

TEACHERS TOPICS

Nausea and Vomiting of Pregnancy

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Nausea and vomiting symptoms affect 70% to 85% of pregnant women during early pregnancy. These symptoms can have a dramatic effect on a woman's family, social, and occupational functioning. Hence, nausea and vomiting of pregnancy is a medical condition that should be taken seriously by health care professionals responsible for providing care to pregnant women. This manuscript reviews the current state of knowledge concerning the etiology, underlying mechanisms, and management of nausea and vomiting associated with pregnancy. An abbreviated version of the material found in this article is presented to second year PharmD students at the University of the Pacific as part of an elective course on evidence-based complementary and alternative therapies.

Keywords: nausea and vomiting, pregnancy, drug therapy, complementary and alternative therapies

INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is an obstetric syndrome that affects a majority of pregnant women, with symptoms that range from mildly unpleasant to disabling.¹ Healthy women experience the symptoms and bear normal and healthy babies. The common term for nausea and vomiting of early pregnancy is "Morning Sickness," which is a misnomer. The uncomfortable symptoms can and do occur at all hours of the day, not just in the morning. NVP is certainly a more appropriate, descriptive, and objective term to use when discussing or referring to gestational nausea and vomiting.

Seventy percent to 85% of pregnant women experience NVP beginning by the fourth week and often ending by the twelfth week after conception. Symptoms may persist throughout pregnancy in up to 20% of pregnant women.² Of this large group, 1% to 3% experience a more severe form of NVP called *hyperemesis gravidarum*, described as intractable vomiting associated with weight loss of more than 5% of prepregnancy weight, dehydration, and electrolyte imbalances, which may lead to hospitalization and serious potential consequences to the pregnant woman

and the fetus. Even when the condition is not so severe, symptoms can cause considerable distress and temporary disability.³ Nearly 50% of employed women believed their work efficiency was substantially reduced by NVP, and as many as 25% required time off from work. Almost one half of women with NVP said that it had adverse effects on their relationships with their spouse, and 55% of pregnant women with NVP felt depressed. The financial burden of severe NVP on the American health system has been estimated to be about \$130 million per year, which is based on an annual average of 39,000 hospital discharges at a mean cost of \$3,300 per stay. These figures do not include physician fees, loss of productivity at home or on the job, or the cost for patient treatment.

There is a great deal of variation among women with respect to the severity and duration of NVP symptoms.⁴ For the majority of pregnant women, nausea is transient in nature and has few long-term consequences for their pregnancy or their life, although it is undoubtedly unpleasant in the short term. For as many as 35% of pregnant women, the NVP symptoms are severe enough to seriously disrupt their lives, causing them to change their usual activities. An average of 2.5% of pregnant women require hospitalization because of *hyperemesis gravidarum*. Predicting which patients are likely to suffer from NVP is difficult. There are no reliable indicators. Fatigue appears to be associated with nausea during pregnancy. Women who have a history of severe nausea during pregnancy or whose mothers suffered from severe nausea during pregnancy are at greater

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risk. Multiple gestation and molar pregnancies are also associated with increased nausea. Despite the unpleasant and disruptive nature of NVP symptoms, nausea during pregnancy is considered a normal part of pregnancy. Nausea and vomiting in the first trimester of pregnancy are associated with a decreased risk of miscarriage, preterm delivery, low birth weight, stillbirth, and fetal and perinatal mortality.¹ Women suffering from severe NVP do not appear to have different birth outcomes from those of women who experience mild nausea.⁵

Although the proximate, physiological mechanisms underlying NVP have been extensively studied, the cause of NVP remains unknown. There currently are no scientifically based treatments that address the cause of NVP. Management of NVP focuses mainly on alleviating the symptoms.⁶ Concerns about the potential teratogenic effects of drugs administered during the critical embryogenic period of pregnancy, especially in the wake of the thalidomide tragedy of the 1960s, drastically limit the use of pharmacologic treatments for this condition.⁷ Several nonpharmacologic interventions, such as dietary modifications and avoiding certain aggravating odors or foods, are often recommended, but unfortunately, few women report complete relief after these interventions.³ As a result, many pregnant women seek alternative therapies to treat NVP, including vitamins, herbal products, homeopathic preparations, acupressure, and/or acupuncture.⁸ Some clinical trials have suggested significant relief of nausea and vomiting with the use of some of these alternative approaches, however, there is an overall dearth of research on the efficacy of a wide variety of remedies used by women for the treatment of NVP. The risk of potential adverse effects of these approaches also needs to be adequately addressed.

The 'Syndrome' Model for NVP

NVP symptoms are the result of complex interactions between genetic and environmental factors beginning during the period of organogenesis.⁹ The trigger, which is a product of the placenta, may be modified in intensity by genetic variation or specific disease states to produce more or less severe NVP. A woman's response to the trigger is altered at 2 levels: the receptor level, such as estrogen or human chorionic gonadotropin (HCG) receptors, and the level of the major pathways leading to nausea and vomiting (vestibular, gastrointestinal, olfactory, gustatory). Once the emetic response has been triggered, the clinical impact and severity of the condition is further

modified by nonspecific factors such as the establishment of behavioral cues to nausea and vomiting or the existence of a chronic illness. How family members and caregivers respond to the condition also contributes significantly to the clinical impact and severity of the condition.

Much of the frustration that clinicians experience while managing NVP is caused by a lack of understanding of the various factors underlying NVP and how these factors interact in pregnant women. Currently, all patients with NVP are treated as if the condition were a single entity disorder. Approaching NVP as a syndrome will allow clinicians as well as family members to provide better care to NVP patients.⁹ A proposed new conceptual framework for NVP is shown in Figure 1.

