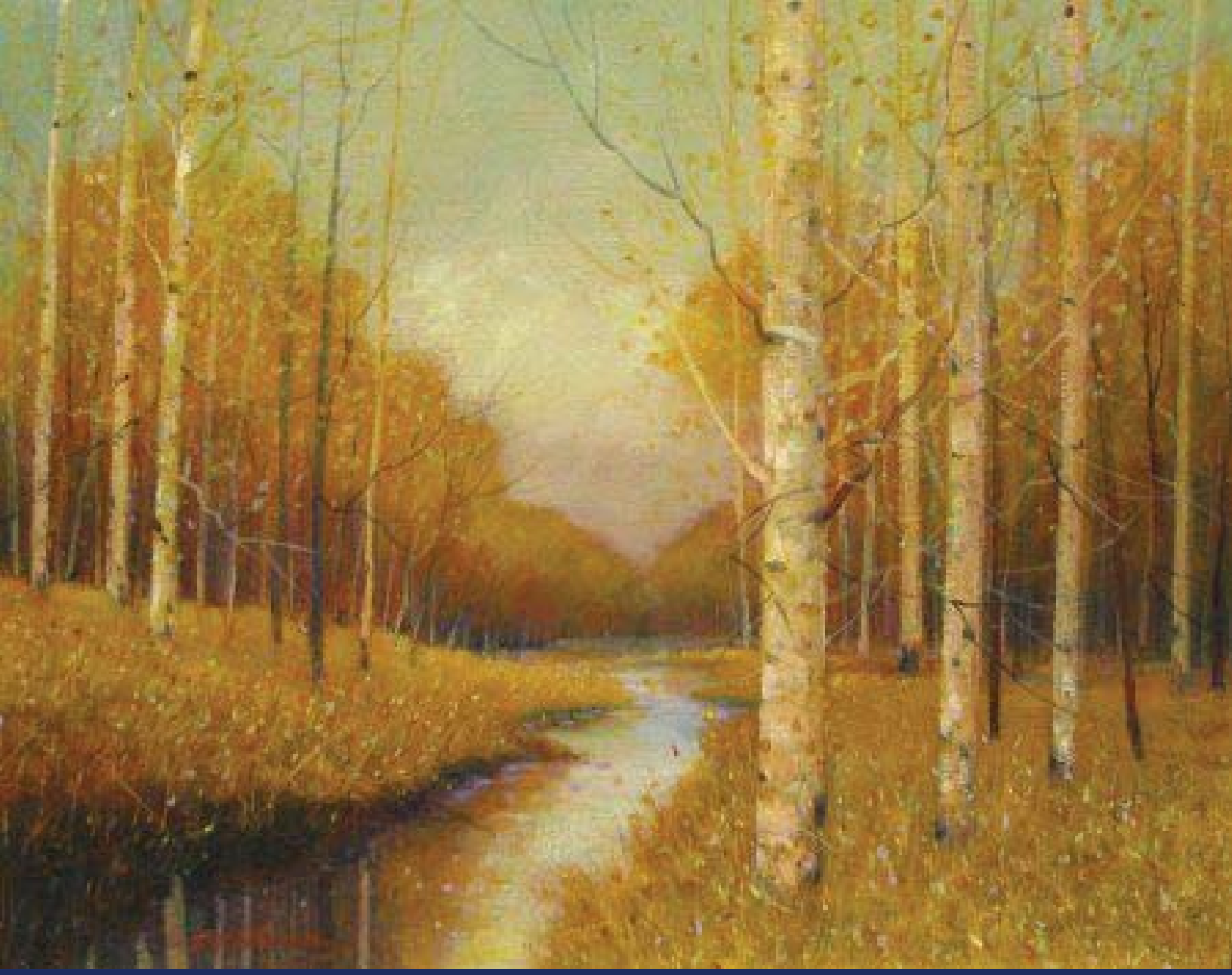

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Nausea and Vomiting *of* Pregnancy

APGO *Continuing Series on Women's Health Education*

APGO EDUCATIONAL SERIES ON WOMEN'S HEALTH ISSUES
NAUSEA AND VOMITING OF PREGNANCY

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Dr. William Herbert, Dr. T. Murphy Goodwin, Ms. Caroline Maltepe, and Dr. Sharon Phelan have each disclosed that they do not have any financial associations/special relationships with proprietary entities/commercial supporters related to the subject matter of this module. Dr. Gideon Koren has disclosed receipt of research grants from Bayer, which produces folic acid, and Duchesnay, which produces drugs used for NVP. He also has consulting agreements with both companies.

Discussion of Off-Label Use
Because this course is meant to educate physicians with what is currently in use as well as what may be available in the future, there may be "off-label" use discussed in the presentation. Speakers have been requested to inform the audience if and when off-label use is being discussed.

Acknowledgment
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This continuing medical education offering is jointly sponsored by the University of Texas Southwestern Medical Center and the Association of Professors of Gynecology and Obstetrics.

Target Audience
Many physicians remain unaware of the potentially serious effects of Nausea and Vomiting of Pregnancy (NVP) on the health and general welfare of a pregnant woman, or on her fetus's health. This teaching module is for use of obstetrician-gynecologist educators in teaching medical students and residents to help them understand the effect of NVP on the outcome of pregnancies, and how to institute appropriate management strategies. It also will serve as a valuable resource for practicing physicians and other healthcare professionals, including nurse practitioners, and physician assistants.

NVP is perhaps the most common ailment of pregnancy, yet one of the least understood. Treatment approaches are often erratic, and women dealing with NVP may feel misunderstood, at a loss for where to turn for help, or both. This teaching module summarizes current knowledge of NVP—including the scope, impact, diagnosis, and treatment—in an effort to help physicians provide optimal care for their patients with this syndrome.

Learning Objectives

Upon completion of this continuing education activity, participants should be able to:

1. Describe the pathophysiology of NVP
2. Diagnose NVP in patients
3. Interpret instances for differential diagnoses (such as food poisoning, gastrointestinal disorders, Helicobacter pylori infection, hepatitis, and eating disorders, among others)
4. Recognize NVP-related complications
5. Explain the history of the medical interpretation of NVP and historical modes of management
6. Explain the various pharmacological and non-pharmacological treatments

Instructions for Obtaining Medical Education Credit

Participation in this continuing medical education activity should be completed in approximately 3 hours. To successfully complete this program and receive credit, participants must follow these steps:

1. Read the learning objectives.
2. Read the article text and tables and review the figures.
3. Complete the registration information on the form included in this monograph.
4. Read, complete, and submit answers to the self-assessment examination and program evaluation questions. Participants must receive a test score of at least 70% to receive a certificate by mail.
5. Mail the enclosed registration, evaluation, and self-assessment examination form and a check for $15 payable to:

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This monograph, with a release date of March 1, 2011, is valid for 3 years. Requests for credit must be received no later than March 1, 2014.

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CONTENTS

FOREWORD

In the course of their pregnancies, many women turn to their healthcare providers seeking relief from nausea and vomiting of pregnancy (NVP). In fact, 70–85% of pregnant women experience this uncomfortable condition in varying intensities and for various lengths of time.[1,147] Symptoms range from mild to severe and—despite the common term *morning sickness*—discomfort can occur morning, noon, or night, and in some cases persist around the clock. Affected women feel the negative impact of NVP on their home life, work life, and general well-being.

The historical record shows that women have suffered from NVP through the ages. Yet, few members of the general public or the medical community understand how NVP, although widespread, affects women's lives. Unfortunately, optimal management and treatment of NVP is often supplanted by a "wait-and-see" approach.

For most women, symptoms of NVP subside after 17 weeks of pregnancy, but some may experience nausea and vomiting throughout their entire pregnancies.[2] About 0.5–2% of pregnant women develop hyperemesis gravidarum (HG), a severe form of NVP that usually requires hospitalization to reverse dehydration, electrolyte imbalances, and nutritional deficiencies.[3,4] Hyperemesis gravidarum can be life-threatening if not treated promptly and can increase the risk of fetal loss and low birth weight. In a very limited number of cases, NVP or HG proves so severe that women choose to terminate otherwise wanted pregnancies.[5] With proper medical attention and support, this unfortunate outcome can be avoided in almost all cases.

A Silent Syndrome

Despite the pervasiveness and potential severity of the problem, NVP has received limited attention from the medical community. Little contemporary research has been conducted to pinpoint its etiology, characteristics, complications, and management.[6] Often cast as a "necessary evil" of pregnancy, the condition is frequently regarded as something a woman must simply cope with—and indeed many do, when possible. However, many women with NVP require treatment to help them function in their daily lives and maintain a healthy pregnancy.

Physicians are often confounded by how to best help patients with NVP. There is no uniform management strategy for treatment; patients and physicians often fear the use of pharmacologic therapies during pregnancy, and the efficacy of non-pharmacological approaches varies widely from patient to patient. The result is often trial-and-error NVP management. Yet managing NVP by using evidence-based guidelines can dramatically improve an affected woman's quality of life, reduce the risk of maternal and fetal complications, and cut healthcare costs.

