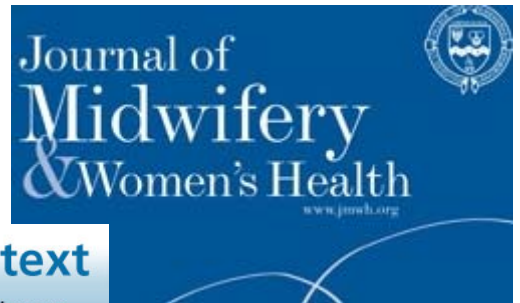


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Evidence-Based Approaches to Managing Nausea and Vomiting in Early Pregnancy

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Abstract and Introduction

“. . . psychological treatments (e.g., hypnosis) may help some individuals.^[8,19,20]”

Abstract

Nausea and vomiting in pregnancy is a continuum that ranges from mild discomfort to significant morbidity. Systematic assessment with the use of the Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) index and timely treatment using evidence-based protocols can decrease the time that many women spend using treatment recommendations that are inadequate. This article reviews the epidemiology of nausea and vomiting in pregnancy, use of the PUQE index, and the evidence for specific nonpharmacologic and pharmacologic treatment regimens. A protocol for clinical management is presented.

Introduction

Nausea and vomiting are among the cardinal signs of early pregnancy, recognized as such since at least the time of Hippocrates. In contemporary Western societies, an estimated 50% to 80% of pregnant women experience nausea and/or vomiting during the first trimester of pregnancy.^[1,2] The problem is generally time-limited, with onset about the fifth week after the last menstrual period (LMP), a peak at 8 to 12 weeks, and resolution by 16 to 18 weeks for most women; approximately 5% of women will have symptoms throughout pregnancy.^[3] Although commonly termed "morning sickness," only 17% of women report being affected only in the morning.^[4] In a prospective study in which 160 women provided daily diaries in early pregnancy, 74% reported nausea with a mean duration of 34.6 days, "morning

sickness" occurred in only 1.8%, and 80% reported nausea lasting all day. Only half of women reported relief by 14 weeks, but 90% had relief by 22 weeks.^[5]

The most severe manifestations of nausea and vomiting of pregnancy (NVP) result in hyperemesis gravidarum (HG). Although there is no standard definition of HG, most diagnostic criteria include: persistent vomiting before 9 weeks after the LMP, weight loss >5% of initial body weight, electrolyte imbalance (hypokalemia), and dehydration and/or ketonuria.^[6] Severe HG symptoms are the second most common reason for prenatal hospitalizations in the United States (11.4% of all nondelivery antenatal admissions).^[7] Risk factors for HG include: clinical hyperthyroid disorders, prepregnancy psychiatric diagnosis, previous pregnancy complicated by HG, molar pregnancy, multiple gestation with a male and female fetus, diabetes, and gastrointestinal disorders. Women 30 years of age and older and women who smoke have a lower risk of HG.^[6,8]

Quality of life (QOL) and work efficiency are adversely affected by NVP for women who have these symptoms.^[2,9] Fifty percent of women say NVP affects their ability to work, as many as 35% require time off from jobs (mean, 62 hours), 50% say it affects their relationships with family and partners, and 55% report being depressed.^[9,10] When QOL measures are used in research studies, the scores for women with NVP are worse than the scores of women who report chronic depression.^[11] More than 80% of women with HG who responded to a recent survey stated that NVP caused adverse psychosocial effects, including concerns about economics and employment, depression, anxiety, and fear about future pregnancies.^[12] Among women with severe NVP or HG, 76% changed plans for future children, 15% terminated pregnancy secondary to HG, and 7% reported long-term psychological sequelae.^[13] A 2002 study estimated reduced productivity, visits to health care professionals, and the cost of medications and other remedies at \$2947 per woman with moderate to severe NVP.^[11]

Conversely, nausea in pregnancy is sometimes a positive sign. The absence of nausea is one of the factors associated with spontaneous miscarriage.^[14] Because there is a close temporal relationship between NVP and beta-human chorionic gonadotropin (β -hCG) levels, some have theorized that nausea-associated nutrient restriction during early pregnancy may be beneficial to fetal and placental development.^[15] Nonetheless, given the widespread prevalence of NVP, potential severity, and adverse effects on QOL, pregnant women and their providers need treatments that are effective yet safe to use during the period of embryonic and early fetal development. This article provides an evidence-based review of effective and safe treatments for NVP.

Etiology of Nausea and Vomiting in Pregnancy

Although the fundamental trigger is pregnancy, NVP results from a complex interplay of influences that include endocrine, gastrointestinal, vestibular, and olfactory factors; possible genetic predisposition; and responses that are modified by behavioral cues, support (or lack thereof), and psychology.^[16] Proposed etiologies include high levels of β -hCG and estrogen due to the close temporal relationships between the average peaks of NVP and peak of β -hCG levels and the correlations between NVP and conditions with higher estradiol levels. Progesterone or corticosteroid deficiency related to the observed associations between NVP and lower levels of these hormones has been proposed. Thyroid dysfunction, infectious disease (specifically infection with *Helicobacter pylori*), and psychosocial, cultural, and psychogenic causes have all been theorized to play a role in the etiology of this condition. NVP is correlated with a transient biochemical hyperthyroidism related to β -hCG stimulation of the thyroid. Genetic causes are suggested by observations that NVP is more frequent in monozygotic twins; is more common in women whose siblings and mothers are affected; shows ethnic variation; and is correlated with other genetically determined conditions, such as taste sensation, anosmia, and glycoprotein receptor defects.^[16,17]

An infectious origin is suggested by 14 published case-control studies that found a significant association between the presence of *H pylori* and HG. However, there are no directed studies addressing the efficacy of antibiotic treatments for *H pylori* in resolving the symptoms of HG.^[18] The most likely relationship is that women with *H pylori* and gastritis experience a more severe end of the NVP spectrum.

