of nausea and vomiting. Leukocytosis should not be seen in NVP and may point to an infectious or inflammatory cause such as cholecystitis, urinary tract infection, and pancreatitis. Elevations in the aminotransferases could indicate chronic hepatitis. An abnormal TSH could indicate hypothyroidism or hyperthyroidism, both of which can cause nausea and vomiting. Elevation in serum glucose could indicate diabetes and may produce nausea and vomiting by decreasing antral contractility and precipitating gastric dysrhythmias [91].

Radiographic imaging is generally not needed for the diagnosis of NVP. A pelvic ultrasound can be considered to document pregnancy and evaluate for conditions which increase the risk for NVP such as multiple gestation. Abdominal x-rays are generally not helpful, and although pose low risk to the fetus, are still relatively contradicted during the first trimester.

Upper endoscopy can be performed safely in pregnancy and can be considered to rule out gastritis and PUD as causes of nausea and vomiting in pregnancy. In one large center, nausea and vomiting was the second most common indication for upper endoscopy in pregnancy after upper gastrointestinal bleeding [92].

Outcome

Most studies have found NVP to be associated with a favorable outcome for the fetus. A meta-analysis of 11 studies by Weigel et al. found a strong significant association between nausea and vomiting of pregnancy and decreased risk of miscarriage (common odds ratio = 0.36, 95% CI 0.32 to 0.42), and no consistent associations with perinatal mortality [93]. Moreover, women without NVP have been found to deliver earlier compared to women with NVP [94].

Adverse outcomes, however, have been reported in some studies, especially when NVP is deemed severe. Deuchar et al. found an increased risk for intrauterine growth retardation in women with severe NVP, but could not account for potential confounding by antiemetic medication use on fetal growth [95]. Similarly, Zhou et al found an increased risk for low birth weight in women with severe NVP, likely due to the deleterious effects of nausea and vomiting on maternal nutrition [96].

In a prospective study of 16,398 women, no difference was found in congenital abnormalities between those with and without NVP [97]. In addition, a retrospective study showed a lower risk of congenital heart defects in infants born to women with early onset of NVP requiring antiemetic use compared to women without nausea [98].

It is not entirely clear how NVP protects the developing fetus, however, several theories have been described. Some have argued that nausea and vomiting allows the pregnant woman to avoid or expel foods that may be teratogenic or induce abortion. This may explain the close temporal relationship between the development of food aversions in pregnancy and the onset of nausea [99]. NVP may also lower energy intake and lower levels of anabolic hormones, insulin, and insulin growth factor leading to a shunting of scarce nutrients to the placenta and fetus [100].

Despite its favorable effects on the fetus, the psychosocial morbidity in pregnant women with NVP is substantial and perhaps underemphasized. In a study by Smith et al. of 593

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Australian women with NVP, most reported that their symptoms produced major negative impacts on employment, household duties, and parenting with 96% of women reporting mild to moderate distress from nausea and 28% reporting moderate to severe distress [101]. Similarly, a study by Mazzotta et al. of Canadian women found more severe nausea and vomiting to be associated with more frequent feelings of depression, consideration of termination of pregnancy, adverse effects on women's relationships with their partners or their partners' everyday lives, and the perceived likelihood that NVP would harm their baby. Notably, women with mild symptoms also reported experiencing the same psychosocial problems, suggesting that the severity of nausea or vomiting does not adequately reflect the distress caused by NVP [2].

O'Brien and Naber also showed significant psychosocial morbidity in women suffering from NVP. They found that affected women reported a decline in social commitments and impaired relationships with spouses and children. Women with severe symptoms also reported frequent tearfulness, irritability, increased sleep disturbances, and lowered mood [102]. Using the Short-Form 36, Attard et al. found that women with NVP had lower scores in physical functioning, physical role, bodily pain, vitality, social functioning, and emotional role on survey evaluating quality of life compared to healthy pregnant controls in early pregnancy and women with chronic depression. Mental health scores for the women with NVP were similar to those of the women with depression [103].

In addition to causing psychosocial morbidity, NVP also poses a significant financial burden. In 2002 the cost of severe NVP was estimated to be approximately $130 million based on hospital costs linked to an average of 39,000 hospital admissions. This figure is likely a gross underestimate as it does not include the loss of productivity at home, physician fees, or cost of treatments [104].