A Long History

Historical accounts of NVP date back to times when scholars recorded their thoughts on papyrus. The first elaborate description of severe NVP appears in the writings of Soranus in the 1st to 2nd century AD,[7] and there is little doubt that NVP existed well before a written history was established. However, perceptions about the etiology of NVP have varied greatly over the years, as have approaches to treatment.

Some of the oldest theories attribute NVP to psychological or behavioral factors.[8] Women complaining of nausea or experiencing vomiting during pregnancy have, at various points in history, been assumed to be rejecting their pregnancies; rejecting their femininity; troubled by an unplanned pregnancy; too dependent on their mothers;[9] or repulsed by the sexual approaches of their partners.[10] In 1920, Lucille Dooley hypothesized that the renowned writer Charlotte Bronte died due to HG in the fourth month of her first pregnancy.[11] In Dooley's psychoanalytic evaluation of the events surrounding Bronte's death, she stated that "pernicious vomiting always has…psychogenic features" and concluded that Bronte was "fearful, conflicted and reluctant to accept her future marriage and childbearing."[11] As recently as 1972, Rhodes reattributed Bronte's death to HG, but maintained the psychoanalytic thread in his analysis, stating that "hyperemesis gravidarum only seems to be excessive in those who display neuroticism."[11] This is a case of hyperemesis that killed.

In a departure from the neurosis-based theories that prevailed until the mid-20th century, some members of the medical community believed that NVP was caused by reproductive tract abnormalities such as endometriosis, deep cervical tears, or incarcerated retroflexed uteruses, which were then manipulated into the "normal" position to relieve the NVP.[12]

Some more recent studies have tried to substantiate early claims, as well as investigate other possible psychological root factors such as eating disorders.[13] Other lines of investigation have questioned whether NVP is a Darwinian response, essentially protecting pregnant women from ingesting potentially harmful substances during a time when the fetus is especially vulnerable to teratogens.[14] Still others have investigated more organic etiologies for the syndrome, as described in the pages ahead.

Traditionally, mild to moderate NVP was treated by managing a patient's food intake and controlling her environment to any degree possible to minimize her symptoms. However, in 1956 the drug Bendectin® (a formulation of pyridoxine, the antihistamine doxylamine, and the anticholinergic dicyclomine) was introduced to treat NVP. In 1976, the formulation of

Bendectin® was modified to include only pyridoxine and doxylamine. Bendectin® was the first pharmaceutical option designated specifically for controlling symptoms of NVP, although use of a number of other drugs had previously been described for the treatment of the syndrome. Bendectin® was used in approximately 33 million pregnancies before the manufacturer voluntarily withdrew it from the market in 1983, due to claims of teratogenicity and pursuant lawsuits.[15] Despite the fact that scientific evidence supports its safety, Bendectin® remains unavailable to date.[15] A combination of pyridoxine 10 mg and doxylamine 10 mg is currently marketed in Canada under the trade name Diclectin®, and various formulations of these two agents are available in other countries (such as South Africa, Spain, India, Taiwan, and Vietnam).[16,17] However, as of this writing, none of these combination products are available in the United States (US). In the US, doxylamine is available over-the-counter (OTC) as the active ingredient in Unisom® Sleep Tabs™, and various formulations of vitamin B_6 (pyridoxine) are available as well.

Indeed, patients with NVP may eschew drug therapies that could alleviate or eradicate symptoms, due to fear of teratogenicity. However, women should be reassured as to the safety and benefits of certain medications during pregnancy. For example, due to the special risks posed by the H1N1 virus to pregnant women, the Centers for Disease Control's Advisory Committee on Immunization Practices designated those patients among the top priority groups to receive the H1N1 vaccine.[18] Yet, despite the urgent threat the H1N1 flu presented to pregnant women, many still forwent the vaccination or failed to take antiviral drugs out of fear of harming the fetus.[19]

Given the further reluctance of manufacturers to pursue the development of agents to treat NVP from a medicolegal standpoint, and the perceived risk of teratogenicity from the viewpoint of many patients and physicians, few pharmacologic alternatives for NVP have emerged. Alternative therapies including herbal remedies and acupressure have been investigated as the medical community attempts to find new strategies to help patients cope with NVP.

Although studies testing the safety of medication use during pregnancy are somewhat limited, a broad multicenter research effort to study drug therapy effects on mothers and their babies is currently underway (Medication Exposure in Pregnancy Risk Evaluation Program [MEPREP]) and will guide future regulatory policy and influence medical practice on NVP-related and other medication use during pregnancy.[20]

Helping Physicians Manage NVP

NVP is perhaps the most common ailment of pregnancy, yet one of the least understood. Treatment approaches are often erratic, and women dealing with NVP may feel misunderstood, at a loss for where to turn for help, or both. This teaching module summarizes current knowledge of NVP—including the scope, impact, diagnosis, and treatment—in an effort to help physicians provide optimal care for their patients with this syndrome.

SUMMARY OF CONTENTS

Nausea and vomiting of pregnancy (NVP) affects between 70 and 85% of pregnant women. The severity of NVP ranges from mild or moderate to severe, and can occur at any time of the day and last for varying lengths of time. NVP is best classified according to its impact on the life of the pregnant woman: mild (minimal effect on family life or employment); moderate (interferes with family life or employment and may require intravenous [IV] hydration); or severe (interferes with family life or employment, may require hospitalization or IV hydration). Although several theories have been proposed, the etiology of NVP has yet to be clearly defined. The leading candidates for the fundamental stimulus for NVP are human chorionic gonadotropin (hCG) or one of its isoforms, and estradiol. Additionally, women with nausea and vomiting (NV) after estrogen exposure, a history of motion sickness, or acute taste sensations are all more likely to experience NVP than other women. Perhaps the oldest theory about the etiology of NVP—and especially HG—is that it arises due to underlying psychological problems. More recent studies have not identified any psychological traits persisting beyond pregnancy that predispose the mother to NVP, although some traits may contribute to the severity of the NVP.[21,22]

Usually, persistent nausea and vomiting during pregnancy are caused by NVP. However, other conditions can cause nausea and vomiting as well, and failure to detect these other causes can result in serious complications for a pregnant woman and need to be considered. It is also important to note whether the patient has a history of preexisting conditions associated with NVP (e.g., migraines, porphyria, cholelithiasis, and gastroparesis). A number of physical findings can also point to other conditions. Elevations of liver enzymes, bilirubin, and amylase all present to some degree with severe NVP, and may confuse the diagnostic picture in such cases. Ultrasonography may identify a predisposing factor such as multiple gestation or molar gestation.

The presence of NVP symptoms can have a profound effect on women's daily lives—infringing upon household activities and paid work, straining family relationships, and altering social plans. This level of impact occurs in 30–40% of pregnancies. Although mild to moderate NVP has generally not been shown to have any adverse effect on the fetus, more severe vomiting can have a significant adverse effect on birth weight.

It is important for clinicians to realize that pregnant women who complain about nausea, vomiting, and/or retching during pregnancy are asking for help. They may be worried about how NVP may affect their unborn child, as well as their quality of life. They are seeking relief from the relentless feeling of being sick. While there is no uniform strategy for the management of NVP, physicians can offer many solutions to help women cope.

Early treatment of NVP can prevent the escalation of symptoms and hospitalization. If NVP symptoms are beginning to influence the daily functioning of the affected woman some form of management should be initiated. Since the characteristics and impact of NVP vary among women, treatment must be tailored to the individual. All women should be counseled on dietary and lifestyle changes as well as non-pharmacological and pharmacological treatments. One recent study—the first to report the effects of NVP on actual food and nutrient intakes over the course of pregnancy—established that NVP is in fact associated with women's dietary habits in early pregnancy. Lowered intakes of certain foods result in lowered intakes of certain nutrients, and such dietary alterations may affect the growth and development of the fetus, with possible long-term influences in later life.[23]

When management of NVP using dietary and lifestyle measures and non-pharmacological approaches is inadequate, pharmacological intervention is warranted. Managing a patient with intractable vomiting or excessive weight loss is more complicated and usually requires urgent medical care due to dehydration and malnutrition.

SCOPE: CLASSIFICATION, CLINICAL COURSE, AND ETIOLOGY

Classification

NVP has traditionally been classified as mild (nausea; may not include retching and/or vomiting); moderate (nausea; with or without retching and/or vomiting); or severe (persistent vomiting leading to dehydration).[11] Whether mild, moderate, or severe, women can experience nausea with or without vomiting and/or retching. Retching can be as debilitating and stressful to women as vomiting.[24,25] This classification is inadequate to characterize the full effect of the condition on the pregnant woman. Most women describe nausea as more bothersome than vomiting per se.[22] A study by Lacroix et al concluded that NVP is comparable in severity to the nausea and vomiting associated with cancer chemotherapy of moderately emetic potential.[26] In approximately 40% of women, the severity of NVP is sufficient to interfere with the woman's family life, social interactions, and employment. Whether symptoms are mild, moderate, or severe, they can have a negative effect on the pregnant woman's quality of life.