There is little evidence that NVP represents a psychiatric, conversion, or psychosomatic disorder; most studies suggesting this association are older and have flawed methodologies that call the findings into question. However, other studies show that NVP and HG can result in anxiety and depression, and it appears that the psychological responses to this physiologic condition can become entrenched and/or conditioned. This possibility is supported by evidence that psychological treatments (e.g., hypnosis) may help some individuals.^[8,19,20]

In summary, the etiology of NVP is physiologic, and the cause of more extreme forms remains unclear. Therefore, assessment of the condition focuses on severity, and management is largely supportive.^[21]

Assessment: The Pregnancy Unique Quantification of Emesis/Nausea Score

Most clinicians attempt to manage the early symptoms of NVP in order to prevent progression to severe symptoms. Given the subjective nature of conditions such as nausea, retching, and vomiting, consistency of the assessment is critical. The Rhodes Index^[22,23] is an

objective, validated measure used to grade the severity of nausea and vomiting and to follow the course of the condition. It has been revised to measure nausea, vomiting, and retching.^[22] This scoring system, originally used to assess nausea and vomiting in chemotherapy patients, quantifies physical symptoms and the resulting stress and psychological symptoms. Although the tool has been used in many research studies of NVP treatments, it is detailed, time-consuming, and cumbersome for use in assessing women in a clinical setting. A shorter assessment guide was developed by clinicians and researchers from the Motherisk NVP helpline in Canada to streamline assessment and correct some of the problems associated with use of the Rhodes Index. The Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) Index (Figure 1) is based on only three questions, is highly correlated with scores on the Rhodes Index, and has been validated in clinical use.^[24,25]

Medscape				
1. In the last 12 hours, how many hours have you felt nauseated or sick to your stomach?				
> 6 hrs (5 pts)	0-6 hrs (4 pts)	0-3 hrs (3 pts)	0-1 hr (2 pts)	Not at all (1 pt)
2. In the last 12 hours, how many times have you vomited?				
7 or more (5 pts)	0-6 (4 pts)	0-4 (3 pts)	0-2 (2 pts)	None (1 pt)
3. In the last 12 hours, how many times have you had retching or dry heaves without bringing anything up?				
7 or more (5 pts)	0-6 (4 pts)	0-4 (3 pts)	0-2 (2 pts)	None (1 pt)

Source: J Maternity Womens Health © 2009 Elsevier Science, Inc.

Figure 1. Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) index. Total score is sum of replies to each of the three questions. Nausea Score: Mild NVP = ≤6; Moderate NVP = 7–12; Severe NVP = ≥13. Reprinted with permission from Koren G et al.^[24]

The original PUQE Index focused on symptoms experienced during the previous 12 hours—and was later modified to 24 hours^[26]—reflecting the appropriate time frames to judge the efficacy of therapy for hospitalized women or those provided with frequent evaluation and follow-up. The index was recently modified to address symptoms of NVP over a longer period of time (Figure 2).^[27]

Medscape				
1. On an average day, for how long do you feel nauseated or sick to your stomach?				
> 6 hrs (5 pts.)	4-6 hrs (4 pts)	2-3 hrs (3 pts)	≤1 hr (2 pts)	Not at all (1 pt)
2. On an average day how many times do you vomit or throw up?				
7 or more (5 pts)	5-6 (4 pts)	3-4 (3 pts)	1-2 (2 pts)	None (1 pt)
3. On an average day how many times do you have retching or dry heaves without bringing anything up?				
7 or more (5 pts)	5-6 (4 pts)	3-4 (3 pts)	1-2 (2 pts)	None (1 pt)
Source: J Midwifery Womens Health © 2009 Elsevier Science, Inc.				

Figure 2. Modified Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) index. Total score is sum of replies to each of the three questions. Nausea Score: Mild NVP = ≤ 6 ; Moderate NVP = 7–12; Severe NVP = ≥ 13 . Reprinted with permission from Lacasse A et al.^[27]

The PUQE Index score can be used to determine if the NVP is mild, moderate, or severe. If the score is moderate or severe (score of ≥ 7), a thorough assessment includes any changes in weight, the presence or absence of dehydration, and lab indices to check for electrolyte imbalances. Finally, if the initial onset of nausea and vomiting occurs after 10 weeks' gestation, the etiology is not likely to be NVP, and other causes need to be considered.

Management: Safety and Efficacy

Regimens to treat NVP and HG have included abortion, antiemetics, complementary and alternative treatments such as herbs, dietary restriction, hydration, psychotherapy, psychotropic medication, and total parenteral nutrition. Historically, treatments have also included cervical dilation, leeches, sensory deprivation, and vocal exercises.^[21]

Remedies used in early pregnancy must be safe in that they do not increase the risk of spontaneous abortion, birth defects, or other adverse events of pregnancy. Such assessments require directed investigation and large enough sample sizes to determine if the occurrence of adverse events is higher than expected. For example, the incidence of spontaneous abortion in the first trimester of pregnancy is as high as 20%^[28,29] and the prevalence of birth defects detected at birth is 2% to 3%,^[30] therefore, any investigation of the risk associated with medication use must follow women long enough to evaluate the

newborn and have a large enough sample size to determine with statistical certainty whether or not the risk is increased.

A determination of efficacy requires studies with appropriate outcome measures. For remedies that treat NVP, periodic assessment of nausea (using a validated objective measure) and episodes of retching or vomiting are the most common outcomes. Weight gain or weight loss and some type of QOL evaluation are also used. Because NVP is a time-limited condition, studies with comparison groups are important to assess whether there is a true benefit of the intervention rather than naturally occurring improvement over time.

Dietary and Lifestyle Recommendations

Dietary and lifestyle changes are common first-line approaches for the woman with mild NVP. These include taking only small amounts of liquid or food at a time at frequent intervals; avoiding an empty stomach; avoiding rich, fatty, or spicy foods (even smelling or cooking these types of foods); eating dry crackers before getting out of bed in the morning; and eating a high-protein snack before retiring at night. There has been no evidence-based research on the effectiveness of these approaches, although their safety is not in question. In one survey, women reported that these measures help, but few women report complete relief and most do not rank them high in importance for alleviating their symptoms.^[9,31] In a recent international survey by Goodwin et al.,^[32] 22% of women who had HG stated that dietary interventions were either maybe effective or effective.

One randomized trial and an observational study found that taking a general multivitamin before pregnancy and/or before 6 weeks' gestation is associated with a decreased incidence of NVP.^[33,34] No clinical trials have directly tested the use of multivitamins as a preventative treatment for NVP. Conversely, the iron in prenatal vitamins is known to cause gastrointestinal symptoms in some women, and therefore one of the first treatments clinicians often suggest for women with NVP is to discontinue the prenatal vitamin until the NVP is resolved.

Nonpharmacologic Treatments

Many women turn to nonpharmacologic therapies for NVP because of concerns about adverse effects of drugs during embryonic and early fetal development. In one survey report, 61% of callers to the Motherisk NVP HelpLine reported using complementary and alternative medicine (CAM) therapies, but only 8% had discussed these therapies with their health care providers.^[35] Herbal remedies were commonly mentioned as treatments for NVP and HG in a recent survey of midwives in Texas.^[36]

Use of Herbs

A review of 300 nonmedical sources of advice about herbal remedies in pregnancy (books, magazines, and Web sites) found that ginger, chamomile, peppermint, and red raspberry leaf tea were the most commonly cited herbal remedies for "morning sickness."^[37] Only the efficacy of ginger has been studied in appropriate trials.