It has been estimated that 206 work hours are lost for each employed woman with NVP [2] and that NVP accounts for 28% of all sick leave during pregnancy before week 28 [19]. Furthermore, work by Vallacott et al. reveals that 50% of affected women believe their work efficiency to be significantly reduced [105].

HYPEREMESIS GRAVDIARUM

Hyperemesis gravidarum (HG) is a condition of severe nausea and vomiting during pregnancy leading to fluid, electrolyte and acid-base imbalance, nutritional deficiency and weight loss [8]. Some have defined it as the occurrence of greater than three episodes of vomiting per day accompanied by ketonuria and a weight loss of more than 3 kg or 5% of body weight [63]. HG is the most common reason for hospitalization in early pregnancy and second only to preterm labor throughout the whole of pregnancy [106]. In the United States, more than 36,000 women are admitted to the hospital each year due to HG, and the cost of care is estimated to be more than 250 million dollars annually for hospitalization alone [107]. Unlike NVP which is associated with favorable fetal outcomes, HG poses significant health risks to mother and fetus.

Diagnosis and Clinical Features

HG presents in the first trimester of pregnancy, usually starting at 4 to 5 weeks gestation. In addition to severe nausea and vomiting, 60% of women with HG also have excess salivation or ptyalism [108]. Patients may also complain of gastroesophageal reflux symptoms such as retrosternal discomfort and heartburn. A pregnancy-unique quantification of emesis and nausea (PUQE) score that is calculated using the number of hours of nausea per day, number of episodes of emesis per day and number of episodes of retching per day can be used to track the severity of symptoms [109].

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Patients may present with signs of dehydration such as dry mucus membranes, tachycardia, poor skin turgor, and postural hypotension. Severely affected patients may also have muscle wasting and weakness and/or mental status changes.

Laboratory abnormalities in women with HG may include increased serum blood urea nitrogen, creatinine, and hematocrit, as well as ketonuria and increased urine specific gravity. In addition, electrolyte disturbances supporting a diagnosis of either hypochloremic metabolic alkalosis or metabolic acidosis with severe volume contraction may be found [39]. Pre-albumin (plasma transthyretin) levels may be low, reflecting poor protein nutrition status in the mother and possibly predicting lower fetal birth weights [110]. Vitamin and mineral deficiencies such as vitamin B1 (thiamine), iron, calcium, and folate are also possible [74].

Liver function tests may be abnormal in up to 50% of hospitalized patients with HG [111]. Mild hyperbilirubinemia (bilirubin < 4 mg per deciliter) and/or a rise in alkaline phosphatase to twice the upper limit of normal may be seen [112]. A moderate transaminitis is the most common liver function test abnormality with alanine aminotransferase (ALT) levels generally greater than aspartate aminotranferase (AST) levels. The transaminase elevation is usually two to three times the upper limit of normal; however, levels greater than 1000 U/ml have been reported [113]. The abnormal liver tests resolve promptly upon resolution of the vomiting.

Serum amylase and lipase elevation are seen in 10–15% of women [39]. One study found elevated amylase levels in 24% of patients with HG [114]. This is felt to be due to excessive salivary gland production of amylase rather than pancreatic secretion and a result rather than a cause of HG [8].

Thyroid stimulating hormone levels may be low in HG due to cross-reaction between the alpha-subunit of HCG with the TSH receptor. In the majority of cases, this biochemical thyrotoxicosis is not clinically relevant as patients are euthyroid. Thyroid hormone levels generally normalize without treatment after delivery.

HG is a clinical diagnosis based on symptoms and the exclusion of other conditions. Like NVP no specific testing is needed to diagnose HG; however, ultrasound of the abdomen and pelvis may be helpful in excluding other causes such as gallbladder disease, hydatidiform mole and in assessing for multiple gestations. The differential diagnosis includes NVP, acute thyroiditis, eating disorders, biliary tract disease, viral hepatitis, and gastroesophageal reflux disease.

Outcome

Unlike NVP, HG is associated with both adverse maternal and fetal outcomes. In a study of over 150,000 singleton pregnancies, infants born to women with hyperemesis and low pregnancy weight gain (<7 kg) were more likely to be low birth weight, small for gestational age, born before 37 weeks of gestation and have a 5-minute Apgar score of < 7 [5].

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 and spontaneous pneumomediastinum [47]. Vasospasm of the cerebral arteries due to increased sympathetic activity has also been reported [115].