As outlined above, NVP is best classified according to its impact on the life of the pregnant woman: mild (minimal effect on family life or employment), moderate (interferes with family life or employment and may require hospitalization or IV hydration), or severe (interferes with family life or employment and may require hospitalization or IV hydration).[27,28,29] A study investigating weekly cost of NVP showed that even mild symptoms were associated with costs to society, the patients, and the healthcare system.[30]

Overall, approximately 70–85% of pregnant women experience this uncomfortable condition in varying intensities and for various lengths of time.[1] The most severe form of NVP is commonly referred to as hyperemesis gravidarum (HG) and is characterized by persistent vomiting, weight loss exceeding 5% of pre-pregnancy weight, and ketonuria.[3] This occurs in approximately 0.5–2% of pregnancies.[3,4]

Clinical Course

The symptoms of NVP may vary among women from a slight feeling of nausea in the morning to more severe nausea and vomiting and/or retching that continue throughout the day.[31] Although published reports vary slightly with regard to onset and cessation of NVP, trends appear to be consistent across studies. NVP will usually begin between 4 and 9 weeks' gestation.[4,32,33]

The severity and frequency of symptoms generally peak between 7 and 12 weeks and then begin to subside.[34,35] Symptoms of NVP cease by 10 weeks in 30% of women; by 12 weeks in 30%; and by 16 weeks in another 30%.[34] Symptoms persist beyond 16 weeks in approximately 10–15% of women with NVP, but only a small proportion of women experience symptoms beyond 20 weeks or for the duration of the pregnancy.[3] For nearly 40% of women, symptoms appear to stop suddenly, rather than gradually taper over a period of weeks.[34] Symptoms generally cease at approximately the same time (e.g., 10–16 weeks), regardless of their timing of onset or severity.[34]

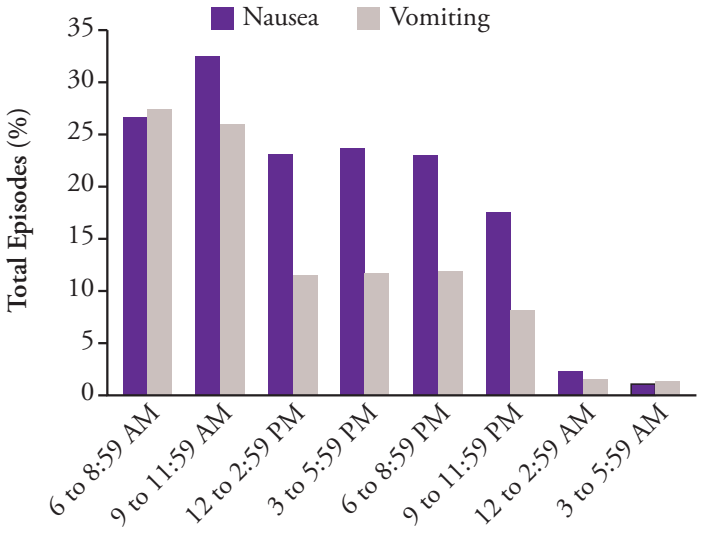
Because symptoms of NVP may persist beyond the first trimester of pregnancy, it is important for healthcare providers to explain this possibility to women to prevent disappointment if symptoms do persist. Moreover, when NVP persists into the second and third trimesters, the intensity remains fairly stable and generally does not lessen.[22] However, if symptoms do increase, then the differential diagnosis should be explored. Some reports indicate that more severe NVP is associated with a longer duration.[31]

Although NVP has historically been referred to as *morning sickness*, few women (<2%) experience symptoms solely in the morning.[22] The vast majority of women (80%) experience NVP throughout the day,[22] although symptoms do tend to occur more frequently during the period from

6:00 AM to noon (Figure 1).[34] The exact timing and pattern of NVP vary from woman to woman and from pregnancy to pregnancy.

NVP, particularly more severe forms, may be associated with reversible laboratory changes. When these changes occur, there is a need to determine if they are secondary to the NVP or if they represent a different etiology such as hepatitis or pancreatitis. These include biochemical hyperthyroidism; elevations of serum liver enzyme, bilirubin, amylase, and lipase levels up to about five times normal; hypokalemia; and hypochloremic metabolic alkalosis (or, with profound dehydration, acidosis) may be noted as well.[36]

Figure 1: Frequency of NVP by Time of Day*



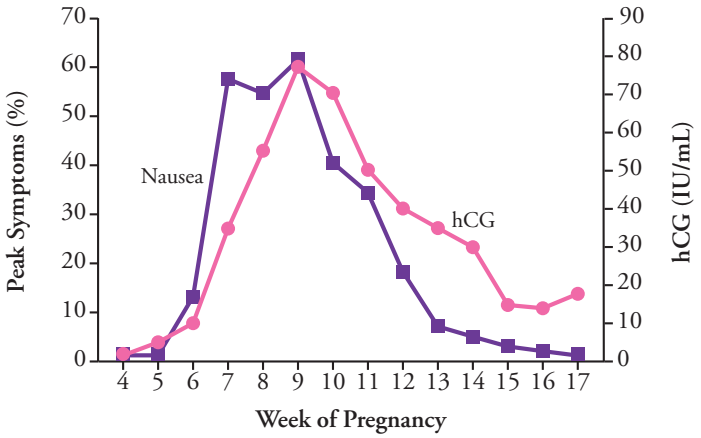
*Adapted from Gadsby et al, 1993[34]

Etiology

Although several theories have been proposed, the etiology of NVP has yet to be clearly defined. NVP is best conceived of as a syndrome in which a product or products of the placenta directly stimulate the vomiting center and lower the threshold for vomiting by the classic pathways (e.g., vestibular, gastrointestinal, or via the area postrema). The leading candidates for the fundamental stimulus for NVP are hCG (or one of its isoforms) and estradiol. The principal reason for considering hCG initially was the close temporal association between peak hCG concentrations and peak NVP symptoms (Figure 2). In the last 30 years, more than 20 studies have presented new data on a wide range of non-thyroid hormones and NVP. Only investigations of hCG or estradiol have shown any association with NVP. The failure of some studies to show an association of NVP with hCG may be due to the varying biologic activity of different hCG isoforms.

Also supporting a role for hCG, virtually all of the many studies of thyroid hormones in pregnancy have demonstrated an association between biochemical hyperthyroidism and NVP. There is little doubt that hCG is the thyroid stimulator

Figure 2: Association Between Peak Symptoms of NVP and hCG Levels*



*Adapted from Gadsby et al, 1993[34], and Danzer et al, 1980[37]

of pregnancy,[38] and given that hyperthyroidism itself is rarely a cause of nausea and vomiting (NV), this finding has focused attention on hCG. Structurally, hCG is related to TSH, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The major difference between these hormones is that hCG contains a carboxy terminal portion (β-CTP) not shared by the others. Isoforms of hCG lacking the β-CTP are structurally more similar to TSH and are more thyrotropic than the intact hCG molecule.[38] Hyperglycosylated forms of hCG, on the other hand, have longer half-lives and greater bioactivity.[39] In addition to stimulating the thyroid gland, these hCG isoforms could stimulate the production of sex steroids by the maternal and, possibly, the fetal gonad.[3] Jordan et al demonstrated the relationship between various hCG isoforms, estradiol and thyroxine production, and severity of NVP.[39] It is not known how hCG itself causes NV, although it may act by changing osmolarity and vasopressin levels.[40,41] While elevated vasopressin levels have been linked to nausea and gastric dysrhythmias, the pathophysiology of acute and chronic nausea in specific clinical settings needs further clarification in order to better control the symptoms of NVP.[42]

The hCG stimulus is modified by placental conditions that may increase or decrease the concentration of these hormones (e.g., multiple gestation, molar gestation) and by hormone-receptor interactions modifying the effect of the hormone. An example of this is familial HG associated with a mutation in the TSH receptor rendering it supersensitive to hCG.[43] The effect of this stimulus on NV pathways is modified by background variation in vestibular, gastrointestinal, olfactory, and behavioral function. Women with a history of motion sickness, for example, are much more likely to experience NVP than those without such history.[44] Taste, which is closely linked to olfaction, is genetically controlled, and so called "supertasters" are more likely to experience NVP than those who are less sensitive to bitter-taste perception.[45] Nausea during the first trimester isassociated with gastric slow-wave dysrhythmias that

correlate closely with symptoms.[46] Nausea and vomiting in some women may be worsened by susceptibility to behavioral cues—this phenomenon is similar to anticipatory NV associated with chemotherapy.[47]

Estrogens in the combined birth control pill have been shown to induce nausea and vomiting in a dose-related fashion,[48] and the numerous reports of variation in post-operative NV by menstrual cycle phase are best explained by an estrogen effect. Another study has demonstrated a relationship between the menstrual cycle and the susceptibility of a woman to nausea and motion sickness.[49] Women with NV after estrogen exposure are much more likely to experience NVP than other women. The effect of the primary placental stimulus, modified as it acts through the common central nervous system pathways, creates the initial clinical manifestation of the condition. This primary manifestation is modified further by the patient's individual response to chronic suffering and the degree of support from caregivers and family. A number of reversible responses to subacute disease states have been described in NVP, including depression, somatization, and hypochondriasis.[50] Poor support by the partner is noted by 85% of women who called a hotline for NVP.[22]

Psychological factors

Perhaps the oldest theory about the etiology of NVP—and especially hyperemesis gravidarum—is that it arises due to underlying psychological problems.[8] Psychological theories can be sub-categorized in three ways:[3]