Ginger Ginger (*Zingiber officinale*) has a long history as an antinausea remedy. Its effects are thought to be related to increasing tone and peristalsis in the gastrointestinal tract caused by anticholinergic and antiserotonin actions.^[38–40] Ginger acts directly on the digestive tract and is not associated with the central nervous system (CNS) side effects that are common to centrally acting antiemetic drugs.

Ginger is a thromboxane synthetase inhibitor,^[41] and a frequently cited comment by Backon^[42] cautions that ginger could affect testosterone receptor and sex steroid differentiation in the fetus. There is no clinical evidence to suggest that this is the case. In traditional medical systems and herbalist literature, ginger is often contraindicated for use by pregnant women because of its reputation for inducing menstruation or promoting bleeding, but there is no clinical evidence that it acts as an abortifacient.^[43] In the directed randomized clinical trials (RCTs) of ginger as a treatment for NVP,^[44–46] participants were followed to term in three of the studies and no adverse events were noted, but in none of these studies was the sample size large enough to make this determination with confidence. In two other studies,^[47,48] outcomes were compared to population estimates of adverse events; although the results were reassuring, the sample sizes were still not large enough to be statistically stable. Portnoi et al.^[49] matched 187 callers to the Motherisk Helpline who took ginger in early pregnancy to 187 women who took nonteratogenic drugs that were not antiemetics. They found no increase in rates of spontaneous abortions, stillbirths, birth weight, or gestational age at birth, and no increased risk of major malformations above the baseline rate of 1% to 3%.

Seven RCTs assessing the efficacy of ginger as a treatment for NVP have been published in the world literature, representing a variety of dosages and treatment durations. Fischer-Rasmussen et al.^[44] studied women hospitalized with HG in Denmark. In this randomized, double-blind, placebo-controlled, crossover trial, participants received either 250 mg of powdered ginger root or a placebo 4 times a day for 4 days and then switched groups after a 2-day washout. Both severity of nausea and number of episodes of vomiting were reduced during the treatment with ginger, and participants reported a preference for the ginger treatment.

The other trials were all conducted in ambulatory nonhospitalized populations. Three randomized blinded trials compared ginger treatment with a placebo. All studies used different measures to evaluate the effects on nausea, vomiting, and other outcomes. Dosages were 125 to 250 mg of ginger taken 4 times a day. Overall, ginger was associated with some improvement in nausea severity and vomiting.^[45-47]

Four studies compared the use of ginger to the use of pyridoxine (vitamin B6). In all of these studies, participants were ambulatory and <17 weeks pregnant. Dosages of ginger were 1 to 1.5 g per day, and dosages of pyridoxine ranged from 30 to 75 mg per day. Ginger was at least as effective as pyridoxine, and in some studies appeared to be more effective in alleviating symptoms of NVP.^[48,50-52]

In summary, RCTs suggest that ginger in doses equivalent to at least 1 g per day (in divided doses) can reduce symptoms of nausea and vomiting in both ambulatory and hospitalized pregnant women with NVP. It is not clear whether ginger is superior to pyridoxine, but studies indicate that it is at least equivalent. Ginger is available in a variety of forms, and an evaluation of products purchased in pharmacies and health food stores found a wide variation in the amount of active ingredients and suggested serving sizes.^[53] Exact dosing relies on use of standardized extracts. For women who have preferences for the form of ginger used, in general, 1 g of standardized extract is equivalent to 1 tsp of fresh grated rhizome, 2 droppers (2 mL) of liquid extract, four 8-oz cups of prepackaged ginger tea, four 8-oz cups of tea made with 0.5 tsp of grated ginger steeped for 5 to 10 minutes, 8 oz of ginger ale (made with real ginger), 2 pieces of crystallized ginger (1 inch square, 0.25 inches thick), or 2 teaspoons (10 mL) of ginger syrup.^[54] Capsules of ginger come in various dosages, ranging from 100 to 1000 mg, and chewable tablets contain 67.5 mg.

Other Herbs There have been no directed investigations of other herbs for the treatment of NVP. However, there have been investigations of herbal treatments for the treatment of postoperative or chemotherapy-induced nausea and vomiting. In one study, peppermint oil was superior to placebo for postoperative nausea,^[55] but it is also considered an emmenagogue (i.e., a promoter of menstrual flow) in some herbal literature and therefore is not often recommended for use in pregnancy.^[43] Cannabis (marijuana) has been well studied as an antiemetic for patients undergoing chemotherapy;^[56] concerns have been identified about adverse effects on the fetus/child from prenatal use of marijuana, but it is not clear whether these concerns are pertinent to occasional recreational or medicinal use of the herb.^[57] Alcoholic extracts of cannabis, as opposed to the smoked herb, may have oxytocic properties and should not be used in pregnancy.^[43]

Acupressure and Acupuncture

Traditional Asian systems use a number of acupuncture points for antiemetic treatments, and the P6 or NeiGuan point is a major site for the relief of nausea and vomiting. It is located on the volar aspect of the wrist approximately 3 cm above the wrist crease, between 2 easily palpated tendons. It can be stimulated via the insertion of thin acupuncture needles, using transcutaneous electric nerve stimulation devices, or by applying pressure to the site. Pressure can be applied manually (using fingers or thumbs) or with wristband devices that provide steady pressure from a small button or disc on the site. The SeaBand is one commercial type of such devices. There are no concerns about the safety of properly applied acupressure and acupuncture. Points that are used to induce labor are different from the commonly used P6 point.

A number of studies of various acupuncture modalities have been conducted assessing the efficacy of acupuncture or acupressure for treating NVP with varying methodologies. Sham acupuncture is often used for comparison in studies of these remedies. Sham acupuncture consists of applying needles or pressure to sites that are considered to be nontherapeutic. Studies have suggested that there may be some benefits from sham acupuncture.^[58] Placebo acupuncture mimics the acupuncture process without actually applying pressure to any site.

A Cochrane review published in 2003^[4] summarized data from trials of adequate methodologic quality.^[59–65] Compared to no treatment, acupuncture remedies significantly reduced nausea (odds ratio [OR], 0.25; 95% confidence interval [CI], 0.14–0.43). Compared to sham acupuncture remedies, the effect was reduced and of marginal statistical significance (OR, 0.35; 95% CI, 0.12–1.09). The analysis of continuous outcomes showed no statistically significant beneficial effects. The authors concluded that the evidence for the benefits of P6 acupuncture or acupressure in treating NVP is mixed. The same conclusion was reached in a 2002 review.^[66]

Since the 2003 Cochrane review, several new trials have been published. Two involved participants who were hospitalized for HG and the intervention was either SeaBands^[67] or manual acupuncture^[68] in conjunction with routine care. Heazell et al.^[67] found no differences in median length of stay, antiemetic medication, or need for intravenous (IV) fluid comparing intervention to control groups. Shin et al.'s study^[68] was conducted in Korea and used researcher-applied manual acupressure; women up to 30 weeks' gestation were included in the trial. This study found some benefit to acupressure in both NVP scores and improvement of ketonuria. Jamigorn and Phupong^[69] compared acupressure using SeaBands to vitamin B6 (50 mg twice daily) and found no difference between the groups.