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HG contributes to many psychological problems and can result in termination of an otherwise wanted pregnancy and decreased likelihood to attempt a repeat pregnancy [116]. Poursharif et al. found that 15% of 808 women with HG had at least one termination because of their illness. Interestingly, those women who terminated did not have more severe disease than women with HG who kept their pregnancy but were twice as likely to perceive that their physician was uncaring or did not address the severity of their illness [117].

The long-term consequences of HG on mothers are unknown. Several studies show an increased risk of breast cancer [118]. There are also reports of increased rates of depression, post-traumatic stress disorder, and various neurological disorders [39].

Some studies have found no increased risk for adverse fetal outcomes in women with HG. Bashiri et al., for example, reported a lower incidence of spontaneous early pregnancy loss in women with HG compared to the general population and found no differences in perinatal outcomes [6]. However, other studies have found an association between HG and, fetal growth retardation, preeclampsia, and small-for-gestational-age [119] In a retrospective study of 3,068 women, HG was associated with earlier delivery and lower birth weight. These outcomes were most likely in women who had lost more than 5% of their prepregnancy body weight [120]. Similarly Dodds et al. found higher rates of low birth weight, preterm birth, fetal death in women with HG who gained less than 7 kg overall during pregnancy [5]. Multiple admissions to the hospital for HG appear to be another risk factor for lower neonatal birth weight [108].

Various congenital malformations have been observed more in women with HG [32]. These include Down's syndrome, hip dysplasia, undescended testes, skeletal malformations, central nervous system defects, and skin abnormalities. Fetal coagulopathy and chondrodysplasia has been reported from vitamin K deficiency [121] with third trimester fetal intracranial hemorrhage [122]. Several childhood cancers such as testicular cancer or leukemia have also been linked to maternal HG, however, data are conflicting [39].

TREATMENT

The goal of treatment is to improve symptoms while minimizing risks to mother and fetus. To attain this a multimodal approach tailored to each individual is usually needed. Treatment modalities range from simple dietary modifications to drug therapy and total parental nutrition. Severity of symptoms and maternal weight loss are useful in determining the aggressiveness of treatment. The PUQEscore and the Hyperemesis Impact of Symptoms Questionnaire (HIS) can be considered to assess the severity of symptoms. The updated PUQE score evaluates symptoms over 24 hours [123] while the HIS takes into account psychosocial factors in addition to physical symptoms [124].

Currently studies demonstrate that management of NVP is suboptimal. One recent prospective study of 283 women with NVP during the first trimester found that only half were asked about the intensity and severity of their symptoms less than a quarter were asked if their symptoms were interfered with their daily tasks and work. In this study by Lacasse et al, only 27% of women were offered an anti-emetic and an additional 14% were recommended a nonpharmacologic approach [125].

Nonpharmacologic therapy

Dietary measures—The initial therapy for NVP and HG should include dietary changes. Affected women should avoid large meals and instead eat several small meals throughout the day that are bland and low in fat as fatty foods may further delay gastric emptying.

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Eating protein more than carbohydrates and taking in more liquids than solids may also help nausea by improving the gastric dysrhythmias associated with NVP [82]. Small volumes of salty liquids such as electrolytes-replacement sport beverages are advisable, and if the smell of hot foods is noxious, cold foods should be prepared [126].

Emotional support—Emotional support should always be offered by a medical professional. In addition, supportive psychotherapy, behavioral therapy, and hypnotherapy may be beneficial to women with severe symptoms and/or those in whom personality characteristics, marital or family conflict play a role [60]. The goal of psychotherapy is not to delve into the psychology which may be contributing to NVP but rather to encourage, explain, reassure, and allow the patient to express stress [95].

Acupressure/acupuncture—Acupressure of the Chinese acupuncture point P6 (Neiguan) has been found to decrease nausea in patients with chemotherapy-induced nausea and postoperative nausea and vomiting and may be helpful in treating HG. According to the principle of chi, application of pressure to this point blocks abnormal energy slow and relives symptoms related to the pressure point [13]. Pressure may be placed manually or with elastic bands on the inside of the wrist. In addition, the ReliefBand, a battery-operated electrical nerve stimulator worn on the wrist has recently been approved by the FDA and can also be used to stimulate the P6 site [127].