Etiology and Underlying Mechanisms

Although the cause of NVP is not known, there is strong evidence in the literature linking HCG or estrogens.⁹ In many studies, the incidence and severity of NVP is linked to temporal and pathologic alterations in these hormones during pregnancy. The way in which a pregnant woman responds to the primary stimulus to NVP appears to depend primarily on her susceptibility mediated by vestibular, gastrointestinal, olfactory, and behavioral pathways.

The 4 major sources of stimuli that can induce emesis are the gastrointestinal tract (GIT), the vestibular system, the higher brain, and the area postrema.¹⁰ Examples of conditions acting via each one of these mechanisms are listed in Table 1. There is significant variation in how individuals respond to the same emetic stimulus, rendering some highly susceptible and some remarkably resistant. The mechanisms by which a number of nausea and vomiting conditions, such as NVP and postoperative nausea and vomiting, trigger the central neuronal circuitry are unknown. It is likely that NVP is produced by 2 mechanisms: The first is a direct stimulus to nausea and vomiting via some as yet unknown pathway; the second is a lowering of the threshold to nausea and vomiting mediated by known pathways such as the vestibular and gastrointestinal mechanisms.⁹ Whatever the specific trigger is, the emetic response is essentially the same: a marked reduction in gastric tone and motility is followed by a retrograde contraction that is responsible for moving the contents of the small intestine into the stomach. Thereafter, contractions of the diaphragm and abdominal muscles combine with relaxation of the gastroesophageal sphincter to allow passage of gastrointestinal contents.¹⁰ Although the mechanism of emesis is well understood, the mechanism responsible

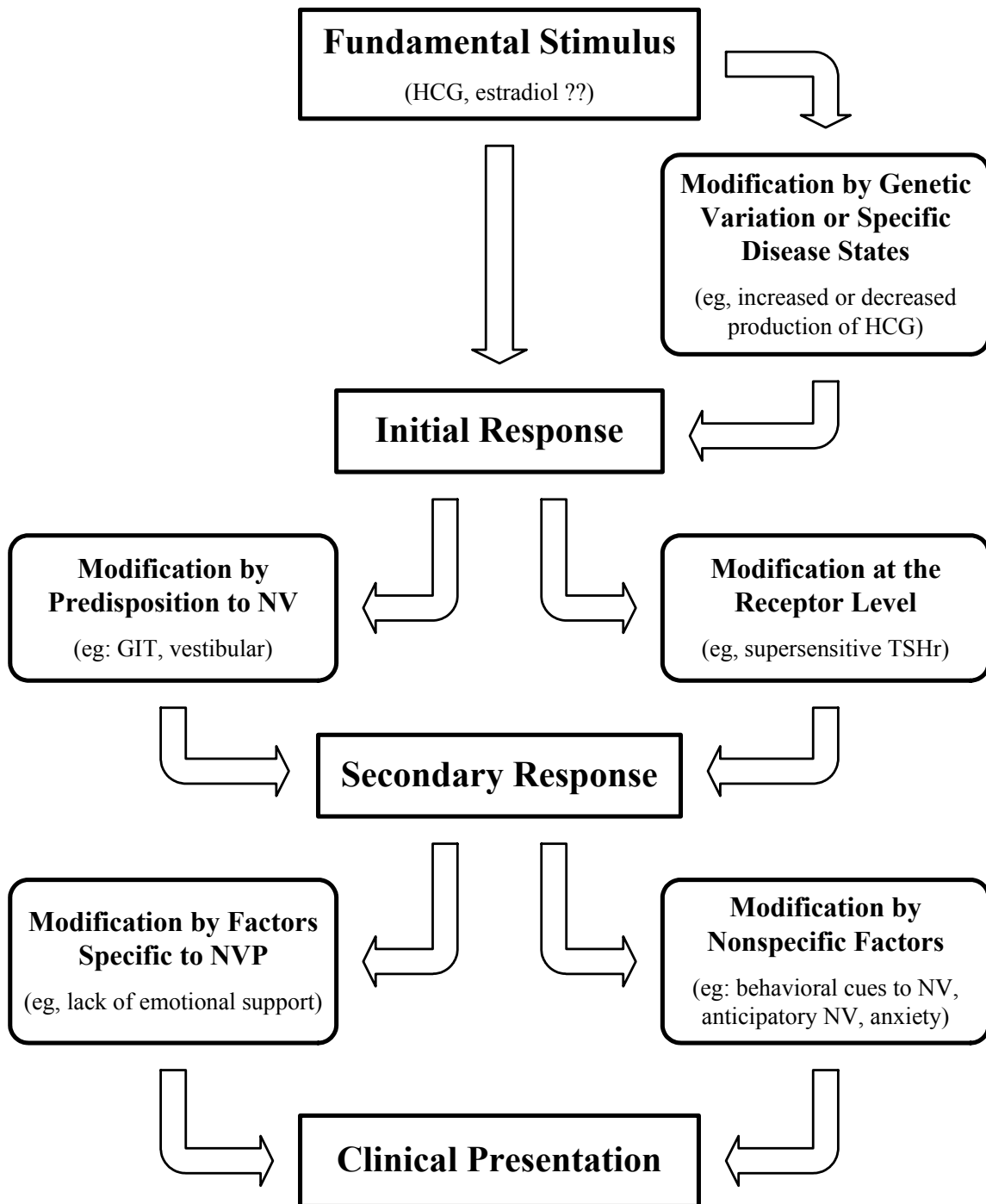


Figure 1. Proposed new conceptual framework for nausea and vomiting of pregnancy (HCG, human chorionic gonadotropin; GIT, gastrointestinal tract; TSHr, thyrotropin receptor; NV, nausea and vomiting; NVP, nausea and vomiting of pregnancy).