The summary evidence for benefits of acupressure or acupuncture in alleviating symptoms of NVP remains mixed. Certainly, manual acupressure or acupressure using products such

as SeaBands is a low-cost intervention with no apparent adverse effects and could be suggested to women requesting intervention. Acupuncture using transcutaneous elective nerve stimulation devices would be more costly because of the cost of the device, and traditional acupuncture even more costly because of the need for visits to an acupuncturist.

Hypnosis, Behavior Modification, and Psychotherapy

Reports of benefits of hypnotherapy or other behavioral therapies in treating NVP are from case series describing women hospitalized with NVP and did not include control groups; therefore, it is not possible to differentiate true treatment benefits from normal recovery.^[70] However, Apfel et al.^[71] found that women with NVP are more hypnotizable than women in a control group, suggesting that they are more suggestible. It is possible that in some women, vomiting becomes a conditioned or anticipatory response^[19] and would be amenable to interventions such as hypnosis or other psychotherapeutic approaches.

Pharmacologic Therapies

Several different categories of pharmaceuticals either singly or in combination are used to treat NVP. The drug categories, based on different mechanisms of action (Figure 3), include vitamins, antihistamines, anticholinergics, dopamine antagonists, phenothiazines (which antagonize the dopamine receptor in the CNS), butyrophenones, serotonin antagonists, and corticosteroids. Common doses and schedules are listed in Table 1. All drugs must be assessed for both safety and efficacy before being recommended for use in clinical practice and are presented here in the usual order of use in clinical practice. The US Food and Drug Administration (FDA) categorizes drugs according to the evidence for safety in pregnancy;^[72] these ratings are summarized in Table 2. Because vitamin B6 is often used alone or in addition to other pharmacologic therapies, it is reviewed first.

Table 1. Doses of Antiemetics Used to Treat Nausea and Vomiting in Pregnancy

Drug Name (Trade Name)	Dose	Major SEs (Recommendations)	FDA Pregnancy Category
Antihistamines (H₁ antagonists)			
Diphenhydramine (Benadryl)	50–100 mg q 4–6 h PO/IM/IV	May cause drowsiness (can be used to offset anxiety caused by metoclopramide or phenothiazines)	B
Dimenhydrinate (Dramamine)	50–100 mg q 4–6 h PO/PR ^a ; 50 mg (in 50 mL of saline over 20 min) q 4–6 h IV	May cause drowsiness (can be used to offset anxiety caused by metoclopramide or phenothiazines)	B

Doxylamine (Unisom)	12.5 mg twice a day PO or 12.5 mg in morning and 25 mg at night PO		A
Phenothiazines (central D₂ antagonists)			
Prochlorperazine (Compazine)	5–10 mg q 4–6 h PO/IM/IV; 25 mg rectal suppository bid; maximum dose is 40 mg/day	Sedation, anticholinergic effects, mouth, EPS, hypotension if given IV too quickly	C
Promethazine (Phenergan)	12.5–25 mg q 4–6 h PO/IM/IV/PR	Sedation, anticholinergic effects, mouth, EPS, hypotension if given IV too quickly	C
Benzamides (central and peripheral D₂ antagonists)			
Metoclopramide (Reglan)	5–10 mg PO q 8 h PO/IM; 1–2 mg/kg IV; continuous SQ dose regimens available ^b	EPS, agitation, anxiety, acute dystonic reactions (give 50 mg diphenhydramine before dose to prevent EPS)	B
Serotonin antagonists			
Ondansetron (Zofran)	4–8 mg PO 3–4 times per day 4–8 mg over 15 min IV q 12 h; may be given 1 mg/h continuously for 24 h	Headache	B
Butyrophenones			
Droperidol ^c (Inapsine)	0.625–2.5 mg IV over 15 min then 1.25 mg or 2.5 mg IM as needed; can be given IV continuously at 1–1.25 mg/h	EPS, prolonged QT syndrome (give 50 mg diphenhydramine before dose to prevent EPS; reserve for persons who have failed other regimens)	C

bid = Two times daily; EPS = extrapyramidal effects; FDA = US Food and Drug Administration; IM = intramuscular; IV = intravenous; PO = per os (orally); PR = per rectum (rectally); SE = side effect; SQ = subcutaneous.

^aMaximum dose is 200 mg/day if taken concomitantly with doxylamine, 400 mg/day if taken as a single agent.

^bContinuous dose regimens can be found in Buttino Jr et al.^[89]

^cTo be used only after medical consultation and if other medications have failed to resolve symptoms, secondary to risk for prolonged QT syndrome.

Table 2. US Food and Drug Administration Ratings for Drug Use in Pregnancy^a

Category	Interpretation
A	Adequate, well controlled studies in pregnant women have not shown an increased risk of fetal abnormalities to the fetus in any trimester of pregnancy.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well controlled studies in pregnant women. OR Animal studies have shown an adverse effect, but adequate and well controlled studies in pregnant women have failed

	to demonstrate a risk to the fetus in any trimester.
C	Animal studies have shown an adverse effect and there are no adequate and well controlled studies in pregnant women. OR No animal studies have been conducted and there are no adequate and well controlled studies in pregnant women.
D	Adequate well controlled or observational studies in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
X	Adequate well controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or risks. The use of the product is contraindicated in women who are or may become pregnant.

Source: US Food and Drug Administration (21 CFR §201.57).^[72]

^aNote that the US Food and Drug Administration has proposed changes to prescription drug labeling for use in pregnancy and lactation. (See www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093311.htm for additional information.)