1. psychoanalytic theories describing NVP as a conversion or somatization disorder

2. inability of the mother to respond to excessive life stressors

3. heightened susceptibility of the mother to certain sensations, resulting in vomiting as a conditioned response

A widely quoted study from 1968 described psychiatric interviews of 44 women with HG.[7] These interviews led to an enduring viewpoint that women with HG have an infantile personality with hysteria and excessive dependence on their mothers.[7] More recent studies have not identified any psychological traits persisting beyond pregnancy that predispose the mother to NVP.[50] Vomiting as a conditioned response may contribute to NVP just as it does to chemotherapy-induced vomiting, but this does not imply a psychological or behavioral disorder of the mother as a basis for the NVP. However, the presence of preexisting depression or anxiety disorders may increase the severity of the nausea and vomiting associated with pregnancy.[21] The quality of social support offered by the woman's spouse/partner and family, as well as the pressure of social roles and responsibilities, can negatively impact both physical and mental symptoms of NVP, as has been well-summarized by Munch et al.[51] The problem of caregivers and family members attributing NVP to psychological disease has also been observed by Mazzotta et al.[5]

Miscellaneous factors

Other factors have been evaluated in the etiology of NVP, including liver abnormalities, elevated cytokine levels, theories regarding fetal protection from teratogens, Helicobacter pylori infection, and vitamin deficiency (such as B_6, thiamin, and vitamin K). Liver abnormalities are associated with HG[8] but hepatic metabolism is not affected, making it unlikely that liver dysfunction is central to NVP. Elevated cytokine levels, especially the interleukins, have also been suggested in the development of NVP. Nausea and vomiting are possible side effects of interleukin-2 (IL-2) immunotherapy, and IL-2 levels may be elevated in some pregnant women. Fatigue, another symptom associated with early pregnancy, is also associated with increased levels of interleukins. Studies have not, however, found consistent differences in cytokine levels between women with NVP and non-pregnant controls.[52]

Recently, there has been interest in the concept that NVP is a mechanism of fetal protection from teratogenic phytochemicals. Proponents of this theory argue that in the majority of cases, NVP does not fit the definition of disease. Rather, NVP is seen as a mechanism that evolved to serve a vital, protective function. In this view, NVP is most appropriately considered and treated as an adaptation. A comprehensive statement of this position is published.[14] Some problems with this theory include an incomplete understanding of environmental teratogenesis and a controversial interpretation of cause and effect in the data showing better outcomes in pregnancies characterized by NVP. The fundamental critique of this theory for the purposes of the practicing clinician, however, is that the extent to which the adaptive process functions for the woman's benefit at this point in the course of evolution is unclear. Misplaced emphasis on certain aspects of this theory could deter clinicians from addressing clinically significant NVP.

H. pylori is a common bacterial infection found in up to 40% of the population in developed countries and in upwards of 70% of the population in developing countries.[53] Well-documented risk factors for HG, such as age, smoking, and ethnicity, are also associated with H. pylori infection. Over the last decade, studies have suggested an association between H. pylori infection and HG and/or severe NVP, and the bacterium has been recognized as part of the etiology of HG.[54] A systematic review published in 2009 showed an association between H. pylori and hyperemesis gravidarum. Other studies corroborated the association between H. pylori and HG.[55,56,57] However, it is not clear that treatment of the H. pylori will directly result in

improvement of the NVP.[33] Screening for Helicobacter pylori infection either by blood or breath test may be considered for women who have a previous pregnancy with HG, or are currently pregnant and experiencing moderate to severe NVP.

At each step along the pathway leading to the final clinical phenotype of NVP, genetically controlled factors modify the sequence. In addition to examples previously discussed, evidence for genetic influences in NVP include familial recurrence,[58,59] monozygotic twin pair correlation,[60] and reported population variation in NVP worldwide.[14]

Another approach to the genetic effect is through examination of the relationship between NVP and different partners in the same women. Einarson et al demonstrated that changes in partners did not affect the severity of NVP, and the severity of NVP experienced by these women remained stable and predictable.[61] 80–85% of women who have experienced severe NVP in a previous pregnancy have recurrent symptoms with each subsequent pregnancy.[62,63]

IMPACT: ON THE PATIENT, FAMILY, AND FETUS

How NVP Affects the Pregnant Woman

Mild to severe nausea and/or retching with or without vomiting during the first trimester of pregnancy is normal, with variations in the severity, combination of symptoms, and general impact on the affected woman's quality of life.[11,34,63,64,65,66,67,143] For some women, the onset of NVP is perceived as verification of their pregnancy—for those eagerly awaiting this state, it is an explicit and welcome sign.

Despite the commonly used term *morning sickness*, most women with NVP experience nausea and /or retching, with or without vomiting, throughout the day.[22,34,64,67] Some studies have shown that younger women are at increased risk of NVP and may have more severe symptoms.[63,68,69,70] Depue et al reported that women over the age of 35 had half the risk of HG compared with women under 20.[68] Järnfelt-Samsioe et al found no relationship between maternal age and NVP, yet the mean age in their patient population was 33 years (range, 23–45).[67] Approximately 70–85% of all pregnant women experience some form of NVP,[1] and surveys have shown that approximately 55% of pregnant women have *daily* episodes of vomiting.[30] Furthermore, approximately 15% of those affected experience nausea—and 5% experience vomiting—extending into the second and even third trimesters.[22,34]

Many pregnant women experience food cravings and aversions, as well as aversions to odors.[64,69,70,71] Exposure to odors perceived as unpleasant is often reported to induce episodes of nausea, retching, and/or vomiting. Nausea and vomiting coupled with food aversions may result in dehydration and thirst.[64] Increased salivation (ptyalism), which may itself cause vomiting, has also been reported in pregnant women.[64,72] Also, pregnant women develop a bitter, metallic, or sour taste in their mouth, which may prevent them from drinking fluids and may result in dehydration.[70]

Hyperemesis gravidarum, which occurs in approximately 0.5–2% of pregnancies, is epitomized by intractable vomiting and can result in dehydration and malnutrition.[3] Severe NVP can progress to a life-threatening problem requiring immediate therapy; hospitalization is often required for optimal management of fluid, electrolyte, and acid-base imbalances. Depending on the clinical course of NVP and the patient's nutritional status, aggressive nutrition support may be indicated. Severe NVP can lead to nutritional deficiencies—for example, a severe episode of epistaxis secondary to acute vitamin K deficiency[73] or the possibility of Wernicke's encephalopathy due to thiamin (vitamin B_1) deficiency.[74] In this day and age, HG rarely causes death; however, left untreated, the effects can include maternal neurologic, renal, retinal, and hepatic damage, similar to changes observed in starvation.[75]

One might expect that NVP in its moderate to severe forms would affect maternal weight gain. Indeed, weight gain in patients with vomiting is reduced in the early weeks of pregnancy; however, by the end of the pregnancy, total weight gain is similar to women with no NVP or nausea only.[63,66,85] This may not be true in cases where nutritional status was inadequate prior to pregnancy or in women with HG, particularly if the patient's clinical course included multiple hospital admissions.[68,76,77]

Impact on Work Life

Nausea and vomiting in pregnancy can have a profound impact on the daily lives of affected women. Studies show that both household activities and paid work are affected. In telephone interviews of 1,444 women (42% from the US and 58% from Canada), 578 women (40%) reported losing anywhere from 174–294 hours of work outside the home because of NVP.[78] In their British private practice cohort, Gadsby et al reported 73 women (35%) having lost time from work due to NVP, with an average of 62 hours of employed work and 32 hours of housework lost per affected woman.[34] A Norwegian study found that 43% of total societal costs related to pregnancy were for sick leave.[76] Along with actual hours lost from paid employment, impaired work ability, including decreased attention, reduced efficiency, and communication difficulties have also been reported by women with NVP.[71] Piwko et al established the total cost (both direct and indirect) of NVP per woman-week with mild symptoms at $132; $355 with moderate; and $653 with severe.[30]

In addition, a widely-cited 1992 study found that 82% (120/147) of women with NVP reported that their usual activities were affected, with 34% of those affected (41/120) reporting that the severity of symptoms resulted in alterations of their daily schedule.[71] Alterations in daily activities due to symptoms of NVP were reported by 12% of Swedish women surveyed in a similar study.[67] Women in these studies cited a variety of reasons for alterations in usual activities, including: a change in usual role from being a support person to becoming the one who needed support; embarrassment resulting from the need to excuse oneself in order to be sick; and cancellation or disruption of social plans. In a 2-month interview-based study by Mazzotta et al, 1.5% (17/1,100) of women terminated their pregnancies due to severe NVP.[5] These 17 women reported losing a total of 20 ± 21 days of work because of NVP symptoms.