The evidence for acupressure is conflicting. One review of seven trials indicated that acupressure of the Neiguan point could help symptoms of nausea [128]. A recent placebo-controlled study of 60 women with NVP found that the treatment group experienced relief from nausea the day after starting acupressure over the P6 site which lasted until the end of the observation period. In comparison, the group treated with acupressure over an insignificant site experienced initial symptom relief but by day 6 symptoms had returned and were no different than the non-treated group [129].

While studies regarding the benefits of acupressure have been inconclusive, some experts believe this intervention should be offered as there are no known adverse side effects [130].

Acupuncture has been less studied, but one single-blind randomized, controlled trial with 593 women less than 14 weeks gestation showed that there was less nausea and dry retching in women treated weekly with acupuncture for 4 weeks versus controls [131]. However, it is possible that some women may have improved simply with advancing gestational age [13].

Ginger—Ginger is the single nonpharmacologic intervention recommended by the American College of Obstetrics and Gynecology [132]. Ginger is believed to help improve NVP by stimulating gastrointestinal tract motility and stimulating the flow of saliva, bile, and gastric secretions. One component of ginger has been shown to have similar activity as the 5-HT3 antagonist, ondansetron. In addition, its extract has been found to inhibit the growth of some strains of *H. pylori* [133].

In a double-blind randomized cross-over trial 70% of women with HG treated with 250 mg of the powdered root of ginger four times daily preferred the period on ginger compared to the period on placebo. Significantly greater relief of symptoms was also reported by the women when on ginger [134].. Similarly, a second trial of 70 pregnant women at 17 weeks' gestation or less treated with either 250 mg of ginger four times a day or a placebo for 4 days found that women in the treatment group had significant improvement in nausea symptoms compared with women in the placebo group ($P<.001$) [135].

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With regards to the safety of ginger in pregnancy, a case-control study of 187 pregnant women found no increase in the rate of major malformations with first trimester use [136]. A theoretical risk for bleeding, however, does exist as ginger inhibits thomboxane synthetase and may inhibit platelet function. Thus, the concomitant use of anticoagulants with ginger is not advised [137].

Pharmacologic treatment

Pyridoxine-doxylamine—The combination of pyridoxine (vitamin B6) (pregnancy category A) and doxylamine (category B), previously available as Bendectin, is the only medication that is specifically labeled for the treatment of NVP by the Food and Drug Administration. It remains available in Canada in a delayed-release tablet of 10 mg of pyridoxine and 10 mg of doxylamine under the trade name Diclectin.

Benedectin was taken off the market in 1983 in the United States due to reports of congenital malformations with first trimester use. Prior to its withdrawal, however, 30 million women had taken it over a nearly 25 year time span. Several small randomized controlled studies support its efficacy [138]. In addition, a meta-analysis which included 170,000 exposures found the pyridoxine-doxylamine combination to be safe and not cause adverse effects in the fetus [139]. Other large studies have also shown no increase in congenital anomalies over the background rate [140]. Nevertheless, Benedectin remains off the market in the United States. Women can make their own preparation, however, by combining 10 mg of pyridoxine with a half tablet of Unisom which is 25 mg of doxylamine.

Alternatively, pyridoxine can be taken on its own. Although no relationship has been found between pyridoxine levels and NVP, several studies have shown improvement in nausea scores in patients who take pyridoxine with severe nausea [141] and a reduction in the episodes of vomiting when compared to women taking placebo [138]. There is no known evidence of vitamin B6 toxicity, however, in large doses pyridoxine has been linked to reversible peripheral neuropathy in nonpregnant adults [13].

Antiemetics—The phenothiazines, chlorpromazine (Thorazine) and prochlorperazine (Compazine), are central and peripheral dopamine antagonists which have been shown to reduce symptoms in NVP and HG [142]. They are pregnancy category C.

A study of 12,764 pregnant women found a slightly increased risk of birth defects with phenothiazines use in the first trimester, particularly with chlorpromazine use, however, potential confounding factors such as alcohol use and treatment duration were not [143]. Another study showed that infants of mothers who had taken chlorpromazine had extrapyramidal signs and jaundice; there was no significant impairment of postnatal development [144].

Promethazine (Phenergan) was not found to have teratogenic effects in one study [145] but increased congenital hip dislocation was seen in another study [146].