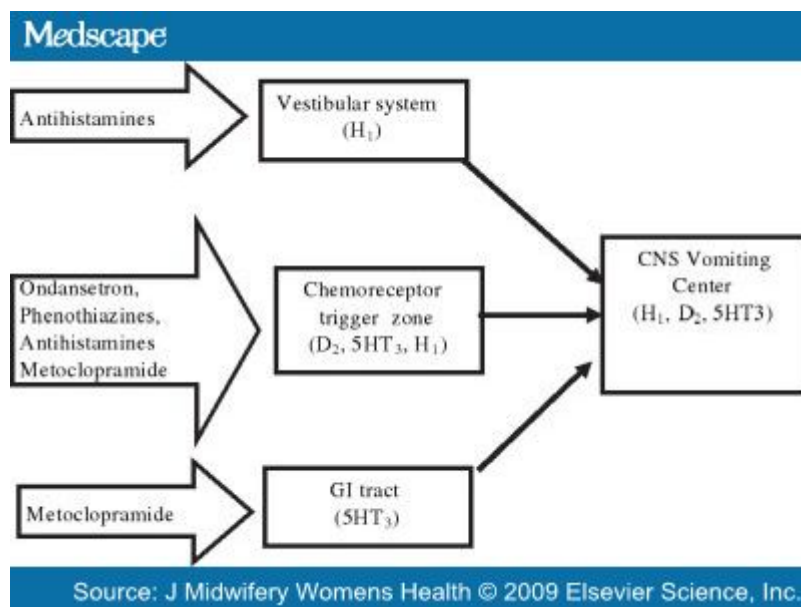


Figure 3. Mechanism of action of antiemetics used to treat nausea and vomiting in pregnancy.

Vitamin B6

Pyridoxine (vitamin B6), a water-soluble vitamin and essential coenzyme in the folate metabolism pathway, was first referenced for use in treating NVP in 1942.^[73] The mechanism of action for how pyridoxine affects nausea is unknown. No teratogenic risks have been associated with use of pyridoxine^[74] and it is considered FDA Pregnancy Category A. Two RCTs have found that regular use of pyridoxine is effective in decreasing the severity of nausea but has no effect on the frequency of vomiting episodes.^[75,76] Vutyvanich et al.^[75]

compared the effects of a 25 mg per day dose of pyridoxine to placebo (N = 336) and found that after 5 days of therapy, the mean nausea scores were lower in the women in the intervention group (2.9 ± 2.2 versus 2.0 ± 2.7 , respectively; $P = .008$), but there were no differences in the number of vomiting episodes. Sahakian et al.^[76] randomized 59 women to a dose of 75 mg pyridoxine daily versus placebo and compared the severity of nausea on a visual analog scale after 72 hours of therapy. The women in the intervention group who reported severe nausea pretreatment reported less intense nausea than those who took a placebo (mean difference in nausea score, 4.3 ± 2.1 versus 1.8 ± 2.2 ; $P \leq .01$), but there was no significant difference in the nausea scores for women who reported moderate or mild nausea at the onset of the trial. This trial also found a significant decrease in vomiting in the women who took the pyridoxine compared to those who took placebo (number of women still vomiting at 72 hours, 8 of 31 versus 15 of 28; $P \leq .05$). Pyridoxine as a single therapy is therefore useful for decreasing the severity of nausea and may have a mild effect on vomiting. The therapeutic benefit of pyridoxine is probably dose-related.

The effective dose of pyridoxine for treating NVP based on the doses used in the studies done to date is 30 to 75 mg per day, which is higher than the recommended daily allowance for pregnant or breastfeeding women (1.9 and 2.0 mg, respectively).^[77] Although there have been no large-scale directed investigations of the safety of pyridoxine alone, the vitamin was an ingredient in a drug called Bendectin, and extensive evaluations of that drug have shown no evidence of teratogenesis. Those studies indicated that pyridoxine doses up to 40 mg per day are safe.^[78,79] More recent studies of pyridoxine doses up to 75 mg have shown no evidence of teratogenesis, but the sample sizes were too small to definitively address the possibility of teratogenesis.^[76] Pyridoxine has been shown to cause neurologic problems in adults when taken in excessive doses.^[80] The determination of the optimal dose in pregnancy is still needed.

Antihistamines

Antihistamines block histamine receptors in both the vestibular system (H_1 receptors) and chemoreceptor trigger zone (H_2 receptors). These agents are the most widely used first-line medication therapy for women who have NVP. Diphenhydramine (Benadryl) and doxylamine (Unisom tablets) can be obtained without a prescription. There have been more than 20 controlled trials of various antihistamines, and interestingly, women who are exposed to antihistamines in the first trimester of pregnancy have a slightly lower risk for major and minor malformations when compared to women who have not been exposed to antihistamines during pregnancy (OR, 0.76; 95% CI, 0.60–0.94).^[81]

Pooled data from 7 RCTs that assessed the effectiveness of various antihistamines found that they significantly reduce vomiting (relative risk [RR] = 0.34; 95% CI, 0.27–0.43),^[82] but

the trials used several different antihistamines with different doses so it is not clear what regimen is the most effective based on the studies. In summary, although antihistamines are both safe and efficacious, their usefulness is limited by an adverse side effect profile. Because antihistamines frequently cause drowsiness, many women are not able or willing to take these medications throughout the day. There are no studies to date that have assessed the safety or efficacy of nonsedating antihistamines (e.g., loratadine [Claritin], cetirizine [Zyrtec], or fexofenadine [Allegra]) for the treatment of NVP.

Anticholinergics

Although scopolamine has been used extensively to treat motion sickness in nonpregnant individuals and was recently found to be of benefit in reducing nausea after cesarean delivery,^[83] it has not been studied for efficacy or safety in the treatment of NVP. However, an epidemiologic study of teratogenic effects of drugs noted scopolamine exposure in the first trimester in 309 women without evidence of teratogenic effects.^[82] The only anticholinergic drug used to treat NVP has been dicyclomine (Bentyl), which is discussed next in the story of Bendectin.

Bendectin

Bendectin, a combination of dicyclomine, doxylamine succinate, and pyridoxine hydrochloride, was approved by the FDA for treating NVP and introduced to the US market in 1956. In 1976, dicyclomine was removed because studies found that it had no independent effect/efficacy, and Bendectin was reformulated to contain 10 mg of doxylamine and 10 mg of pyridoxine in a formulation that was taken three to four times per day.^[78] Bendectin was used by 25% to 30% of pregnant women in the United States through the 1970s. In the early 1980s, lawsuits alleging that Bendectin caused teratogenic effects occurred followed by extensive media coverage. The drug was voluntarily removed from the US market in June of 1983 by the manufacturer.^[84] Despite removal from the US market, the same formulation as in Bendectin is marketed under different brand names and continues to be used in Europe and Canada.