Impact on the Family

With up to 80% of women experiencing some degree of nausea, retching, and vomiting during their pregnancy, these symptoms impact the affected woman, as well as those around her. Often, the symptoms of NVP are not understood as a normal part of pregnancy—either by the pregnant women herself, colleagues and superiors at work, or her spouse/partner and family. Expressions of irritability, lowered mood, tearfulness, anxiety, and sleep disorders can affect the daily life of the pregnant woman and her family.[5,11] These emotional expressions, in addition to the symptoms of NVP, may isolate the pregnant woman, resulting in strained family relationships as personal and social dynamics change. Male partners have no personal reference point regarding this symptomatology; therefore many believe that NVP is primarily a psychosomatic and emotional disorder. On the other hand, some women report a positive effect of NVP, wherein husbands have been more supportive and caring than usual.[71]

In an evaluation of the prevalence of psychosocial morbidity among women with NVP, Mazzota et al found that women with moderate to severe nausea were significantly more irritable, had more sleep disturbances, and were more fatigued than women with mild or no nausea.[22] Feelings of depression were reported as occurring "always/most of the time" by more than 20% of women with mild NVP, more than 20% of women with moderate NVP, and more than 50% of women with severe NVP in a telephone survey of 3,201 women in the US and Canada.[22] The physical and emotional impact of NVP often results in general feelings of anxiety and worry about the effect of the symptoms on the fetus. The physical problems of coping with NVP can lead to emotional problems, which can in turn exacerbate the physical problems.[22] However, the impact on the overall quality of life of the affected woman may already be present before more severe physical symptoms appear.[34] Women with NVP may require assistance with usual daily activities, such as housework, caring for children, and food preparation. Cooking and shopping for food may be difficult for women with NVP due to food and odor aversions.[71] Women with more flexible work schedules may be able to cope with their symptoms more easily by taking time off, resting, lying down, or going outside when nausea and/or vomiting is particularly troublesome. As the disorder is generally self-limiting, the symptoms of NVP usually decrease or stop altogether by the second and third trimesters.

In the case of a woman with HG, there exists the possibility of hospitalization. Costs associated with HG in 1999 were an average of $5,900 per patient.[79] The hospitalization itself (along with the potential cost of hospital care and time lost from paid employment) may put physical, psychological, and financial stress on the family—particularly if the woman is the sole caregiver or the health and survival of the woman and/or fetus are in question.

How NVP Affects Pregnancy Outcome

Fetal gender and birth weight

NVP and hyperemesis in particular are more common in women carrying a female fetus. James reviewed 10 prior studies[80] and several more have been published since, which all come to the same conclusion.[81] The higher levels of hCG and estradiol in pregnancies with a female fetus suggest an etiological relationship.

Overall, there does not seem to be an adverse effect on birth weight due to NVP.[63,80] However, controlling for gestational age, more severe vomiting has been associated with significantly lower birth weights.[77,79,82] In teenage mothers with inadequate weight gain during pregnancy coupled with continued NVP (mild or severe; may or may not include retching and/or vomiting), Behrman et al reported a significantly lower birth weight for their infants.[77] A more recent study indicated that women with NVP had shorter pregnancies as compared to those without, but neither pregnancy weight gain nor infants' weight or length differed.[23]

Birth defects

Boneva et al, using data from a population-based case-control study of infants born between 1968 and 1980, investigated the risk for congenital heart defects (CHD) in infants of women with various levels of nausea in pregnancy.[83] They found that there was a significantly lower risk of CHD in mothers with the highest severity of nausea (i.e., early onset, high frequency, and long duration). Recent Swedish registry data (1995–1997) of 5,266 women who reported taking antinauseant/antiemetic agents (promethazine or meclizine) during their first trimester shows an association with higher rates of female and twin births, but no increase in the rates of low birth weight infants, shorter gestation, or congenital malformations.[84] Furthermore, women with HG had an increased rate of low birth weight

and short gestation, whereas the use of medications for NVP was associated with a decreased rate of low birth weight and increased length of gestation. In a comparison between six women with HG and a control group of three women who had never vomited, Depue et al found an increased risk (odds ratio [OR] 4) of central nervous system and related skeletal malformations in the infants of mothers with HG.[68] The authors investigated whether this increased risk of malformations could have been due to the treatment for HG rather than the condition itself, and found that only two of the nine women had received any drug treatment; the drugs used (meclizine and prochlorperazine) are commonly used to treat NV. Källén's registry study of patients with HG showed a slight increase in congenital hip dysplasia (P=0.05) and Down's syndrome ($0.01<P<0.05$).[84]

Miscarriages

Numerous studies have shown a positive outcome in women with NVP, who experience statistically fewer miscarriages or stillbirths than women without NVP.[63,68] A meta-analysis by Weigel and Weigel gives a common odds ratio of 0.36 (95% confidence interval [CI] 0.32–0.42) for the decreased risk of miscarriage with NVP within the first 20 weeks of gestation.[85] The authors further comment that this reduced risk "is apparently not restricted by cultural, genetic, or environmental variability."

Therapeutic abortions

The most dramatic negative outcome of a pregnancy with regard to NVP is therapeutic abortion. Cases of therapeutic abortion in women with severe HG have been reported.[5,86] A significant proportion of North American women participating in a two-month interview-based study by Mazzotta et al thought it likely that NVP might harm the fetus and reported considering termination of their pregnancy due to the severity of NVP symptoms.[5] In fact, Mazzotta et al found that 1.5% (17/1,100) of women terminated their pregnancies because of severe NVP.[5]

DIFFERENTIAL DIAGNOSIS

The diagnosis of NVP is clinical in nature, based on its typical presentation and the absence of other diseases that could explain the symptoms.[90,144] Although other causes of persistent nausea, retching, and/or vomiting are rarely encountered, failure to distinguish them from NVP can result in serious complications. The differential diagnosis of the patient with suspected NVP includes the conditions listed in Table 1.

History and Physical Findings

Several points in the history are helpful in distinguishing NVP from other causes of NV in pregnancy. NVP begins before 10 weeks' gestation.[34,144] Symptoms that present *after* 10 weeks' gestation are commonly due to other causes. As noted previously, it is important to determine whether the patient has a history of preexisting conditions associated with NV.

A number of physical findings point to conditions other than NVP as the cause of nausea and vomiting. Abdominal pain is not a prominent feature of NVP; abdominal tenderness, other than epigastric discomfort secondary to prolonged retching, is not seen with NVP. Pain that precedes or is out of proportion to the NV suggests an intra-abdominal or retroperitoneal cause for the vomiting. Fever is not present in NVP, but is characteristic of many other diseases associated with nausea and vomiting. Headache is not characteristic of NVP. An abnormal neurologic examination suggests a primary neurologic disorder as the cause of the nausea and vomiting, although it may rarely be encountered as a consequence of severe NVP (e.g., thiamin-deficient encephalopathy or central pontine myelinolysis). Although biochemical hyperthyroidism may be seen with moderate and severe NVP, a goiter is not found. If a goiter is present, primary thyroid disease should be suspected.

Laboratory Values

Common laboratory abnormalities in severe NVP that may confuse the diagnostic picture include elevations of liver enzymes (<300 U/L), serum bilirubin (<4 mg/dL), and serum amylase levels (up to 5 times greater than normal level).[36,87] When primary hepatitis causes NV, the liver enzyme elevations are much higher, often in the thousands, and the bilirubin concentration is usually much higher as well. Acute pancreatitis may cause vomiting and hyperamylasemia, but serum amylase concentrations are usually 5 to 10 times higher than the elevations associated with NVP. TSH is commonly suppressed in NVP. Because there is an inverse relationship between the severity of NVP and the TSH concentration,[88,89] a non-suppressed TSH level suggests that the cause of the nausea and vomiting is something other than NVP. A TSH level greater than 2.5 μU/mL is rare with severe NVP, unless the patient has preexisting hypothyroidism.

Other Diagnostic Tests

An ultrasound evaluation should be performed in cases of severe presumed NVP as it may identify a predisposing factor such as multiple gestation or molar gestation.

If the differential diagnosis rules out other likely causes of NV, and the patient has no known preexisting conditions for NV that began before 10 weeks' gestation, then NVP is the likely diagnosis for her symptoms.

Table 1. Differential Diagnosis of NVP*

Gastrointestinal
- Gastroenteritis
- Gastroparesis
- Achalasia
- Biliary tract disease
- Hepatitis
- Intestinal obstruction
- Peptic ulcer disease
- Helicobacter pylori
- Pancreatitis
- Appendicitis

Genitourinary Tract
- Pyelonephritis
- Uremia
- Ovarian torsion
- Kidney stones
- Degenerating uterine leiomyoma

Metabolic
- Diabetic ketoacidosis
- Porphyria
- Addison's disease
- Hyperthyroidism/hypothyroidism

Neurologic Disorders
- Pseudotumor cerebri
- Vestibular lesions
- Migraine headaches
- Tumors of the central nervous system

Miscellaneous
- Drug toxicity or intolerance
- Psychologic and psychiatric disorders
- Infections

Pregnancy-related Condition
- Acute fatty liver of pregnancy
- Preeclampsia

*Adapted from Goodwin, 1998[3], and Koch, 2003[90]

MANAGING NAUSEA AND VOMITING OF PREGNANCY AND HYPEREMESIS GRAVIDARUM

Assessing the Risk

The characteristics and impact of NVP vary among women; therefore treatment modalities must be tailored to the individual. Both the physician and patient should understand that NVP is common during pregnancy (approximately 70–85% of women experience some form of NVP), and that in the majority of women: 1) NVP is transient, 2) it peaks by 7–12 weeks' gestation, 3) it usually subsides after the first trimester (12–16 weeks), and 4) it can often be managed by lifestyle and dietary alterations. Patients should be questioned early in their pregnancy about symptoms of nausea and vomiting and their severity, and advised to start implementing dietary and lifestyle changes and possibly, non-pharmacological or pharmacological approaches. They should also be questioned about their quality of life, family relationships, and symptoms of depression as these domains can be affected by NVP (see Impact). If these symptoms are beginning to impact the daily functioning of the affected woman, some form of management should be initiated in order that worsening of symptoms or progression to HG does not occur. The spouse/partner of the patient with NVP should be invited to attend prenatal physician visits. Presence of the spouse/partner can provide support for the affected woman, and allows the physician to reassure both expectant parents that symptoms of NVP are normal and physiological. The physician can attempt to identify whether the patient needs help coping with symptoms of NVP (particularly in severe cases), and help outline coping strategies (such as physical comfort measures, medication options, or assistance with household activities including child care, cooking, and cleaning).