for nausea remains unclear. Because nausea and vomiting frequently coexist and are elicited by similar stimuli, it is believed that their mechanisms share important common elements. The major problem with studying nausea is that it is extremely subjective. For many NVP patients, nausea contributes as much or

more to the severity of the condition and overall suffering than does vomiting per se.³

Genetic Factors

Genetic predisposition to NVP is supported by the following findings:

Table 1. Major Pathways Leading to Nausea and Vomiting

Pathway
Gastrointestinal
Cancer chemotherapy
Radiation-induced emesis
Food poisoning
Vestibular (visual and inner ear)
Motion sickness
Space sickness
Meniere's disease
Higher Brain
Chemotherapy-induced anticipatory nausea and vomiting
Olfactory-induced vomiting
Area Postrema
Blood poisoning
Others
Nausea and vomiting of pregnancy (NVP)
Postoperative nausea and vomiting
Cranial nerve (V and IX) afferents

a. Monozygotic twins experience the same frequency and severity of NVP symptoms.¹¹

b. Siblings and mothers of NVP patients are more likely to suffer from NVP than relatives of women who do not experience NVP.^{12,13}

c. Variation in the frequency and severity of NVP between ethnic groups. Pacific Islanders, for example, were found to be four times more likely to experience *hyperemesis gravidarum* than other residents in a study conducted in New Zealand.¹⁴ Another study found that 8 of 30 societies with sufficient information on NVP reported none at all.¹⁵

d. The higher frequency of NVP in patients with predisposing conditions that are genetically determined such as taste sensation.¹⁶

e. The occurrence of NVP in women with inherited glycoprotein hormone receptor defects.¹⁷

form mole, are associated with NVP.^{18,19} *Hyperemesis gravidarum* is 4 to 5 times more common with multiple gestations than in singletons. Hyperemesis is also common in 8% to 23% of hydatidiform mole cases.

c. NVP is more common in women bearing female offsprings (HCG levels are high in pregnancies with a female fetus).²⁰ No study has found that pregnancies with male fetuses were more likely to be complicated by NVP.

d. Trisomy 21 pregnancies, which are associated with higher maternal HCG concentrations, are more common in *hyperemesis gravidarum* cases.²¹

e. NVP is less common in circumstances known to be associated with low HCG levels, such as smoking.²²

f. HCG is the thyroid stimulator of pregnancy.²³ Numerous studies of thyroid hormones in pregnancy have established an association between transient biochemical hyperthyroidism and NVP. The degree of biochemical hyperthyroidism correlates closely with the severity of NVP.²⁴ Because hyperthyroidism itself is rarely a cause of nausea and vomiting, these studies provided strong evidence implicating HCG as a triggering factor for NVP. HCG is structurally related to thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The main structural difference between these hormones is that HCG has a

The Fundamental Stimulus

The triggering factor for NVP has not been identified, although HCG and estrogens have been implicated. The primary reasons for considering HCG as a likely trigger are as follows:

a. The close temporal association between peak HCG concentrations and peak NVP symptoms.

b. Conditions associated with higher HCG production, such as multiple gestation and hydatidi-

carboxy terminal moiety which is not present in the others. Isoforms of HCG lacking the carboxy terminal group are very similar to TSH and are more thyrotropic than the intact HCG molecule.²⁵ Hyperglycosylated forms of HCG exhibit even greater thyrotropic activity and have longer half-lives. In addition to stimulating the thyroid gland, HCG isoforms stimulate the production of sex steroids by the maternal and, possibly, the fetal gonad. A positive correlation has been shown to exist between various HCG isoforms, estradiol, thyroxine production, and severity of NVP.²⁶ It is not known, however, how HCG itself would cause nausea or vomiting.

In addition to HCG, estrogens have also been implicated in the NVP triggering mechanism because of the following findings:

- a. NVP is more common in conditions of higher estradiol levels such as low parity and mole with theca lutein cysts.^{27,28}
- b. NVP is less common among smokers. Smoking is associated with lower estradiol levels.²⁹
- c. Estrogens in birth control pills have been shown to induce nausea and vomiting in a dose-related fashion.³⁰
- d. Women who tolerated estrogen-containing oral contraceptives in the nonpregnant state are less likely to suffer from NVP.³¹
- e. The variation in postoperative nausea and vomiting by menstrual cycle phase in female patients is best explained by an estrogen-related effect.³² Postoperative nausea and vomiting are more frequent in women than men, most prevalent around the time of menarche, and less prevalent around the time of menopause. Similarly, exacerbation of nausea and vomiting symptoms in female patients with Meniere's disease (idiopathic endolymphatic hydrops), a vestibular disorder associated with adult-onset motion sickness, was found to correlate with the late luteal phase of the menstrual cycle (premenstrual period).³³

Modification of the Maternal Response

Variation among women in their response to the fundamental trigger of NVP may be attributed to genetic variation in the receptor/ligand interaction. This has been established in the case of familial hyperemesis. A mutation of the TSH receptor rendering it hypersensitive to stimulation by HCG was shared by several family members.¹⁷ Severe NVP and spontaneous ovarian hyperstimulation has also been associated

with a mutation at the junction of intron 10 and exon 11 of the HCG/LH receptor.³⁴ In addition, the maternal response to the stimulus is highly influenced by the susceptibility of the mother to stimulation of the major nausea and vomiting pathways. These include the neurovestibular, gastrointestinal, olfactory, and gustatory pathways leading to nausea and vomiting. Women with a susceptibility to nausea and vomiting because of a subclinical vestibular, gastrointestinal or olfactory dysfunction are more likely to experience NVP when exposed to the pregnancy triggering factors that are capable of eliciting nausea and vomiting.⁹ On the other hand, women who do not have a specific susceptibility to nausea and vomiting may experience NVP only in response to an overwhelming stimulus (eg, large molar pregnancy or multiple gestation).

