Managing nausea and vomiting of pregnancy

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Faculty

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Intended audience

Nurse practitioners (NPs), nurse-midwives, and other advanced practice clinicians who care for pregnant women

Continuing education (CE) approval period

Now through August 31, 2016

Estimated time to complete this activity

1 hour

Program description/identification of need

This CE program presents practical strategies to meet the needs of NPs, nurse-midwives, and other advanced practice clinicians who provide prenatal care for women. In particular, the program will help clinicians identify and treat women who have experienced nausea and vomiting of pregnancy (NVP).

The traditional classification of NVP—that is, the continuum ranging from mild to moderate to severe—is inadequate to characterize this condition's full effect. According to a recent meta-analysis, about 70% of pregnant women experience NVP, and about 1.2% suffer from hyperemesis gravidarum, the most severe form of NVP. Symptoms, including nausea, gagging, retching, dry heaving, and vomiting, may persist 'round the clock—despite the common term *morning sickness*. In a recent literature review, mean onset of NVP was day 39 from the last menstrual period (LMP); 13% of women began to experience NVP before day 28 and 90% before day 56 (i.e., the end of week 8 after their LMP). Peak incidence of NVP occurred during weeks 7-9. By week 16, NVP ceased in 91% of women. Recent reports indicate that NVP persists beyond week 20 in 2.5%-10% of women.

Educational objectives

At the conclusion of this activity, participants should be better able to:

- Describe the etiology and impact of NVP.
- Evaluate the need for management of NVP in the individual patient.
- Describe the safety and efficacy of available nonpharmacologic and pharmacologic approaches to NVP and select the appropriate strategy for each individual patient.

Credit designation statement

This Activity (No. J-15-05) has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioner in Women's Health (NPWH) for 1 contact hour of CE credit, including 1 contact hour of pharmacology content. Each participant should claim only those contact hours that he/she actually spent in the educational activity.

Faculty disclosures

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Disclosure of unlabeled use

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Disclaimer

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integrating the information in this activity with those of established recommendations of other authorities, national guidelines, FDA-approved package inserts, and individual patient characteristics.

Successful completion of this activity
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Despite its pervasive nature and potential severity, nausea and vomiting of pregnancy (NVP) is frequently regarded as something a woman must endure—even though effective management of the condition can greatly improve quality of life, reduce risks for maternal and fetal complications, and cut healthcare and societal costs. To help healthcare providers and their pregnant patients reach these goals, this article details the scope, etiology, impact, assessment, and management of NVP.

KEY WORDS: **nausea and vomiting of pregnancy, NVP, quality of life, pyridoxine, doxylamine**

Scope of the problem

The traditional classification of nausea and vomiting of pregnancy (NVP)—that is, the continuum ranging from mild to moderate to severe—is inadequate to characterize this condition's full effect.[1-3] According to a recent meta-analysis, about 70% of pregnant women experience NVP, and about 1.2% suffer from hyperemesis gravidarum (HG), the most severe form of NVP.[4] Symptoms, including nausea, gagging, retching, dry heaving, and vomiting, may persist 'round the clock—despite the common term *morning sickness*.[3,5] In a recent literature review, mean onset of NVP was day 39 from the last menstrual period (LMP)[6]; 13% of women began to experience NVP before day 28 and 90% before day 56 (i.e., the end of week 8 after their LMP). Peak incidence of NVP occurred during weeks 7-9. By week 16, NVP ceased in 91% of women. Recent reports indicate that NVP persists beyond week 20 in 2.5%-10% of women.[7,8]

Etiology

To address the unpleasant symptoms of NVP and the adverse impact of the condition on quality of life (QOL), it would be useful to know the etiology. Unfortunately, although several theories have been proposed, the etiology of NVP has not yet been clearly defined.[9] NVP is most likely due to a complex interplay of hormonal, metabolic, physiologic, and psychosocial factors.[5] Because of the close temporal association between peak human chorionic gonadotropin (hCG) concentrations and peak NVP symptoms, one of the most likely candidates for the emetogenic stimulus arising from the placenta is the rising level of hCG or one of its isoforms.[10] Other authors theorize that NVP may serve as the body's natural mechanism for avoiding ingestion of teratogenic substances during embryogenesis.[11,12]

Impact

Although the etiology of NVP has not been precisely determined, its effect on pregnant women is clear. Studies utilizing a wide range of measurement tools have identified detrimental and far-reaching consequences of NVP on maternal QOL.[7] In particular, women report adverse effects of NVP on physical functioning, energy, social functioning, work, performance of household duties, and parenting.[13,14] A prospective study of 367 pregnant women who completed a QOL questionnaire showed that those with moderate to severe NVP had scores similar to those of women with breast cancer or myocardial infarction, and those with severe NVP had QOL likened to postnatal depression.[15]