This is an unfortunate story, because Bendectin has been shown to be both safe and efficacious.^[85] In summary analyses, the pooled RR for fetal malformation is 0.98 (95% CI, 0.93–1.02),^[78] and the efficacy of Bendectin in treating NVP (summarizing 2 RCTs) has a RR of 0.53 (95% CI, 0.41–0.68).^[82] Kutcher et al.^[78] compared Bendectin sales prevalence with birth defects and hospitalization rates for HG over a 20-year period (1974–1994) and found that when Bendectin was withdrawn from the marketplace, birth defect rates remained unchanged but that hospitalization rates for HG drastically increased (Figure 4). In 1999, the FDA issued an advisory statement stating that Bendectin was not removed from the market

because it was unsafe or ineffective and invited companies to resubmit applications for similar formulations.^[86] However, no pharmaceutical company has submitted a new drug application to date.

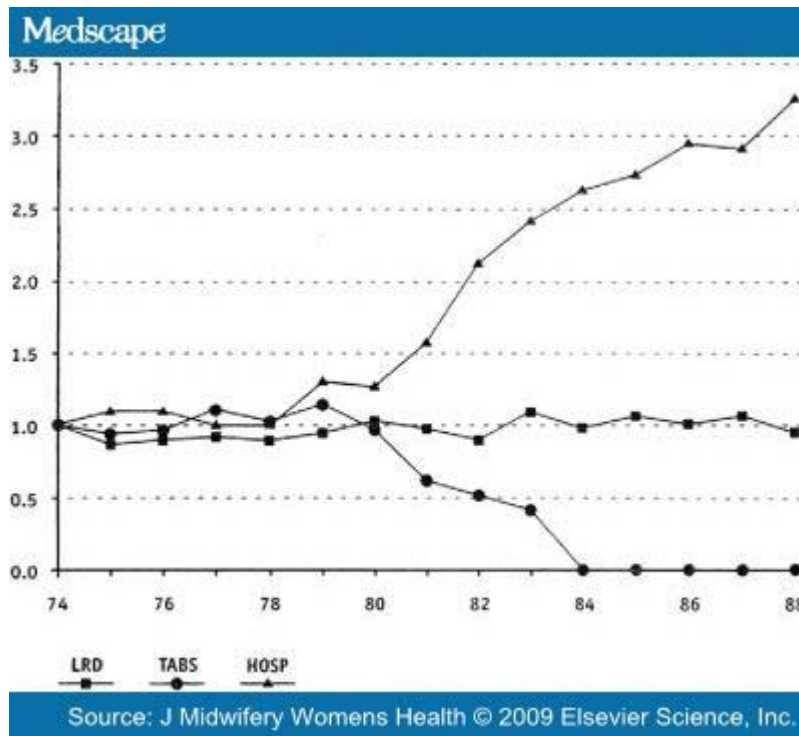


Figure 4. 1974–1988 US temporal trends (as proportion of 1974) for limb reduction deformities, Bendectin sales, and hospitalizations for nausea and vomiting of pregnancy. Source: Lamm.^[120]

The ingredients that were in Bendectin are available over the counter in United States. Women can get doxylamine (Unisom SleepTabs) in 25 mg tablets and vitamin B6 in 25- or 50-mg tablets (note that Unisom SleepGels contain diphenhydramine, not doxylamine). There are various dose regimens possible, none of which have been studied in depth. The original Bendectin formulation was 10 mg of pyridoxine and 10 mg of doxylamine combined in a single tablet that could be taken up to 4 times per day. This dosing can be approximated by using half of a tablet of doxylamine twice during the day and 1 tablet of doxylamine at night, with a 25-mg tablet of pyridoxine (vitamin B6) 3 times per day. Because the studies on effectiveness of pyridoxine used 25 mg 3 times per day for a total of 75 mg per day, a 25-mg tablet or a 50-mg tablet broken in half can be used. One study of the Canadian formulation of Bendectin found that women who take suboptimal doses have higher levels of nausea. In this study, 40 mg of pyridoxine with 40 mg of doxylamine per day was the optimal dosing regimen for treating mild to moderate NVP.^[87]

Dopamine Antagonists

Phenothiazines, benzamides, and butyrophenones are the three classes of drugs that antagonize dopamine receptors. The primary drugs used for NVP are promethazine (Phenergan), prochlorperazine (Compazine), metoclopramide (Reglan), and droperidol (Inapsine).

Promethazine and Prochlorperazine The phenothiazines promethazine and prochlorperazine antagonize the dopamine (D₂) receptor in the CNS chemoreceptor trigger zone and also have a modest effect on H₁ receptors. There is no evidence of increased risk for teratogenic effects secondary to the use of these medications, and they are FDA Pregnancy Category C.^[82]

Phenothiazines are more effective than antihistamines in preventing or alleviating vomiting. Three RCTs have evaluated the effectiveness of phenothiazines for severe NVP (N ≈ 400). Various drugs were used, but when the results were pooled, the RR for NVP in women who took phenothiazines compared to women who took a placebo was 0.31 (95% CI, 0.24–0.42). The primary side effect of phenothiazines is sedation, which anecdotally may be the most common reason why women do not use these medications when prescribed.

Metoclopramide Metoclopramide (Reglan), a benzamide, has both a central and peripheral mechanism of action. This drug antagonizes both the dopamine (D₁) and serotonin receptors (5-HT₃) centrally and increases gastric emptying. Metoclopramide has not been found to have any association with congenital defects and is FDA Pregnancy Category B.^[82,88] No randomized studies of the effectiveness of oral metoclopramide have been conducted in pregnant women. Despite the lack of studies on effectiveness, this drug is widely used as a second step in treatment of NVP when phenothiazines or antihistamines are ineffective. Metoclopramide does not cause sedation, and many clinicians now prescribe metoclopramide orally for outpatient treatment without a previous trial of phenothiazines. In addition, metoclopramide is frequently used as a first-line treatment given intravenously or subcutaneously when women are admitted to an inpatient setting for treatment of HG, and has been shown to reduce the need for hospital visits and IV hydration.^[89,90]

Prochlorperazine, Promethazine, and Metoclopramide: Which Works Best? Bsat et al.^[91] prospectively randomized women with severe NVP (N = 156) to one of three groups: 1) 25-mg rectal suppositories of prochlorperazine (Compazine) to take every 12 hours as needed; 2) 25 mg of promethazine (Phenergan) to take orally every 6 hours as needed; or 3) one 50-mg intramuscular injection of pyridoxine (vitamin B6) with 10 mg metoclopramide (Reglan) taken orally every 6 hours as needed. After 3 days of treatment, the women in group 3 (pyridoxine/metoclopramide) had fewer number of emesis events when compared to the women in the other two groups. The RR for emesis when group 3 was compared to group 1 was 0.59 (95% CI, 0.39–0.88). The RR for emesis when group 3 was compared to

group 2 was 0.62 (95% CI, 0.42–0.91). The subjective scores for how much better they felt after 3 days of treatment were also higher in group 1. Although this study did not specifically document or assess side effects, one woman in group 1 withdrew from the study secondary to a dystonic reaction; there were no reports of adverse side effects from the women in either of the two phenothiazine treatment regimens.^[91]