The Vestibular System

Chronic nausea and vomiting in the nonpregnant adult population is largely attributed to disease of the GIT and the neurovestibular system. The most common vestibular disorders that result in chronic nausea and vomiting and are associated with adult-onset motion sickness include idiopathic vertigo, Meniere's disease, and perilymph fistulas. Apart from discrete disease states, there is a spectrum of susceptibility to vestibular-mediated sickness or other dysfunction in the general population.³⁵ For example, 50% to 70% of otherwise healthy individuals suffer from space motion sickness upon entering a weightless, microgravity environment.³⁶ A similar proportion of candidates for jet pilot service are rejected on the basis of subclinical vestibular problems that can be predicted by using the vestibular auto-rotation test.³⁷ Another common vestibular-mediated phenomenon is motion sickness, which affects up to 90% of the population at some point during their lives. A number of physiologic changes that occur in normal pregnancy are also known to accompany nausea and vomiting in patients with motion sickness and certain vestibular disorders.³⁸ Because vestibular disorders are so prevalent in the general population, a subclinical or compensated vestibular disorder may be unmasked by the normal physiologic changes that accompany pregnancy. The unmasking of subclinical vestibular disorders may account for some cases of *hyperemesis gravidarum*.

A comparison of the symptom constellation of motion sickness and the symptom pattern of NVP reveals striking similarities.³⁸ The gastrointestinal changes associated with NVP (delayed gastric emptying, reduced esophageal sphincter pressure, decreased gall bladder motility, and increased gut transit time) are almost identical to changes in the patient with motion sickness.

Given the symptomatic similarity between NVP and the nausea and vomiting of motion sickness and the fact that hormonal factors play a role in both conditions, obstetricians have long noted an association between a history of motion sickness susceptibility and the occurrence of NVP. In a survey of 1000 women between 14 and 28 weeks' gestation, 12% had a history of motion sickness.¹² The frequency of NVP was significantly higher in women with the history of motion sickness than in those without a history of motion sickness. Another survey revealed that 63% of respondents identified lying down and remaining still as the best maneuver to improve NVP.³⁹ Nearly 25% of women also identified recumbent rest as a means of improving NVP in a third survey.³ Women with chronic vestibular dysfunction frequently show deterioration during various phases of the menstrual cycle.³³ Although the precise hormonal mechanism responsible for the deterioration has not been elucidated, it is possible that the significant hormonal changes of early pregnancy could cause analogous changes in the vestibular system.

Similarities between NVP and motion sickness suggest that the inner ear may influence the incidence and/or severity of NVP. Studies related to plasma osmolarity during pregnancy and in women with vestibular disorders have also suggested that vestibular-mediated nausea and vomiting may be induced by hormonally mediated change in osmolarity in early pregnancy. Minor fluctuations in plasma osmolarity can result in severe vestibular-mediated nausea and vomiting in women with vestibular disorders such as Meniere's disease.⁴⁰ In addition, high levels of arginine vasopressin have been found in patients suffering from Meniere's disease. The period of pregnancy that corresponds to the onset of NVP is characterized by a significant decrease in plasma osmolarity.⁴¹ The decrease in plasma osmolarity in early pregnancy has been attributed to decreased sensitivity to vasopressin, an effect linked to the actions of HCG.⁴² Motion-induced nausea is mediated by gastric dysrhythmias and increased vasopressin release in the nonpregnant state.⁴³ Based on all the evidence, participation of the vestibular system in the pathogenesis of NVP may be attributed to either a preexisting, subclinical vestibular dysfunction that renders a pregnant woman more susceptible to the hormonal trigger for NVP, or a very strong hormonal trigger for NVP that can adversely affect the normal vestibular system of a pregnant woman.

The GIT

Gastric neuromuscular dysfunctions of the stomach include abnormalities in gastric myoelectrical activity, gastric tone, and contractility, all of which may result in gastroparesis. These abnormalities in gastric neural activity and smooth muscle function are associated with nausea and vomiting in nonpregnant patients.⁴⁴ Neuromuscular abnormalities of the stomach associated with nausea and vomiting have also been described in women with NVP. The cardinal abnormality in these conditions is gastric dysrhythmias. Gastric dysrhythmias are disturbances of the electrical pacemaker activity patterns of the stomach known as "pacesetter potentials" or "slow waves."⁴⁵ Pacesetter potentials, which originate in the pacemaker region along the greater curvature of the stomach, control the rhythmic peristaltic contractions of the stomach. Gastric dysrhythmias can be easily detected on the electrogastrogram (EGG), a recording from surface electrodes of the myoelectrical activity of the stomach.

Gastric myoelectrical abnormalities are pathophysiologic events that underlie the noxious and vague epigastric sensations and nausea. A variety of gastric dysrhythmias (tachygastrias and bradygastrias) have been recorded in patients with dyspepsia symptoms and nausea,⁴⁵ nausea of motion sickness,⁴⁶ drug-induced nausea,^{47,48} nausea and vomiting caused by diabetic and idiopathic gastroparesis,⁴⁹ and in women with NVP.⁵⁰ A variety of drugs (glucagon, morphine sulfate, estrogen, progesterone) and other stimuli are capable of inducing gastric dysrhythmias and nausea in healthy control subjects. The dysrhythmias precede nausea and resolve with treatments that reduce nausea. Healthy individuals who are prone to gastric dysrhythmias can be identified. In one study, 17% of apparently normal control subjects had dysrhythmias in response to a water load test compared with more than 50% of subjects with a history of functional dyspepsia.⁵¹ These normal subjects with abnormal provocative testing are likely to be more susceptible to the vomiting stimulus of pregnancy.