In fact, studies suggest that NVP of any magnitude can jeopardize women's mental health.[15] An interesting aspect of the burden that NVP places on a woman and her psyche is that this condition is considered a *normal* part of pregnancy; frequent nausea and

vomiting (N/V) in any other setting would be considered pathologic and worthy of evaluation, diagnosis, management, and emotional support. As a result, NVP might not be taken as seriously because it is so common and because it is temporary, leading some sufferers to feel frustrated and guilty that they are even complaining about their symptoms.[16]

Nausea and vomiting of pregnancy can take a physical and psychological toll on a pregnant woman, and may have an adverse effect on her partner, family members, and even co-workers. However, mild to moderate NVP has not been shown to harm the fetus and may, in fact, be associated with favorable pregnancy outcomes, particularly in terms of rates of miscarriage, congenital malformations, and preterm births.[17] Of note, though, infants of HG sufferers may be born prematurely, be small for gestational age, have significantly lower birth weights, or have 5-minute Apgar scores <7.[18]

Assessment

The first step in assessment of a pregnant patient who reports experiencing distressful N/V is to rule out other possible causes of the N/V besides pregnancy itself. Healthcare providers (HCPs) should ask about the onset, timing, and severity of the N/V; aggravating and alleviating factors; and appearance of the vomitus.[3,8] A clinical picture of a positive pregnancy test result coupled with N/V that (1) began 30-60 days after a patient's LMP, (2) occurs nearly every day between 9 AM and noon, and (3) is relieved to some degree by eating dry foods or carbohydrates is likely to represent NVP.

Differential diagnosis

Although NVP is the most obvious diagnosis when a pregnant woman presents with N/V, it is not the only possibility. An important distinguishing feature of NVP is that it begins prior to 10 weeks' gestation; N/V onset after 10 weeks usually has an alternate cause. A history and physical examination should rule out these conditions[19,20]:

- Gastrointestinal disorders such as gastroenteritis, cholecystitis, hepatitis, peptic ulcer disease, pancreatitis, appendicitis, and *Helicobacter pylori* infection;
- Genitourinary tract disorders such as pyelonephritis or uremia;
- Metabolic disorders such as diabetic ketoacidosis, porphyria, Addison's disease, and hyper/hypothyroidism;
- Neurologic disorders such as vestibular lesions, migraines, and central nervous system tumors; and
- Infections and drug toxicity/intolerance.

NVP is a diagnosis of exclusion.[3]

Physical findings

Certain physical findings may suggest conditions other than pregnancy that are causing the N/V. These findings include abdominal pain/tenderness that precedes N/V or that is out of proportion to the N/V (although some epigastric pain secondary to prolonged retching may occur with NVP); fever, which is not present in NVP; and concurrent neurologic findings such as headache, neck stiffness, and/or changes in vision.[20]

Testing

When a cause of N/V other than pregnancy is suspected, HCPs should order laboratory tests for urinary ketones, blood urea nitrogen, creatinine, liver enzymes, electrolytes, amylase, and thyroid-stimulating hormone.[8] Ultrasonography is recommended to check for multiple gestation or molar gestation. If other causes of N/V have been ruled out, and if a woman's symptoms are severe and persistent, HCPs should investigate possible complications such as dehydration and thiamine deficiency.

Providers may base their initial approach to NVP management on a woman's subjective description of her symptoms. To obtain a more complete picture, they can add objective measures that not only help define the magnitude of the problem but also help them monitor treatment response. Several objective measures are available, including the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scale,[21] the Nausea and Vomiting of Pregnancy Instrument,[22] the modified PUQE scale,[23] the Health-Related Quality of Life for Nausea and Vomiting during Pregnancy (NVPQOL) questionnaire,[24,25] and the 24-hour PUQE (PUQE-24) scale.[26]

Management

Clinical evidence suggests that use of antiemetics earlier in pregnancy may improve maternal QOL, prevent severe NVP—along with associated maternal and fetal complications—and reduce hospital-related costs.[17,27] Because the etiology of NVP has not been determined, management is directed at symptoms. A reasonable approach, which is individually tailored, depends on symptom severity and the potential impact of treatment on the patient and the fetus. For mild to moderate NVP, dietary and lifestyle alterations

may be sufficient. Some patients may prefer to try OTC (over-the-counter) or CAM (complementary and alternative medicine) therapies before progressing to pharmacologic interventions. However, pharmacologic treatment may be necessary and beneficial for some patients if symptoms persist. Patients with severe NVP may require hospitalization and extensive medical management.