Droperidol: Pharmacologic Treatments for Severe Nausea and Vomiting in Pregnancy

Droperidol (Inapsine) is the most recent dopamine antagonist to join the pharmacologic regimens used to treat severe NVP and/or HG. Droperidol belongs to the family of butyrophenones. It is more potent than phenothiazines and is commonly used by anesthesiologists intraoperatively to control postoperative nausea. There is no association between droperidol and congenital malformations, but there is a small risk of the mother developing prolonged QT syndrome which can lead to a potentially fatal arrhythmia.^[82] The American College of Obstetricians and Gynecologists (ACOG) recommends that this medication be used with caution.^[92]

Only one randomized trial has been conducted to date that has evaluated the effectiveness of droperidol. Nageotte et al.^[93] compared the outcomes of women hospitalized for HG who had a continuous infusion of droperidol with diphenhydramine (Benadryl) added to prevent extrapyramidal symptoms (see the next section on dystonic reactions to dopamine agonists) to the outcomes of women hospitalized in the same setting for HG but who did not receive this treatment regimen. The women who received the droperidol and diphenhydramine mixture had a decreased number of days hospitalized (3.1 ± 1.9 versus 3.8 ± 2.4 days; $P = .028$) and fewer readmissions (15.0% versus 31.5%; $P = .015$).^[93] Although this regimen was clearly effective, 15% of the women treated with droperidol and diphenhydramine had transient extrapyramidal or psychotropic symptoms despite the use of the diphenhydramine whereas none of the women in the placebo group had these side effects.

Dystonic Reactions to Dopamine Antagonists Dystonic or extrapyramidal reactions are a side effect of all the drugs that antagonize dopamine (D_1) receptors. When dopamine (D_1) receptors in the CNS are antagonized, the normal impulses in the basal ganglia and extrapyramidal system that control involuntary motion, balance, posture, and coordination can be interrupted. The result is a side effect that mimics Parkinson disease, and the patient will present with dystonic, akathisia, akinesia, and/or tardive dyskinesia. Because metoclopramide (Reglan) crosses the blood–brain barrier, dystonic reactions are more likely with metoclopramide than with other dopamine antagonists. Dystonic reactions generally occur 1 to 3 days after the onset of therapy or after an increase in dosage.^[94] Fortunately, the treatment for dystonic reactions is simple and effective. A dose of 50 mg of diphenhydramine (Benadryl) administered intravenously restores the balance between acetylcholine and

dopamine, and extrapyramidal symptoms usually resolve within 15 to 30 minutes after the administration of diphenhydramine.^[95,96]

Serotonin Antagonists

Ondansetron (Zofran), which has an antagonist effect on the serotonin receptor, is a very effective antiemetic for chemotherapy-induced nausea and vomiting but has not been extensively evaluated in pregnant women, although it is being used increasingly off-label for women with severe NVP and/or HG. There are no associations with malformations after the use of ondansetron in the first trimester of pregnancy, and it is FDA Pregnancy Category B.^[82,97]

Sullivan et al.^[98] conducted a double-blind randomized trial (N = 30) that compared 10 mg of ondansetron administered intravenously every 8 hours to 50 mg of promethazine (Phenergan) administered intravenously every 8 hours in women who were hospitalized for HG. The drugs were continued until the participants were able to eat a bland diet without emesis. There was no difference in length of hospitalization, decrease in nausea, or total doses of the medication. Eight women in the promethazine group reported sedation whereas none of the women in the ondansetron group reported uncomfortable sedation.^[98] Despite the negative finding of this RCT, case reports^[99,100] have reported remarkable success in treating women with HG with ondansetron who have failed other therapies, and ondansetron is increasingly used as a rescue antiemetic when women continue to have NVP despite treatment with antihistamines or dopamine antagonists.

Corticosteroids

Corticosteroids are primarily initiated when a woman is hospitalized with HG. There have been several studies evaluating the safety^[82,101,102] and effectiveness^[82,103–106] of corticosteroids for treating HG. Corticosteroids are associated with a small increase in the risk for oral clefts (RR, 3.4; 95% CI, 1.97–5.69),^[102] and at this time, ACOG recommends that they not be used before 10 weeks' gestation.^[92]

The studies conducted on efficacy of corticosteroids have been contradictory. Yost et al.^[106] found no difference in rehospitalization rates between women given methylprednisolone and women not treated with corticosteroids. These authors randomized 110 women who were hospitalized for HG to treatment with 125 mg methylprednisolone given intravenously followed by an oral prednisone taper (40 mg for 1 day, 20 mg for 3 days, 10 mg for 3 days, and 5 mg for 7 days) versus placebo administered with the same regimen. All women were treated with promethazine and metoclopramide for the first 24 hours of their hospitalization.^[106] Conversely, Safari et al.^[103] found no difference in rehospitalization rates between women treated with methylprednisolone and those treated with promethazine

(Phenergan). Safari et al.^[103] randomized women (N = 40) hospitalized for HG to either methylprednisolone or promethazine given orally 3 times per day for 3 days. After 3 days of therapy, the women on 16 mg of methylprednisolone (n = 20) were tapered off the steroid over a 2-week period. Those on promethazine (n = 20) continued the 25-mg dose of promethazine 3 times per day. None of the women who took methylprednisolone required rehospitalization, whereas five of the women who used promethazine were rehospitalized within 2 weeks of the initial hospitalization. Other trials of prednisone or methylprednisolone have used different regimens and different doses. To date, it appears that these agents may affect a rapid resolution of symptoms in the short-term but the efficacy for long-term use is equivocal.^[107,108]

Intravenous Fluids

The use of IV fluids deserves particular attention. IV fluids are an essential treatment for women who are dehydrated, and anecdotally, women report significant improvement for several days after receiving IV fluids. Women who prefer to avoid all medications may choose to rely on intermittent IV hydration only. Dextrose-containing fluids should be avoided because Wernicke encephalopathy can occur in women who are given a large carbohydrate load when deficient in thiamine.^[109] Normal saline is the best choice for an IV infusion because it will resolve hyponatremia. Potassium chloride can be added as needed, as can either thiamine (vitamin B1) or a multivitamin solution. Thiamine is particularly important because the requirement for thiamine increases in pregnancy, deficiency can occur if vomiting is prolonged, and thiamine deficiency is the underlying etiology of Wernicke encephalopathy. The one study to date that has evaluated the effectiveness of IV fluids is the recent survey conducted by Goodwin et al.^[32] Of those who used IV fluids, 83.8% (603 of 1193) reported that IV fluids were either maybe effective or effective.