Gastric motor dysfunction has been implicated in NVP. Women with subclinical gastric motor dysfunction who become pregnant are likely to be more susceptible to NVP. Using electrogastrography to evaluate the prevalence of gastric dysrhythmias in pregnant women, abnormalities were demonstrated in all women with NVP.⁵⁰ In this study, more than 81% of the pregnant women had various degrees of nausea and gastric dysrhythmias: 65% had tachygastrias (4 to 9 cycles/min waves), 19% had bradygastrias, and 15% had a flat-line pattern. Of the pregnant women with minimal to no nausea, all had a normal gastric rhythm (3 cycles/min). The

presence of a dysrhythmia was associated with the report of nausea, whereas the presence of normal EGG pattern was associated with the absence of nausea. In addition, symptom-free women who were studied after delivery had normal EGG activity, whereas they had a variety of gastric dysrhythmias during the first trimester of pregnancy when nausea was present. The study also found that gastric dysrhythmias and the associated nausea are usually preceded by an increase in plasma vasopressin levels. These findings were further confirmed by other studies^{48,52} that also demonstrated the presence of gastric dysrhythmias in women with NVP.

Collectively, studies have indicated that gastric dysrhythmias represent a pathophysiologic mechanism for NVP. The acute loss of normal gastric rhythm during a wave of nausea, the observation that women in the first trimester of pregnancy without nausea had normal EGG rhythms, and the return to normal gastric rhythm after delivery supported the notion that the presence of gastric dysrhythmias is an objective finding related to stomach dysfunction and nausea symptoms. The mechanisms underlying gastric dysrhythmias are poorly understood. Potential mechanisms that may lead to gastric dysrhythmias include:

- a. A gastric neuromuscular dysfunction or malfunction.
- b. Abnormalities in vagal or sympathetic neural activity involving the stomach.
- c. The neurohormonal and vascular changes that occur in the first trimester of pregnancy.
- d. Hyper- and hypothyroidism, which may disrupt intestinal pacemaker activity.⁵³
- e. Changes in intravascular volume status that affects vasopressin secretion.

The diagnosis of NVP assumes that other common gastrointestinal disorders have been considered and excluded. In NVP patients, any recurrent abdominal pain must be investigated independently from considerations of neuromuscular dysfunctions, such as gastric dysrhythmias or gastroparesis.⁵⁴ Standard gastrointestinal disorders that should be considered and appropriately excluded are gastroesophageal reflux disease, cholecystitis, pancreatitis, gastric and duodenal peptic disease, and irritable bowel syndrome. These disorders are common causes of abdominal discomfort that may be accompanied by some element of nausea.

Olfactory and Gustatory Factors

Developing aversions to certain smells and tastes is one of the most common observations of obstetricians caring for NVP patients. Bitter taste perception has been linked to severe NVP. In one study, 60 women with NVP (21 “high-vomit” and 39 “low-vomit”, based on their obstetric histories) were tested for spatial taste patterns and taste acuity.⁵⁵ Women in the high-vomit group were less likely to be nontasters and more likely to have increased perception of bitterness on the posterior tongue. Nontasters are individuals who cannot taste the bitterness of the standard 6-propylthiouracil. The ability to taste the bitterness of this standard is inherited in an autosomal dominant fashion. Nontasters are homozygous recessive, and tasters are either heterozygous or homozygous dominant for the taste gene. Results from another study indicated that gustatory discernment is diminished during pregnancy.⁵⁶ It is not known, however, whether there is a baseline difference in gustatory discernment that distinguishes women with development of severe NVP.

Olfaction is closely linked to taste. Studies have shown that women have greater olfactory acuity than men and that among women, pregnant and ovulating women have the highest olfactory acuity.⁵⁷ Hence, hyperacuity of the olfactory system during pregnancy, induced by the hormonal stimulus of early pregnancy, may very well be an important contributing factor in NVP.⁵⁸ Pregnant women have long been known to have dietary cravings and aversions, seeking milk, ice cream, sweets (especially chocolate), and fruits, and avoiding coffee, meats, poultry, fish, fatty foods, and sauces flavored with oregano.⁵⁹ The pattern of selective avoidance of meats and fatty foods as olfactory triggers to NVP is consistent with the ethnographic evidence of little or no NVP in primitive societies having grain (especially corn) and fruit diets.⁶⁰ Numerous studies have documented food aversions and cravings of pregnant women; only few, however, describe the relationship between these changes and NVP. One study found that severe NVP is more common in women who report cravings.⁶¹ Interestingly enough, an increased risk of *hyperemesis gravidarum* has been associated with a prepregnancy dietary excess of saturated fat ingestion.⁶²

Behavioral and Psychological Factors

In addition to the plausible biological and pathophysiological theories that have been proposed for the etiology of NVP, psychological theories also exist. However, methodologically sound studies necessary to establish a psychological component in NVP, particularly a psychosomatic one, are lacking. The most fre-

quently discussed psychological theories that have been proposed to contribute to the etiology of NVP include the Psychoanalytic Theory,^{63,64} Stress Hypothesis,⁶⁵ Coping Skills Theory,⁶⁶ and the Behavioral Conditioning Hypothesis.⁶⁷⁻⁷⁰