First-line treatments for NVP are normally conservative measures coupled with reassurance.[91] Some simple strategies are outlined in Table 2. The maintenance of a diary of NVP and daily activities can assist the woman in determining which elements provoke nausea, retching, and/or vomiting and thus avoid them.[86] If there are exacerbating psychosocial issues, then the spouse/partner should be included in discussions regarding the impact and management of NVP.[86] Pharmacologic treatment of symptoms of NVP should be considered when supportive measures fail, symptoms worsen, or the impact on the affected woman is intolerable. There is evidence that early treatment of NVP can prevent escalation of symptoms and hospitalization, especially if one has a previous pregnancy with severe NVP or HG.[61] As mentioned previously, hospitalization for HG can have a tremendous psychological and financial impact on the patient, and contributes to societal costs of HG.

Table 2. Measures Reported Useful in Managing Symptoms of NVP[22, 44, 64, 71, 92, 93, 94, 95]

- Eating frequently in small amounts, every 1 to 2 h
- Eating high-carbohydrate, low-fat foods
- Adding protein to meals and snacks
- Eating a bland, dry, or salty diet; try potato chips, crackers, pretzels, and/or bread
- Drinking small amounts of cold, clear, carbonated or sour liquids (2 L/day), electrolytes
- Keep solids and liquids separate; wait 20 to 30 min to drink after eating
- Lying down as needed; getting plenty of rest
- Changing position slowly, especially when rising
- Avoiding offensive foods and smells, ventilate; going outside for fresh air as needed
- Avoiding iron preparations for first trimester; take folic acid and multivitamin when low or no iron (if anemic, take a prenatal vitamin in divided doses)
- Treat symptoms of heartburn, reflux, or indigestion with H2 blockers or PP1's
- Increase dietary fiber or add stool softener for constipation
- Treat gas/bloating with simethicone or switch to lactose-free
- Not brushing teeth after eating

Dietary Management

The general approach to dietary management of the condition is based on physiologic principles and is appropriate for mild to severe NVP.[95] The success of any dietary alteration is empiric; there is little evidence-based research in this area.[96] Recommendations include eating smaller meals more frequently and ingesting liquids between meals. High-carbohydrate, low-fat foods and dry foods are more easily digestible than fatty foods and will be more likely to stay down.[90,95,97] These types of foods also prevent low blood sugar, provide needed nutrients, and help avoid gastric distension, which may trigger vomiting.[95] Conversely, Jednak et al demonstrated that protein-predominant meals reduced nausea significantly more than equicaloric carbohydrate and fat meals or non-caloric meals (P<0.05).[46] Therefore, it is important to add protein to each meal and snacks (which should be eaten every 1–2 hours). Indeed, a recent study demonstrated the clinical impacts, including shorter duration of gestation, in women with NVP as compared to those without. The distinction was attributable to a lower intake of meat products, vegetables, vitamin B_{12}, magnesium, and zinc in those women with NVP. In contrast to those without, patients with NVP also demonstrated an increased intake of carbohydrates.[23]

Any food taste, texture, and odor aversions should be heeded.[98] Pregnant women have been encouraged to eat as soon as they feel hungry in order to avoid an empty stomach, which may trigger NV.[99] Some researchers have hypothesized that NVP may be linked to hunger in the pregnant woman, in that food intake must be increased in order to support fetal growth.[99] Thus, some practitioners recommend that a regular schedule of small meals and snacks be maintained (at least 1-2 hours), whether the patient is hungry or not.[95] Women with NVP who are having difficulty eating solid foods can use supplemental liquid nutritional products such as Ensure® or Boost®.[94]

With episodic vomiting, there is a danger of dehydration and electrolyte loss; therefore, frequent fluid intake is important.[94,100] It is recommended that small amounts of fluids be ingested between meals.[95] Fluids should be cold, such as Popsicles®, slushies, or ice chips, in order to help minimize the metallic taste that women tend to develop in pregnancy. Electrolytes (such as sports drinks) can also be recommended to facilitate electrolyte balance.[92] Erick reports success in giving lemonade to patients with HG, explaining that the tartness seems to decrease saliva production.[64] Ptyalism is often an additional symptom in NVP.[72] Women should be advised that spitting out the saliva and frequent mouth washing could be helpful.[92]

A randomized, double-blind, placebo-controlled trial by Vutyavanich et al examined the efficacy of vitamin B_6 supplementation for NVP.[101] Patients receiving a daily dose of 30 mg oral vitamin B_6 experienced a significant reduction (P<0.0008) in the severity of nausea. There was a substantial reduction in the mean number of vomiting episodes, but the difference was not statistically significant compared with placebo (P<0.0552). Sahakian et al completed a similar trial comparing vitamin B_6 25 mg three times daily (TID) to placebo in women with NVP.[102] In this trial, the women with severe nausea taking vitamin B_6 experienced significantly less nausea (P<0.01), and the total group of patients experiencing vomiting had a significant reduction in vomiting (P<0.05) after taking vitamin B_6. Furthermore, although the upper limit of vitamin B_6 is 100mg/day, a study involving 192 pregnant

women using doses between 50 and 510 mg/day (mean dose 132.2 mg/day) found no differences in rate of maternal adverse events, in rates of major malformations, miscarriages, or low birth weight. These data suggest that women experiencing moderate to severe NVP can safely receive larger doses of up to 200 mg/day.[103] These studies provide evidence from randomized clinical trials that vitamin B_6 monotherapy is safe and effective as first-line treatment for reducing both nausea and vomiting of pregnancy. Furthermore, vitamin B_6 supplementation is not associated with teratogenicity.

Alternative Therapies

Herbal teas and aromatics containing mint, ginger, and orange have been recommended for the management of symptoms of NVP.[95,97] Mint and orange are thought to aid digestion, and ginger is commonly used in other cultures to treat NV.[97] Ginger has been shown to be effective for the treatment of NVP in three randomized placebo-controlled trials in doses of 125–250 mg four times daily (QID) or 500 mg BID (twice daily).[104,105,106,107] One of the difficulties with ginger and other herbal preparations is the variation in concentrations and labeling of ginger dietary supplements, making it difficult to formally study dosing strategies during pregnancy.[108] Randomized studies on ginger have demonstrated that ginger root powder tablets of up to 1,000 mg/day were not associated with increased fetal risks.[104,105,106] In general, the majority of herbal remedies have not been investigated thoroughly, and should be used with caution for the treatment of NVP.[109]

Stimulation of the P6 (Nei-Guan) point on the inner aspect of the wrist has been used by acupuncturists for thousands of years to treat NV from a variety of causes.[96] In addition to traditional acupuncture, manual pressure or electrical stimulation can be used. The data are conflicting as exemplified by two recent well-designed studies. Knight et al recently published a sham-controlled, subject- and observer-masked, randomized controlled trial of acupuncture in 55 women at 6–10 weeks' gestation with moderate to severe nausea of pregnancy.[110] This trial showed no significant difference between the active and sham treatments. The effect of three or four treatments over a period of 3 weeks resulted in decreased nausea in both the active and sham treatment groups. On the other hand, a multicenter randomized trial of the ReliefBand® device studied 230 pregnant women who were between 6 and 12 weeks' gestation and reported mild to severe NV. 187 women completed the 3-week trial. A significantly greater improvement in the Rhodes Index of Nausea and Vomiting was noted over 3 weeks compared to those with sham stimulation.[111] The subject has been reviewed and verified by Roscoe and Matteson.[112]

Small studies and case reports using psychotherapy and medical hypnosis for the treatment of NVP have been published in the medical literature.[113,114,148] However, no controlled clinical trials of psychotherapy or medical hypnosis have been reported, and this type of trial would be difficult to conduct due to natural inter-patient variability and the self-limiting nature of the disorder. Many authors recommend supportive therapy and counseling for patients with NVP, or a review of psychological factors in cases with persistent symptoms.[5,115]

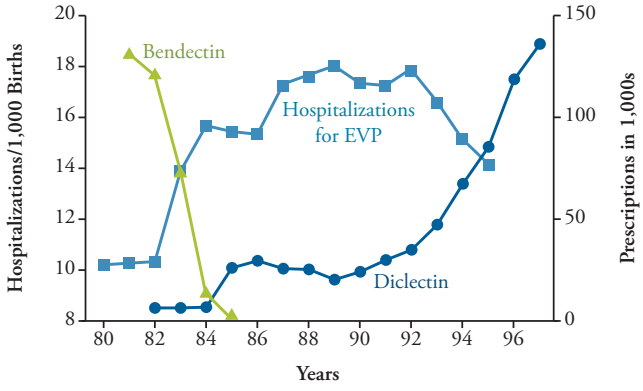
Medical Interventions

When management of NVP using dietary and lifestyle measures and non-pharmacological approaches are inadequate, pharmacological intervention is warranted.