Avoidance of triggers

Many women with NVP report that certain odors stimulate or exacerbate N/V. Avoiding stimuli such as pungent odors from food and perfumes or visual stimuli may alleviate their symptoms.[28] A suggested strategy is to maintain a food diary, which may help determine tastes, textures, and odors that trigger N/V.

Dietary alterations

The most common dietary recommendations are to eat frequent small meals/snacks composed of high-carbohydrate, low-fat foods, with protein added to every snack and meal; and to avoid an empty stomach.[19,29-31] For many women, eating dry food or carbohydrates before getting out of bed in the morning is helpful. Drinking liquids in between meals, instead of with meals, helps avoid gastric distention. Patients should be reassured that their diet during pregnancy, even if not "ideal," will not harm the fetus.

These dietary recommendations apply to women with HG. However, in women with HG who have sustained *significant* weight loss, nutritional deficiencies may result in a compromised fetus or, at the least, cause some harm to the mother.[31] In these cases, more aggressive interventions are needed.

OTC and CAM therapies

Systematic reviews of randomized and/or controlled trials have shown that pyridoxine (vitamin B_6) improves mild to moderate nausea but does not significantly reduce vomiting[27,32] or it has limited evidence of efficacy.[5] When used as monotherapy, the initial dosage of pyridoxine is 25 mg orally every 6-8 hours; the maximum dosage suggested for pregnant women is 200 mg/day.[33] A 2014 systematic review and meta-analysis of randomized trials showed that ginger, relative to placebo, improved nausea but not vomiting.[34] A common dosage is powdered ginger 500-1,000 mg/day.[8]

Acupressure using a wristband or manual pressure at the P6 (Nei-Guan) point, located 4.5 cm above the wrist on the palmar side of the forearm, is a common treatment for NVP.[35] One such wristband, PrimaBella®, has been approved by the FDA for this indication.[36] However, a 2014 systematic review of randomized trials did not find P6 acupressure wristbands to be significantly more effective than placebo.[5]

Clinical evidence to support the efficacy of hypnosis or psychotherapy as a primary treatment for NVP is insufficient. Supportive therapy, counseling, or a review of psychological factors in cases with persistent NVP symptoms, is recommended.

Pharmacotherapy

Dietary changes and OTC/CAM therapy, if tried, may not be sufficient in easing NVP symptoms. If so, patients may benefit from pharmacotherapy.

Doxylamine/pyridoxine

The American Congress of Obstetricians and Gynecologists has stated that pyridoxine, alone or in combination with doxylamine, an H_1-receptor antagonist usually used as an antihistamine or hypnotic, is safe and effective for NVP and should be considered first-line pharmacotherapy.[37] If OTC pyridoxine 25 mg TID alone is inadequate in easing symptoms, patients can add OTC doxylamine 12.5 mg (one-half tablet of Unisom SleepTabs) TID. However, this OTC regimen has its drawbacks: (1) several Unisom products are available; only one of them contains doxylamine; (2) patients must split the small 25-mg tablet in half to get the correct dose; (3) patients must take two separate pills 3-4 times a day; and (4) these immediate-release OTC formulations may not "cover" patients 24/7.[3]

In April 2013, the FDA approved Diclegis,® a combination of delayed-release doxylamine 10 mg and pyridoxine 10 mg, for the treatment of NVP.[38] This product is the only FDA Pregnancy Category A-approved therapy specifically indicated for NVP.[3,39] Diclegis is initially given as two delayed-release pills at bedtime; if symptoms are not adequately controlled, the dose can be increased to a maximum of four tablets daily (one in the morning, one mid-afternoon, and two at bedtime).[3,40]

A doxylamine-pyridoxine combination pill, previously called Bendectin, was removed from the U.S. market in 1983 following unfounded allegations that it caused birth defects. Since that time, numerous meta-analyses and studies have supported the safety of this product—in fact, no other agents given in pregnancy have more conclusive safety data with regard to teratogenicity.[39,41] In addition, a major trial, which was requested by the FDA before it

would grant approval for Diclegis, showed evidence of efficacy.[42] In this double-blind study, 161 women with NVP were randomized to receive extended-release doxylamine-pyridoxine (n = 131) or placebo (n = 125) for 14 days; active treatment, as compared with placebo, resulted in a significantly larger improvement in NVP symptoms based on both PUQE score (–4.8 ± 2.7 vs. –3.9 ± 2.6; $P = .006$) and QOL. If delayed-release doxylamine-pyridoxine alone does not relieve patients' symptoms to a sufficient extent, then alternate or additional interventions can be explored.