The assumption is frequently made that women with severe NVP are transforming purely psychic trauma into physical symptoms. Available studies on the psychological causes of NVP, however, do not support its widespread acceptance as a conversion/psychosomatic disorder. Hence, the pervasiveness of this assumption is most likely the result of a medical gender bias. Such bias was shown to be the cause of frequent misdiagnosis of women with psychological disorders, particularly psychosomatic disorders.⁷¹ This has been attributed to the fact that although women represent more than half of all medical patients, the majority of their physicians are men. Even when faced with a menstrual or reproductive disorder in a female patient that has an established physiological etiology, the evidence also indicates that physicians attribute hysterical features to the aggravation of such a disorder.⁷¹

It is becoming increasingly clear that pathophysiological factors predispose a woman to NVP. The success of hypnosis and other psychotherapeutic approaches in treating NVP does suggest an interaction between physiological, psychological, and sociocultural factors. The interaction of these factors is unique in a particular patient and will differ from one woman to another. Such an interaction is much different than the unsubstantiated assumption held by many that NVP is the result of a particular psychological disorder. Further studies are needed to fully appreciate the interaction of the various factors underlying NVP. Meanwhile, recognizing that women with NVP experience a tremendous amount of psychological distress, and that they are in great need of an emotionally supportive environment, is a very important step toward treating these individuals.

NVP: A Disease or an Adaptation?

Although the overwhelming majority of clinicians believe that NVP is a real disorder, the possibility that NVP symptoms serve a useful function has emerged as a hypothesis which highlights the adaptive and evolutionary significance of nausea and vomiting during pregnancy. The hypothesis, known as the "Maternal and Embryo Protection" hypothesis, suggests that normal levels of NVP (excluding *hyperemesis gravidarum*) and the associated temporary taste aversions protect pregnant women and their embryos from

harmful substances in food, particularly pathogenic microorganisms in meat products and toxins in strong-tasting plants.^{72,73} The hypothesis also indicates that normal levels of NVP will not harm the embryo or mother. Support for this hypothesis comes from studies that demonstrated an association between NVP and positive pregnancy outcomes such as decreased risk of miscarriage. Further support for the maternal and embryo protection hypothesis is based on the fact that NVP symptoms peak when the embryonic tissues are most sensitive to toxins and pathogens (weeks 5 to 18 of pregnancy), and that pregnant women in their first trimester reported significantly more food aversions than nonpregnant control subjects.

Supporters of the maternal and embryo protection hypothesis believe that uncomplicated NVP is a natural phenomenon and, in the vast majority of cases, a normal part of a healthy pregnancy. Hence, they are urging clinicians and patients to seek a balance between the need for eliminating the unpleasant NVP symptoms and the possibility of benefiting from their prophylactic effects. Recognizing NVP as an adaptation may, according to the hypothesis, help reassure patients and enable them to pursue new noninvasive ways of avoiding or minimizing NVP symptoms, such as eliminating potential triggering stimuli (eg, odors from foods that pregnant women find aversive) from the home and work environments during the first trimester of pregnancy.

Despite the evidence presented by the adaptation/protection hypothesis regarding an association between NVP and positive pregnancy outcomes, women who do not experience NVP should not be concerned. In fact, a majority of women in Western societies have positive pregnancy outcomes regardless of whether they experience NVP. The occurrence of NVP does not guarantee a positive outcome of pregnancy, and the absence of NVP symptoms does not signify failure of gestation. In addition, it is important to note that, although this hypothesis is discouraging physicians and patients from eliminating NVP symptoms (excluding hyperemesis), treating NVP and selecting the most appropriate therapeutic approach to ameliorate the symptoms in a particular patient will largely depend on the severity of the symptoms and their effects on the patient's quality of life.

Management of NVP

The cause of pregnancy-induced nausea and vomiting remains unknown. As a result, treatments that address the cause of this condition are not available. Management of NVP focuses mainly on alleviating symptoms. In a recent survey, there was generally a broad

agreement concerning the treatment of both moderate and severe cases of NVP among obstetrician/gynecologists that corresponded well with the current opinion on managing NVP.⁷⁴ The survey revealed that clinicians are willing to treat this condition aggressively even though a majority of pregnant women with NVP do not seek therapy, mainly because of concerns about safety and the teratogenic risk to their fetus. Interestingly, no approved drugs for the treatment of NVP are currently available in the United States. Bendectin, a combination of the antihistamine doxylamine and pyridoxine, was the only FDA-approved drug for NVP in the U.S. before 1983. Bendectin was removed from the U.S. market in 1983 by its manufacturer because of legal costs based on claims of teratogenicity, which were subsequently proven to be unsubstantiated.^{75,76} The combination of vitamin B₆ and doxylamine is available in various formulations in other countries and has been continuously available as Diclectin in Canada, where it is the only drug approved for the treatment of NVP.

When to treat NVP symptoms is as important as what to use to treat them. Evidence suggests that a woman's quality of life may be impaired before severe physical symptoms occur. The importance of treating NVP early to prevent deterioration that may lead to hospitalization was demonstrated by the effect of removing Bendectin from the North American market.⁷⁵ In Canada, hospital admissions of NVP patients increased from 1983 to 1989 and then declined between 1990 and 1995 with rising rates of Diclectin prescriptions. In addition, it is important to rule out other causes of nausea and vomiting during pregnancy, such as gall bladder disease, ulcer disease, hepatitis, gastroenteritis, appendicitis, pyelonephritis, and pancreatitis.⁴⁴ Obstetric explanations for the NVP symptoms should also be considered because NVP is more common in patients with multiple gestations and hydatidiform moles. Once other causes of nausea and vomiting are ruled out, the most commonly recommended therapeutic approach for managing NVP includes dietary modifications and other nonpharmacologic remedies, drug therapy, and non-drug or alternative treatments.^{1,6,8,54}

Nonpharmacologic Remedies

For patients with NVP symptoms, a variety of dietary modifications and other nonpharmacologic remedies are recommended initially.^{54,74} These include the following:

a. Avoiding certain aggravating odors, foods, or beverages that can trigger nausea.

b. Avoiding fatty or spicy foods and eliminating iron supplements from the diet, because they can cause nausea.

c. Eating frequent small meals. The emphasis traditionally has been on bland and dry foods, high-protein snacks, and crackers at the bedside in the morning before arising.

d. Ingestion of sips of fluids throughout the day to prevent dehydration. Sports drinks that contain salt, glucose, and potassium, or high-protein liquid drinks are usually recommended.

e. Recumbent resting whenever tired or nauseous.