Clinical Implications

A stepwise and systematic approach to the clinical management of women with NVP using treatments that have been shown to be both safe and efficacious will best help affected women. Using a systematic approach in combination with frequent clinic visits (every 4 days to weekly for women with severe symptoms) can also prevent escalating morbidity and save health care resources. That said, it is important to note that there are no standard treatment algorithms and to remember that many of medications used to treat NVP are not approved by the FDA specifically for this purpose. The clinical management algorithm currently recommended by both ACOG^[92] and the Society of Obstetricians and Gynaecologists of Canada^[110] is based on the work of the Motherisk Team at The Hospital for Sick Children in Toronto, Ontario, Canada. The algorithm presented in Figure 5 is adapted from

recommendations from Levichek et al.,^[111] ACOG,^[92] the Society of Obstetricians and Gynaecologists of Canada,^[110] and formatted for use by clinicians in the United States.

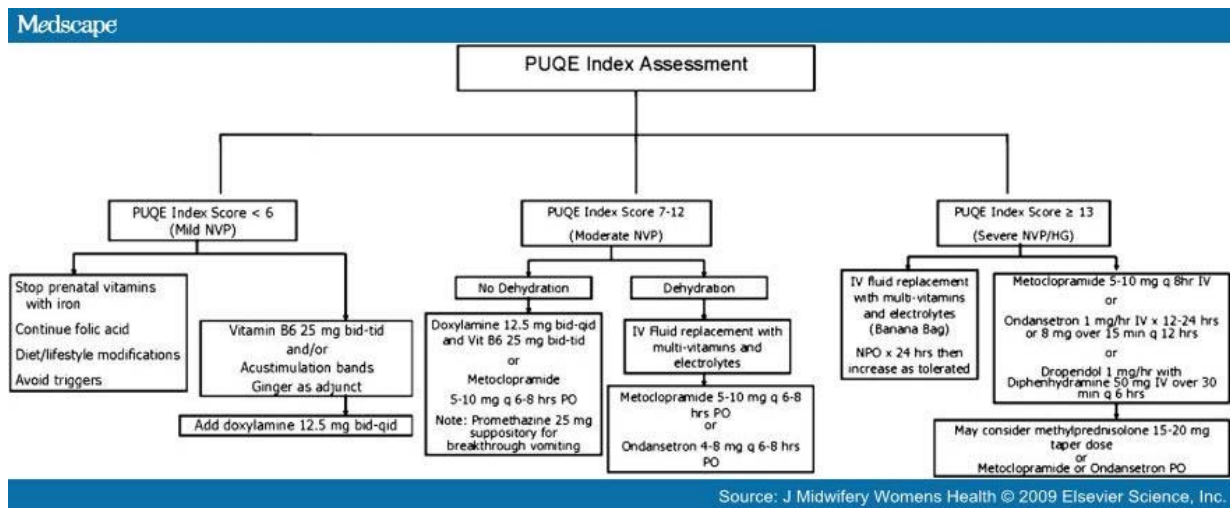


Figure 5. Protocol for assessing and treating women with nausea and vomiting in pregnancy. Adapted from the American College of Obstetricians and Gynecologists,^[92] Arsenault et al.,^[110] and Levichek et al.^[111]

Most women with a PUQE Index score of ≤ 6 (mild) are not retching or vomiting frequently and, in general, they are most likely to manage their NVP with lifestyle modifications and nonpharmacologic treatments. Ginger can be considered as a monotherapy or as an adjunct therapy to other treatments. Acupressure and acupuncture may also be of benefit for some women.

When the PUQE Index score is ≥ 7 or when a woman desires medication to help decrease nausea, start with vitamin B6 25 mg 3 times per day and half of a tablet of doxylamine (Unisom tablets) taken 3 times per day. The safety profile of both of these agents is very good.^[85,112,113] If a woman needs relief from occasional retching and/or vomiting, phenothiazines will reliably stop vomiting episodes, and most professional association guidelines recommend adding phenothiazines first for women who need relief from vomiting.^[92,110,114] Phenothiazines taken orally or used as a rectal suppository can be helpful for breakthrough vomiting, but because they are associated with significant sedation, women may not feel comfortable taking them. Therefore, metoclopramide (Reglan) is recommended if a medication is needed for regular daily use.

Severe nausea or frequent retching/vomiting can quickly result in dehydration. When a woman has signs of dehydration, management is intensified and frequent follow-up needs to be instituted. Treatment of dehydration can involve both IV fluid replacement and antiemetics that suppress vomiting. Metoclopramide can be used intravenously to interrupt an episode of vomiting, and it can be then prescribed orally for use at home after a hospital visit. Weekly

visits to record the woman's weight and assess her urine for signs of dehydration are important, because a woman may need frequent changes in her treatment regimen before an effective and individualized treatment plan can be established.

Ondansetron (Zofran) has a unique role in the treatment of NVP. It has a reputation for being the most effective antiemetic in use, but the single study published to date that compared ondansetron to other antiemetics in pregnant women did not find it to be more effective than phenothiazines.^[115] It is being used more frequently, and because it is very expensive, many insurance companies will not approve its use until a woman has failed more conventional therapies. More research needs to be performed to better determine if the perceived effectiveness of ondansetron is real.

When nausea and retching/vomiting results in dehydration despite a trial of an antiemetic that reliably stops vomiting (e.g., metoclopramide, phenothiazines, or ondansetron), medical consultation and referral is necessary. If the NVP is severe enough to entertain a diagnosis of HG, inpatient management may be required. HG is diagnosed after other etiologies of severe nausea and vomiting, such as molar pregnancy or multiple gestation, are ruled out. Regardless of the etiology, treatment for the nausea and vomiting will be instituted. Inpatient admission can involve several therapeutic regimens that include intravenous fluids, antiemetics, vitamin B1 replacement to prevent Wernicke encephalopathy,^[116] corticosteroids, and nasogastric feeding or parenteral nutrition.^[117] Home health services can be extremely helpful in outpatient care after a hospitalization for HG.^[118] Although the management of HG is not the focus of this review, the interested reader can find more detailed information about inpatient management in several recent reviews.^[32,92,117]

Conclusion

No single therapy for NVP is clearly the safest and most efficacious.^[16] The etiology of NVP is probably multifactorial, the spectrum of illness ranges from mild to severe, and the impact of the disorder on one's life is subjective. In addition, many women do not want to use medications during the first trimester of pregnancy because of concerns about teratogenicity.^[19] Finally, the degree of disability is determined solely by the woman's perception of her ability to function, which may not be reflected in a particular PUQE Index score. Therefore, the treatment of NVP has to be individualized.

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