Pharmacotherapy

It is due to fears of teratogenicity that pregnant women and their healthcare providers often reject the possibility of pharmacological treatment of NVP, despite the contrary evidence for safe and effective drug treatment options. Whether pharmacological treatment is offered or not, NVP can have a negative impact on the quality of life of the pregnant woman. Also, for some women, lack of treatment can progress to HG. An indication of this is presented in Neutel and Johansen's analysis of the impact of withdrawing Bendectin® (pyridoxine 10 mg, doxylamine 10 mg) from the North American market in 1983.[15] In Canada, from 1983 to 1989, admissions for hospitalization doubled due to excessive vomiting in pregnancy (Figure 3). A follow-up review in Canada showed dropping hospitalization rates for that diagnostic code versus rising rates of Diclectin® (pyridoxine 10 mg and doxylamine 10 mg) prescriptions between 1990 and 1995.[116] Lamm showed a similar trend in his analysis of data in the US.[117] Of interest is the fact that congenital malformation rates did not decrease in either country after Bendectin® was withdrawn. As mentioned previously, Bendectin® was withdrawn from all markets in 1983 due to litigation regarding the drug's alleged teratogenicity. However, a five-part analysis of epidemiologic studies, secular trend analysis, animal studies, dose-response relationships, and biologic plausibility was conducted by Dr. Robert Brent of the duPont Institute in order to evaluate the teratogenicity of

Figure 3: Rates of Hospitalizations for Excessive Vomiting in Pregnancy (EVP) and Prescriptions for Bendectin® and Diclectin® in Canada*



*From Neutel, 2000[116]

Bendectin®. This extensive review concluded that, in fact, the therapeutic use of Bendectin® has no measurable teratogenic effects. Moreover, presentations by many of the plaintiff's experts failed to meet the scientific standards that should be expected of knowledgeable scientists and contributed to the persistence of the Bendectin® litigation. In his opinion on the case, Associate Justice of the Supreme Court Harry Blackmun coined the term "junk science" in reference to the quality of the evidence presented by the plaintiff.[118]

Antiemetic therapy and birth defects

Antiemetic treatment of NVP has been reported to either have no effect or to result in a decrease in congenital defects.[83] Swedish registry data on women who reported taking promethazine or meclizine during their first trimester showed no increased rate of occurrence of congenital malformations.[84] McKeigue et al's meta-analysis of epidemiologic studies of Bendectin®-exposed pregnancies showed no difference in the risk of birth defects for exposed infants.[119] Boneva et al found a statistical relationship for *decreased* congenital heart defects in infants born of mothers who had taken antinauseant medication during the first 8 weeks of pregnancy.[83] Seto et al performed a meta-analysis of studies published between 1960 and 1991 on the association between antihistamine use and major malformations.[120] Their results indicated that H_1-receptor blockers, used mainly for morning sickness during the first trimester, might have a protective effect regarding major malformations, with a summary odds ratio of 0.76 (95% CI, 0.60–0.94).[120] A 2009 study shows no long-term neurodevelopment problems with the use of Diclectin®.[121] A randomized, placebo-controlled trial published in 2010 has shown the effectiveness of Diclectin® over placebo in 280 American women studied in three academic centers. This study also showed no increased risk for any adverse effects when compared with placebo.[145]

Medications for NVP

Medications that effectively reduce symptoms of NVP without evidence of teratogenicity include: antihistamines (cyclizine, dimenhydrinate, doxylamine [with pyridoxine as Diclectin® in Canada], hydroxyzine, meclizine); dopamine antagonists (chlorpromazine, metoclopramide, perphenazine, prochlorperazine, promethazine, trifluoperazine, trimethobenzamide); and pyridoxine.[96]

Experience with other agents that have been used to treat NVP (e.g., ondansetron, corticosteroids, droperidol, domperidone) is less extensive.[96] One study found no increased rate of birth defects among 176 ondansetron-exposed offspring;[122] however, the only randomized controlled trial in 30 patients with NVP found that it offered no benefits over promethazine.[123] Therefore, use of ondansetron for NVP should be reserved until other agents have failed to adequately control symptoms. Ondansetron can be used as an oral preparation, intravenous administration every 12 hours or by a pump every hour on an outpatient basis. As ondansetron often causes constipation, a stool softener may be needed when taking it.

Data are conflicting on the efficacy of corticosteroids[124] in the treatment of NVP, with the most recent study questioning their efficacy.[87] Since they have been found to cause a slight increase in facial clefts when taken in early pregnancy,[124] they should only be used as a last resort when parenteral nutrition is contemplated after 10 weeks' gestation. Evidence regarding the safety and efficacy of droperidol and domperidone for NVP is very limited as well. Recent reviews are the most concise way of learning about these agents.[1,17,93,96,100,124,139,140,141]

Medications for indigestion

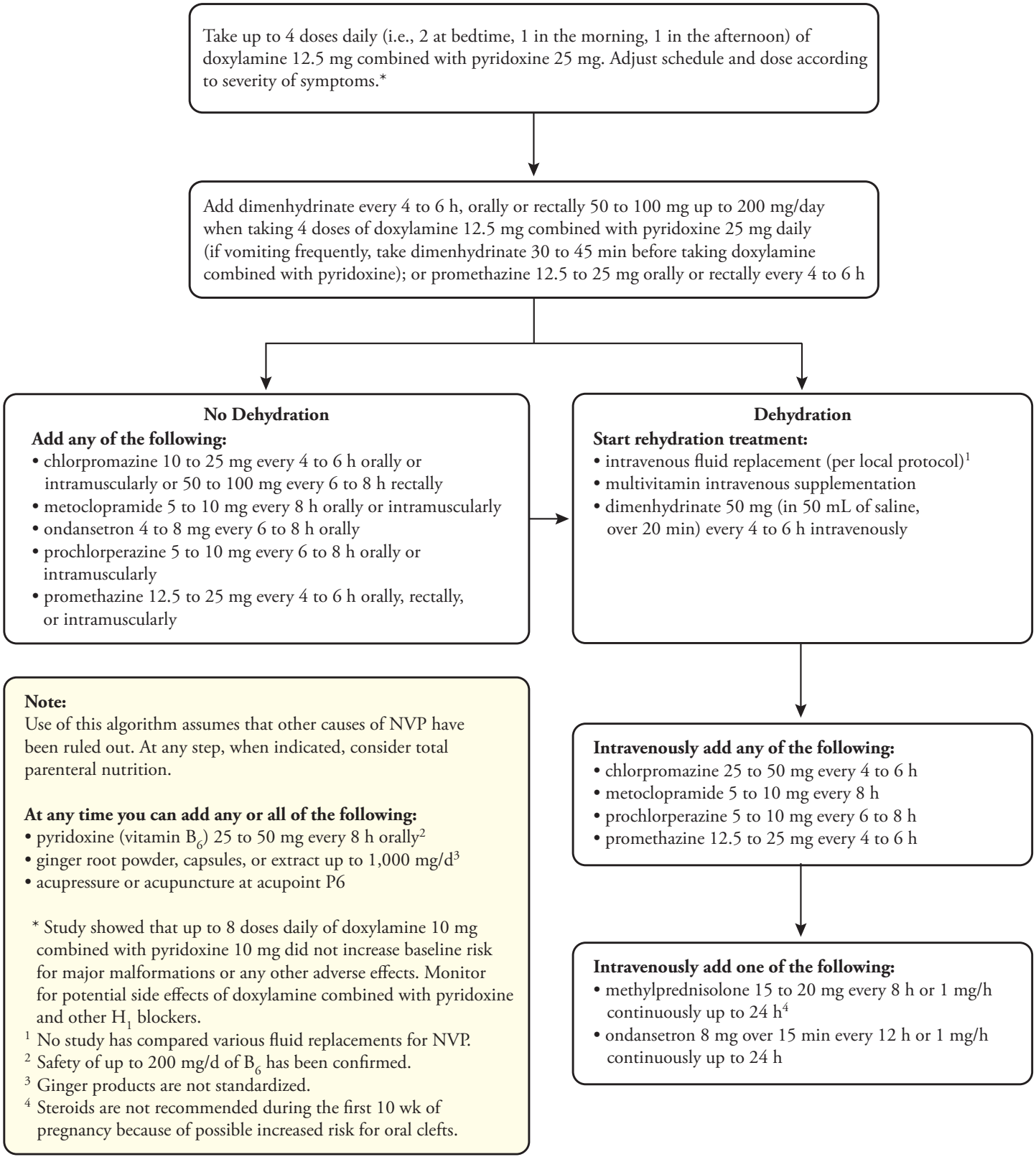
Antacids and H_2-receptor antagonists (e.g., famotidine, cimetidine, ranitidine) have been used safely to treat indigestion in pregnant women; there are no data regarding exposure to nizatidine.[96,125] In addition, antacids can provide added calcium or magnesium.[94] Studies in over 5,000 women have demonstrated that proton-pump inhibitors are not associated with increased risks of major congenital birth defects, spontaneous abortions, or preterm delivery.[126,146] Also, screening and treating Helicobacter pylori with antibiotics can mitigate NVP symptoms.[54,92] Heartburn and acid reflux are associated with increased severity of NVP. A landmark study published published by Gill et al demonstrated that adding acid-reducing drugs (with no changes to anti-emetics) resulted in significant reduction of NVP.[127,128]

The Motherisk Program at the Hospital for Sick Children in Toronto, Canada, has produced a drug treatment algorithm for NVP (Figure 4).[92] The antinauseant/antiemetic agents commonly used to treat NVP (e.g., H_1-receptor antagonists and phenothiazines) may potentiate the desired effect as well as compound adverse effects (e.g., drowsiness, dry mouth/eyes, urinary hesitancy, extrapyramidal effects). Modifications in dose or schedule may be necessary if the patient reports problematic side effects, or a different medication may be indicated. If symptoms worsen, or initial treatment options provide inadequate relief of symptoms, the algorithm presents two treatment pathways depending on whether the patient presents with dehydration.