Drug Therapy

Many women and health care providers frequently overestimate the teratogenic risk of medications during pregnancy.⁷⁷ As a result, a great number of NVP patients do not seek a drug therapy that is proven to be safe and effective. Because NVP is rarely life-threatening, anti-emetic therapy for NVP is aimed at improving the quality of pregnant women's lives. In most cases, anti-emetic therapy should be initiated only when a woman is unable to maintain hydration and/or nutrition. Dietary and lifestyle changes that many women regard as safe options should always be pursued first.

Despite evidence of fetal safety, most anti-emetic medications are contraindicated during pregnancy. However, a recent risk-benefit analysis of the literature on the safety and efficacy of these agents for the treatment of NVP revealed that some of them can be safely prescribed during pregnancy.⁷⁷ Evidence from controlled trials has shown that the following anti-emetic agents are safe and effective for the treatment of varying degrees of NVP: Bendectin/Diclectin (doxylamine and pyridoxine), antihistamines (H₁ blockers), and phenothiazines.⁷⁸ Head-to-head comparative studies for individual drugs are not available. Hence, it is reasonable, if success is not achieved with one of these agents, to switch to another. Many of these agents may also be used in combination along with nonpharmacologic approaches. It is important to note that, particularly with the phenothiazines, the magnitude of effect may differ among individual agents in a class of drugs. The dopamine antagonists, Metoclopramide and Droperidol, and the serotonin antagonist Ondansetron may also be effective, but safety data are insufficient to recommend them as first-line agents. In addition, H₂ blockers and proton pump inhibitors may be safely used in cases where gastric acid secretion is thought to have a role in NVP.^{79,80}

Although Bendectin was withdrawn from the U.S. market because of lawsuits that alleged a teratogenic effect, no other agent given during pregnancy has more conclusive safety data with respect to teratogenicity.⁸¹ An estimated 33 million women have used Bendectin between 1956 and 1983. Thousands of patients exposed to Bendectin have been compared with many thousands of control subjects, with no difference in the incidence of birth defects detected. In the U.S., the ingredients in Bendectin can be constituted by combining doxylamine (marketed over-the-counter as Unisom Sleep Tabs, 25 mg per tablet) and vitamin B₆. Because Bendectin was originally formulated to contain 10 mg of doxylamine, half a tablet of Unisom Sleep Tabs (12.5 mg of doxylamine) approximates the dose. The recommended dosage for Unisom is one tablet at night and half a tablet in the morning and in the afternoon (the dosage for Bendectin was two tablets at night). The FDA is planning on reintroducing Bendectin to the U.S. market and has set the stage for that by republishing its conclusion that Bendectin does not represent an increase in reproductive risks to the fetuses of pregnant women.⁸²

Hyperemesis gravidarum, characterized by severe nausea with prolonged and sustained vomiting during pregnancy, can have serious detrimental effects on both mother and fetus. More than 1 in 50 pregnant women will have to be hospitalized because of *hyperemesis gravidarum*. Other clinical manifestations of *hyperemesis gravidarum* include dehydration, weight loss, and/or signs of nutritional deficiencies. The most common treatment options for patients with hyperemesis are intravenous hydration and the administration of anti-emetic medications (either IV or suppositories).⁷⁴ In some cases, parenteral nutrition is also required. Although a number of reports have described successful use of corticosteroids for treating hyperemesis during pregnancy, recent controlled trials failed to show a significant decrease in nausea or vomiting in patients receiving the corticosteroid.⁷⁸ In addition, a small teratogenic risk associated with first trimester exposure to corticosteroids has been reported.⁸³ As a result, corticosteroids, which have been shown to be effective in treating chemotherapy-induced emesis in cancer patients,⁷⁸ are not recommended for the treatment of hyperemesis in pregnant women.

Pregnant women with *hyperemesis gravidarum* who have vomited for more than 3 weeks develop subacute vitamin B₁ (thiamine) deprivation. Hydration of these patients with intravenous dextrose without prior administration of thiamine will cause Wer-

nicke's encephalopathy, which is a serious neurologic disorder caused by deficiency of thiamine.⁸⁴ Metabolism of the dextrose rapidly consumes the remaining thiamine in these patients, leading to acute encephalopathy characterized by ataxia, dementia, and nystagmus. Maternal death or permanent neurologic abnormality occurred in more than 80% of cases. The recommended thiamine replacement dose is 100 mg to 500 mg parenteral thiamine daily for 3 consecutive days.⁸⁵ Thereafter, the thiamine maintenance dose should be 2 mg to 3 mg daily. IV dextrose should not be administered to pregnant women with hyperemesis without prior thiamine replacement therapy.