Promotility agents—Metoclopramide (Reglan) is widely used for the treatment of NVP [147]. It is pregnancy category B. Metoclopramide is believed to improve symptoms by increasing lower esophageal sphincter pressure and increasing gastric transit. It also corrects gastric dysrhythmias by stimulating antral contractions and promoting antroduodenal contractions. A recent study found 10 mg of metoclopramide given every 8 hours to be as effective in reducing the number of vomiting episodes and increasing well-being in women with HG during their first hospitalization as 25 mg of promethazine given every 8 hours for 24 hours. The, side effect profile was better in the metoclopramide-treated group with less drowsiness, dizziness, and dystonia reported [148].

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With regards to safety, a study of 81,703 births between 1998 and 2007 in Israel wherein there was an exposure of metoclopramide in 4.2% women found no increased risk of major congenital malformations, low birth weight, preterm delivery, or perinatal death with metaclopramide use [149]. Similarly, a Danish study of 309 pregnant women taking metaclopramide found no increased risk [150].

Despite its efficacy, metoclopramide use is limited by its side effect profile which includes dystonia, restlessness, and somnolence. In 2009 the FDA added a black box warning to metoclopramide due to the risk of tardive dyskinesia with chronic use.

Other prokinetics such as domperidone and erythromycin have not been studied in NVP [74].

Antihistamines and Anticholinergics—Antihistamines indirectly affect the vestibular system, decreasing stimulation of the vomiting center [151]. Randomized controlled trials of antihistamine use in NVP are limited; however, meclizine (anitvert), dimenhyrdinate (Dramamine), and diphenhyramine (Benadryl) have all been shown to control symptoms better than placebo [142]. In addition, pooled data from seven trials between 1951 and 1975 found antihistamines to be effective [152]. A meta-analysis of more than 24 controlled studies with more than 200,000 pregnant women found that antihistamines (H1 blockers, in particular) given during the first trimester did not increase teratogenic risk [153]. While meclizine had been previously thought to be teratogenic, studies now show it is safe to use during pregnancy [154]. Dimenhydrinate and diphenhydramine have conflicting results on safety [74].

In one study of women undergoing elective cesarean delivery, transdermal scopolamine was found to be more effective at decreasing nausea, vomiting, and retching due to epidural morphine analgesia compared to placebo [155]. However, studies on first trimester use of scopolamine are lacking as scopolamine may produce chromosomal aberrations and sister-chromatid exchanges in healthy adult lymphocytes, and may lead to congenital malformations, including deformed limbs and trunks [156].

Other Agents—Ondansetron (Zofran) (pregnancy category B) is widely used for the treatment of postoperative and chemotherapy-induced nausea and vomiting and is currently one of the most commonly prescribed anti-emetics [157]. It is thought to work both centrally and peripherally by blocking serotonin receptors in the small bowel and medullary vomiting center [151]. Its safety in pregnancy was determined in a recent study which showed no significant increase in the number of miscarriages, major malformations or birth weight between infants exposed to ondansetron and unexposed controls [158].

There has been one randomized controlled trial of ondansetron for the treatment of HG. In this small study of 30 women no benefit of ondansetron 10 mg given intravenously every 8 hours as needed was found over promethazine 50 mg given intravenously every 8 hours in terms of nausea, weight gain, days of hospitalization or total doses of medicine [46]. Promethazine, however, was found to cause more sedation. Nevertheless, case reports and widespread clinical experience do support the efficacy of ondansetron for the treatment of HG and its better tolerability over older anti-emetics [159, 160].

Droperidol (Inapsine) is a dopamine antagonist that is an effective antiemetic for post-operative nausea and vomiting. A small study of women with HG found that the combination of continuous droperidol infusion and bolus intravenous diphenhydramine led to shorter hospitalizations and fewer readmissions compared to a historic control group which had received other forms of parenteral therapy. In addition, there were no significant

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differences in maternal or perinatal outcomes [161]. Of note, however, droperidol bears a black box warning as it may cause QT prolongation and cardiac dysrhythmias [74].

Oral and intravenous corticosteroids have been used for refractory cases of HG with variable results. They are believed to exert an antiemetic effect on the chemoreceptor trigger zone in the brainstem and are also postulated to correct the “relative adrenal insufficiency” induced by HG in which the hypothalamic-pituitary-adrenal axis is unable to respond to the increased demands of cortisol during early pregnancy.

In a randomized controlled trial of 40 women with HG treated with methylprednisolone 16 mg orally 3 times a day for 3 days followed by a 2 week tapering regimen versus promethazine 25 mg orally 3 times a day for 2 weeks, a lower rate of re-hospitalization was found in the steroid-treated group [162]. Other studies have not shown a statistically significant benefit of corticosteroids. A randomized trial by Yost et al. found no significant decrease in the number of ER visits or re-hospitalizations with the addition of parenteral and oral methylprednisolone to a regimen of promethazine and metoclopramide [163].