Management of Severe NVP

Treatment of mild to moderate NVP using lifestyle and dietary alterations in addition to medication is relatively straightforward. Management of the patient with intractable vomiting or excessive weight loss is more complicated and usually requires urgent medical care due to dehydration and malnutrition. The choice of IV fluid should reflect fluid, electrolyte, and acid-base imbalances. The nutritional reserves of women who have not sought timely help for HG may be dangerously depleted. Van Stuijvenberg et al found the

Figure 4: Algorithm for Treatment of NVP (If no improvement, proceed to next step.)*



*Adapted from Einarson et al, 2007[92]

nutritional status of a group of 20 consecutive HG patients, from a lower socioeconomicclass, who had not taken vitamin/mineral supplementation before hospital admission, was less than two-thirds of the recommended daily allowance for energy, protein, calcium, iron, magnesium, zinc, vitamins D and E, thiamin, riboflavin, niacin, vitamin B_6, and folic acid.[74] Thiamin supplementation (100 mg IV daily for 2–3 days) should be administered to any woman who requires IV hydration and has vomited for more than 3 weeks. IV thiamin supplementation can be followed by multivitamin supplementation (intravenous or per mouth).

Enteral nutrition via nasogastric feeding tube (if tolerated) or parenteral nutrition may be required depending on the patient's nutritional status and clinical course of NVP.[129] The development of Peripherally Inserted Central Catheter (PICC) line technology has decreased the morbidity often associated with a central line placement; however there still are complications with this approach, some of which are very serious. Continued reports of morbidity and mortality associated with parenteral nutrition, even with percutaneous insertion of a central catheter, should encourage more vigorous attempts at enteral feeding.[130,131] Placement of the feeding tube tip into the jejunal, thereby bypassing the gastric stasis, may improve the success of enteral feedings. There have been reports of cases where percutaneous endoscopic gastrojejunostomy or jejunostomy was used successfully to provide enteral nutrition in patients with HG.[132,133,134]

Under most circumstances, HG subsides within 24–48 hours of IV hydration, with or without additional pharmacological treatment. Some clinicians believe fluid and electrolyte corrections are sufficient to reverse the hyperemesis. Although hospitalization for hyperemesis occurs in less than 1% of pregnant women,[135] this translates into a large number of hospital admissions in a given year. A more proactive approach to NVP based on identification of risk factors may help to minimize hospitalizations.[135,136] Refractory symptoms, which remain unresponsive to management, may result in hospitalization. It has also been suggested that hospitalization itself may promote palliation of symptoms (i.e., the removal of many of the stresses and repercussions of HG). Ideally, the symptoms of NVP should be assessed and appropriate nutritional, pharmacological, and medical treatments initiated *before* symptoms progress to HG, at which point the health of the mother and fetus may be threatened.

Considerations for Nutritional Support in NVP

A woman requires an increased intake of macro- and micronutrients during pregnancy in order to meet maternal and fetal nutritional requirements. In cases with *significant* weight loss, nutritional deficiencies in a woman with HG may result in a compromised fetus. Low birth weight infants are at greater risk for morbidity and mortality. The recommended dietary allowances and guidelines for prenatal nutrition are available at the government web sites mypyramid.gov/mypyramidmoms/index.html and mypyramid.gov/mypyramidmoms/foods_to_choose.html.[137,138]

In an extensive review article, Hamaoui and Hamaoui noted four basic questions to address when completing a nutritional assessment of a pregnant woman:[99]

1. "With what nutrient reserves has the woman entered pregnancy?"
2. "What are the baseline physiologic needs, and what are the added requirements during pregnancy?"
3. "Does the pregnant woman have any diseases or receive any therapy that might affect her nutritional requirements or nutrient tolerance?"
4. "Is the current intake meeting the nutritional needs?"

Table 3 summarizes basic points for fluid and nutritional support of a patient with HG.

Table 3. Nutritional Support of the Hyperemesis Patient*

Assessment

- >5% loss of prepregnancy body weight
- Nutrient reserves before pregnancy
- Individual physiologic needs *and* added requirements of pregnancy
- Any disease process or current therapy that might affect nutrient requirement or nutrient tolerance
- Clinical and laboratory findings (urine output, peripheral pulse, temperature, skin color, muscle strength, general fatigue, electrolyte abnormalities)

Correct Hypovolemia

(i.e., acidosis, decreased serum bicarbonate, increased serum lactate, electrolyte imbalances)

- IV fluid, electrolyte, and vitamin replacement
- Lactated Ringer's solution is effective
- Large volumes of normal saline may cause hyperchloremic acidosis

Nutritional Support

Enteral: by oral or tube feeding as tolerated

Parenteral: in cases of severe depletion, and/or continued gastrointestinal dysfunction

- Assess patient's status, urgency, and impact of various routes of feeding
- Consider potential complications of tube feeding (e.g., aspiration, diarrhea)
- Consider consult by nutritionist/dietician
- If deciding on enteral support, identify most appropriate formula
- Consider potential complications of parenteral nutrition (e.g., catheter insertion, line complications, septic and metabolic problems, central versus peripheral line placement); close monitoring required
- Monitor for re-feeding syndrome (e.g., hypokalemia, hypophosphatemia, hypomagnesemia, thiamin deficiency)

Enteral Nutrition

Liquid caloric and vitamin supplement, such as one of the following:

- Meal replacement formula
- Concentrated formula for fluid-restricted patients
- High-protein formula
- Elemental/semi-elemental formula for patients with impaired digestion
- Modular formula for boosting select macronutrients

Parenteral Nutrition**

- With high fat content solutions, calories sufficient for short-term maintenance can be provided through a peripheral vein. If intolerance to oral feeding persists more than several days, peripheral venous nutrition cannot go on as phlebitis may develop when continued for 1 to 2 weeks.
- A representative peripheral nutrition formulation, such as 63 g of amino acids, 150 g of glucose, and 100 g of fat (total 1,762 kcal) with vitamins, minerals, and required electrolytes, provides a total volume of 2,000 mL/day.
- For patients who cannot tolerate oral feeding or for whom the vomiting appears likely to persist more than several days, high-calorie, high-glucose formulations may be required. These must be administered centrally because of the sclerosing effect of the glucose on peripheral veins.
- A representative central venous formulation can provide an adequate nutrient intake within a reasonable fluid volume for as long as necessary, such as 2,400 kcal/day including 100 g amino acids, within 2,000 mL.

*Adapted from Hamaoui and Hamaoui, 2003[99] and incorporating recommendations from Position of the American Dietetic Association: Nutrition and Lifestyle for a Healthy Pregnancy Outcome, 2008.[142]

**Sample formulations given. Each formulation is patient-dependent and should be calculated individually. Once a physician determines that parenteral nutrition is required, a registered dietitian experienced in TPN and medical nutrition therapy should be actively involved in patient care.

CONCLUSION

In the course of their pregnancies, many women turn to their healthcare providers for help in finding relief from nausea and vomiting of pregnancy. Symptoms range from mild to severe and may persist around the clock, despite the common term *morning sickness*. NVP negatively impacts the home life, work life, and general well-being of affected women. NVP is a silent syndrome—despite the pervasive nature of NVP it has received limited attention from the medical community, and the condition is frequently regarded as a problem, and the potential severity of its impacts, as something a woman must simply endure. Outdated notions about the syndrome often complicate optimal management of NVP. Moreover, new research is needed for physicians to better understand the etiology of NVP and the effect on pregnancy outcome, as well as the pharmacological and non-pharmacological approaches to treating it. Even so, adopting certain standards of care for NVP can help the affected patient function more comfortably in her daily life and can also reduce the patient's risk of developing HG—which can lead to hospitalization and increased risks for both mother and fetus. Early intervention, timely diagnosis, and effective management of NVP can dramatically improve an affected woman's quality of life, reduce risks of maternal and fetal complications, and cut healthcare and societal costs.

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