Alternative Treatments

Many pregnant women are seeking a variety of complementary and alternative therapies to treat NVP.^{8,86} These therapies include vitamins, botanical dietary supplements, homeopathic remedies, acupuncture, acupressure and acustimulation, hypnotherapy, aromatherapy, meditation, and behavior modification. However, there is a dearth of research literature to support or refute the safety and efficacy of many of these alternative approaches. Given the prevalence of NVP and the potential for adverse effects, more research in this field is needed. Pregnant women who choose to use one or more of these therapies for the treatment of NVP need to be adequately informed about which modalities have been tested in controlled clinical trials and which rely more on anecdotal evidence for their efficacy and safety data. Pregnant women must also disclose their use of these therapies to their primary care provider.

The most extensively studied vitamin-based therapy for NVP is vitamin B₆ (pyridoxine). Two controlled trials have shown the efficacy of administering pyridoxine to treat NVP patients.^{87,88} The two studies revealed a significant decrease in nausea and the number of vomiting episodes, and that most patients with severe nausea reported considerable improvement in their symptoms (from severe to moderate or mild nausea). Pyridoxine is also safe, inexpensive, and available as an over-the-counter product. Hence, pyridoxine is highly recommended for initial therapy of NVP. The mechanism of action of vitamin B₆ is not known and there is no relationship between indicators of its status in pregnant women (eg, blood levels) and NVP symptoms.⁸⁹ In addition, multivitamin supplementation has been shown to be effective in preventing NVP. A randomized clinical trial reported that women who took preconception multivitamins are less likely to experience severe NVP.⁹⁰ Another study also showed that multivitamin supplementation during the first trimester of pregnancy is associated with decreased vomiting.⁹¹ Based on all the

evidence, prophylaxis with multivitamins and therapy with vitamin B₆, with or without doxylamine, are safe and effective therapies for NVP.

The most commonly cited botanical remedies for the treatment of NVP are ginger, chamomile, peppermint, and raspberry leaf.⁹² Among these remedies, only ginger has been studied in well-controlled trials for the treatment of NVP. Two controlled trials used ground ginger capsules, 250 mg 4 times daily, in the treatment of NVP.^{93,94} These trials revealed that ginger significantly reduced nausea and the number of vomiting episodes in NVP patients of the ginger group as compared to the placebo group. Ginger has also been shown to reduce postoperative and motion-induced nausea and vomiting.^{95,96} The data from the NVP studies are somewhat limited, but ginger appears to be an effective alternative treatment for NVP. However, because concerns have been raised in the literature about possible adverse effects of ginger use,^{97,98} ginger should only be recommended as a second-line agent for the treatment of NVP. More research is certainly needed in this area.

One of the best-studied alternative remedies for the treatment of NVP appears to be acupressure over the Neiguan (P6) point.^{8,99} The acupoint P6 (pericardium 6) is located on the inside of the wrist (approximately 3 fingerbreadths above the wrist on the volar surface of the forearm) and is thought in traditional Chinese medicine to relieve nausea and vomiting. Despite the fact that there is no pathophysiologic model acceptable to Western medicine that specifically relates the P6 acupoint on the wrist to nausea and vomiting, studies suggest that stimulation of this particular acupoint is helpful in controlling nausea and vomiting. Of particular interest are studies that examined the efficacy of acupressure (application of pressure) and acustimulation (application of a mild electrical current) wristbands in treating NVP because of their widespread availability and ease of use.⁹⁹ It is clear from these studies that acupressure may afford relief to many NVP patients. The mechanism of action of acupressure and acustimulation is unknown. One possible explanation of the effect is that stimulation of peripheral somatic sites, such as the P6 acupoint, may modulate afferent and efferent neural activity of the stomach, leading to an improvement in NVP symptoms.¹⁰⁰ It is important to point out that there are acupressure/acustimulation and acupuncture points that are contraindicated in pregnancy because of their potential to produce uterine contractions, but these are not near the Neiguan point.⁸ Although results of published trials on P6 acupoint stimulation for the treat-

ment of NVP were largely positive, its efficacy has not been demonstrated. Shortcomings of these trials include small sample size, inadequate blinding of participants and investigators, and lack of adequate control conditions.⁹⁹ However, considering the low cost (< \$10 for a pair of bands) and absence of side effects, acupressure wristbands should be viewed as a widely available and easy to use treatment option that may help pregnant women in managing their NVP symptoms.

Hypnosis,⁶⁹ imagery⁷⁰ and behavior modification⁶⁸ therapies for NVP may offer some possibilities, but further research is needed to distinguish the effects of short-term therapy from those of the natural course of the disease. In addition, the cost and duration of these therapies will most likely limit their usefulness to very severe cases of hyperemesis. With respect to other alternative approaches, such as homeopathy, aromatherapy, and meditation, there is little or no evidence to support or refute their benefits or risks.

CONCLUSIONS

It is unfortunate that the majority of pregnant women who experience NVP do not receive appropriate treatment for this condition. This is largely attributed to a lack of understanding of the pathophysiology of NVP and a misperception of the teratogenic risk of available treatment options. Hence, there is a great need for further research, both on the cause and treatment of NVP. Deciphering the pathophysiological and psychological aspects of NVP will undoubtedly advance the rational approach to therapies. Because pharmaceutical companies are reluctant to invest in these activities for various reasons, many in the medical community believe that much more can and should be done by Congress and the National Institutes of Health to encourage and support research and development of new drugs for the treatment of NVP and other pregnancy-related conditions.

Once other causes of nausea and vomiting are ruled out, dietary approaches may be effective in alleviating the symptoms of NVP for some women. For other NVP patients, vitamin B₆, alone or in combination with doxylamine, is highly recommended. Ginger may be used if vitamin B₆ therapy was not successful. Conventional anti-emetic therapy should be considered when the aforementioned interventions have failed. Only a small percentage of women diagnosed with *hyperemesis gravidarum* may require hospitalization. Most importantly, a great deal of emotional support must be provided to NVP patients by their family members and caregivers.

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