There are no established guidelines for the use of corticosteroids for HG. A possible regimen which has been suggested, however, is 48 mg of methylprednisolone given orally or intravenously in three divided doses for two to three days. If no response is seen within three days, it is recommended that treatment be stopped, as response beyond 72 hours is unlikely [151].

With regards to safety, a recent meta-analysis showed a slight increase in major malformations and a 3.4 fold increase in oral cleft in infants whose mothers took corticosteroids in the first trimester [164].

There has been recent interest in acid-reducing medications for NVP as one recent cohort study showed that women with both NVP and heartburn and/or acid reflux had more severe nausea and vomiting than women without heartburn or acid reflux [165]. Furthermore, follow-up studies have shown that treatment of heartburn and/or reflux results in improved PUQE scores and quality of life scores [166].

Antacids containing aluminum or calcium are first-line treatment during pregnancy for acid reflux and heartburn and can be used to treat women with NVP. Magnesium-containing antacids are associated with nephrolithiasis, hypotonia, and respiratory distress in the fetus and are not recommended during pregnancy. Bicarbonate-containing antacids can cause fetal metabolic acidosis and fluid overload and are also not recommended [167].

H2 blockers and proton pump inhibitors can be used safely to treat acid reflux and/or heartburn in women with NVP [168, 169].

Nutritional support

For women with intractable symptoms unresponsive to dietary modification and pharmacologic treatment and unable to maintain weight by oral intake, nutritional support may be required. In this population, intravenous fluid therapy, enteral nutrition, or parenteral nutrition should be used to prevent fetal intrauterine growth restriction, maternal dehydration and malnutrition.

The role of intravenous hydration is to increase volume and restore electrolytes. In hospitalized patients, normal saline or lactated Ringer’s solution can be infused rapidly, if needed and then later adjusted to match urine output. Intravenous thiamine should be administered before any dextrose-containing fluids to avoid Wernicke’s encephalopathy.

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Women requiring multiple hospitalizations, may be considered for in-home intravenous hydration [74].

Enteral tube feeding and total parenteral nutrition should be considered if intravenous therapy is not successful in reducing symptoms and there is still a caloric deficit. Studies on enteral feeding for HG, however, are limited. One small study of women with HG treated with enteral feeding using an 8-French nasogastric tube reported symptom improvement within 24 hours of tube placement. After 8 days, patients were discharged with a mean of 43 additional days of outpatient enteral feeding after which oral feeding was able to be resumed [170].

In addition to nasogastric tubes, percutaneous endoscopic gastrostomy (PEG) tubes [171] have been used successfully to maintain nutrition in women with HG. Both of these modes of feeding are limited, however, by the risk of increased nausea and vomiting caused by intragastric feeding. Post-pyloric feeding tubes, both nasojejunal [172, 173] and percutaneous endoscopic gastrojejunostomy [174] have been attempted to reduce this risk, however, dislodgement of the tubes [175] due to ongoing vomiting and retching and gastric coiling is a common complication. In addition, nasoenteric tubes, both nasogastric and nasojejunal, are poorly tolerated by many women due to aesthetic reasons and physical discomfort. Recently, surgical jejunostomy has been described as an alternative mode of nutrition delivery to women with HG. In one small study, five women with HG underwent surgical jejunostomy in the second trimester. Isotonic tube feeds were administered to a goal caloric factor. Maternal weight gain occurred in 5 out of the 6 pregnancies and all pregnancies ended in term deliveries. No major complications occurred suggesting that jejunostomy may be a safe and effective mode of nutrition support in women with HG [176].

For women unable to tolerate enteral feeding, parenteral nutrition should be considered. This therapy, however, is costly and associated with significant maternal morbidity. Russo-Steiglitz et al. reported a 9% complication rate for parenteral nutrition via peripherally inserted central catheters in pregnancy and a 50% complication rate for centrally inserted catheters. Infection and thrombosis were the two most frequently occurring complications and were hypothesized to result from pregnancy-associated hypercoagulability and immunologic suppression [177]. Holmgren et al similarly showed a high rate of complications in women administered parenteral nutrition via PICC. In a study of 94 women with HG, 66.4% of those treated with parenteral nutrition via PICC required treatment for thromboembolism, infection, or both. Patients on parenteral nutrition also had higher rates of neonatal complications including admission to the neonatal intensive care unit, small size for gestational age, termination of pregnancy from HG, and fetal loss compared to women treated enteral feeds [178]. Thus, although it may be more tolerable to patients, parenteral nutrition should be reserved for selected patients with HG.

Conclusion

NVP is an extremely common disorder in pregnancy that ranges in spectrum from mild to moderate nausea and vomiting to pathologic HG. Despite its prevalence its pathogenesis is still largely unknown and consequently treatment is mainly symptomatic, ranging from dietary changes and oral pharmacologic treatment to hospitalization with intravenous fluid replacement and nutrition therapy.

Although most studies suggest that NVP is not harmful to the fetus, this condition is not benign in that it significantly reduces the quality of life of the pregnant woman and places financial burden on the affected individual and the larger society. For women with HG

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maternal and fetal morbidity may occur if the condition is unrecognized and not treated aggressively.

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Table 1

Differential Diagnosis for Nausea and Vomiting in Pregnancy

GI disorders
Gastroenteritis
GERD
Peptic Ulcer Disease
Intestinal obstruction
Pancreatitis
Appendicitis
Hepatitis
Biliary Disorders
Genitorurinary disorders
Nephrolithiasis
Pyelonephritis
Ovarian torsion
Metabolic disorders
Hyperthyroidism
Addison’s disease
Diabetic complications
Neurologic disorders
Migraines
CNS tumors
Pseudotumor cerebri
Vestibular abnormalities
Pregnancy-related disorders
Preeclampsia/HELLP
Acute Fatty Liver of Pregnancy

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Table 2

Drug Name/Category	Pregnancy Category	Recommended Dose	Mechanism of Action	Efficacy in HG	Side Effects
Pyridoxine (136)	A	25 mg po q8h	May treat underlying pyridoxine deficiency	+/−	Paresthesias, nausea, HA, fatigue
Diclectin (10 mg pyridoxine + 10 mg doxylamine) (133) *available only in Canada	A/B	2–4 tabs daily	Treats pyridoxine deficiency and H1 antagonist	+/−	Drowsiness
Antihistamines (147) • Dimenhydrinate • Diphenhydramine	B	25–50 mg po q4-8h 50–100 mg po q3-6h	Peripheral H1 receptor antagonist	+	Drowsiness, dizziness, HA, fatigue
Phenothiazines (44) • Promethazine • Prochlorperazine	C	12.5–25 mg po q6-8h 10 mg po q6-8h	Central/peripheral dopamine antagonist	+	Drowsiness, decreased seizure threshold, akathisia
Metoclopramide (143)	B	10 mg po/IV q8h	Central/peripheral dopamine antagonist	+	Dystonia, restlessness, somnolence *FDA black box warning: tardive dyskinesia
Ondansetron (154)	B	10 mg po/IV q8h	Peripheral and central selective 5HT3 receptor antagonist	+/−	Constipation, diarrhea, HA, fatigue
Corticosteroids (157) • Methylprednisolone	C	16 mg po q8 hr × 3 d, then taper	May treat relative ACTH deficiency, inhibit central PG synthesis or decrease central 5-HT turnover	+/−	Hyperglycemia, possible increased risk of oral facial clefts with first trimester use
Droperidol (156)	C	0.25–2.5 mg iv loading with 1 mg iv/hour	Dopamine antagonist in chemoreceptor trigger zone	+/−	Drowsiness, dizziness; cardiac arrythmias, black box warning for QT prolongation
H2 blockers (137) • Ranitidine	B	150 mg po q12h or 50 mg IV q8h	Peripheral H2 antagonist	Adjunct therapy	HA, drowsiness, dizziness, diarrhea or constipation

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Drug Name/Category	Pregnancy Category	Recommended Dose	Mechanism of Action	Efficacy in HG	Side Effects
PPI • Lansoprazole • Esomeprazole	B	30 or 40 mg po/IV q24h	Irreversible blocker of H+/K+ ATPase of parietal cell	Adjunct therapy	HA, nausea, diarrhea, fatigue

* N.B. Except for Diclectin, no drugs are FDA approved for the treatment of nausea and vomiting during pregnancy or HG. The expected benefits of treatment should outweigh the risk.

Citations are included in parentheses