H_1-receptor antagonists

Other H_1-receptor antagonists besides doxylamine can be tried, including diphenhydramine (e.g., Benadryl®), dimenhydrinate (e.g., Dramamine®), meclizine (e.g., Antivert®), cyclizine (Marezine®), and hydroxyzine (e.g., Vistaril®). If any of these agents is added to doxylamine or Diclegis, low doses are used to avoid compounding antihistamine side effects such as excess drowsiness. Pooled data from seven controlled trials indicated that antihistamines are effective in reducing vomiting in pregnant women and appear to have a protective effect in terms of the risk for fetal malformations.[24] A previous meta-analysis of 24 controlled studies enrolling a total of more than 200,000 women using antihistamines during pregnancy had shown no link of the drugs to birth defects or serious adverse maternal or fetal outcomes.[43] Because no specific H_1-receptor blocker dosing guidelines concerning pregnant women are available, standard adult dosages are recommended—for example, diphenhydramine 25-50 mg orally (PO) every 4-6 hours or 10-50 mg intravenously (IV) or intramuscularly (IM) every 4-6 hours as needed; meclizine 25 mg PO every 4-6 hours as needed; and dimenhydrinate 50-100 mg PO or rectally (PR) every 4-6 hours as needed.[44]

Dopamine antagonists

For women who do not respond to doxylamine and/or pyridoxine, another option is to substitute or add a drug from an different category such as a dopamine antagonist. Within this category are phenothiazine antiemetics (e.g., prochlorperazine [Compazine®], promethazine [Phenergan®]) and metoclopramide (Reglan®), which has antiemetic and prokinetic effects.[3]

A major downside of the phenothiazines is that, although effective as antiemetics, these agents can cause sedation, hypotension, dry mouth, and extrapyramidal symptoms. Although the FDA has placed phenothiazines in Pregnancy Category C, multiple observational studies of patients exposed to various these agents have failed to demonstrate an increased risk for major malformations.[45]

No specific dosing guidelines for the phenothiazines exist for pregnant women. Possible regimens are those established for adults and include promethazine 12.5-25 mg PO or PR every 4-6 hours as needed (promethazine has a black-box warning for severe tissue injuries with IV or subcutaneous administration) and prochlorperazine 5-10 mg PO or 10-25 mg PR every 6 hours as needed.[44]

In terms of metoclopramide, a Pregnancy Category B agent, the largest study to date, published in 2013, showed no increased risk for major congenital malformations with more than 28,000 first-trimester exposures.[46] A randomized controlled trial comparing metoclopramide and promethazine for the treatment of HG showed no difference in efficacy, although metoclopramide was less sedating.[47] Recommended dosing is metoclopramide 5-10 mg PO or IV every 6 hours as needed.[44]

5-HT_3 antagonists

If NVP symptoms are still inadequately controlled, women can try a serotonin 5-hydroxytryptamine 3-receptor (5-HT_3) antagonist such as ondansetron (Zofran®), granisetron (Kytril®), or dolasetron (Anzemet®). Although these agents are used primarily for chemotherapy-related N/V, they are widely used for NVP—especially because, until early 2013, there were no FDA-approved drugs for NVP.[3,48] In fact, the use of ondansetron for NVP has increased from 50,000 monthly prescriptions in 2008 to 110,000 monthly prescriptions in 2013, despite unresolved concerns regarding fetal safety (e.g., risk for cleft palate in the newborn[49]) and FDA warnings about serious maternal dysrhythmias.[3,48]

Using a large Danish birth registry, two groups of researchers reached different conclusions regarding the safety of ondansetron: Pasternak et al[50] reported that ondansetron was not associated with increased rates of spontaneous abortion, stillbirth, major birth defects, preterm delivery, low birth weight, or small size for gestational age, whereas Andersen et al[51] found a 2-fold increased risk for cardiac malformations.

Data from a large Swedish birth registry and a Swedish registry of prescribed drugs were reviewed to investigate the teratogenic effects of ondansetron.[52] A total of 1349 infants born of women who had

taken ondansetron in early pregnancy between 1998 and 2012 were identified. Although no significant increase in risk for major malformations was found, the risk of a cardiovascular defect, particularly a cardiac septum defect, was significantly increased in infants whose mothers had taken ondansetron during pregnancy.

Information is limited regarding the effectiveness of ondansetron for treatment of NVP. The results of one study suggest that this agent can decrease vomiting but is only modestly effective in limiting nausea.[53]

Corticosteroids

Given the risk of maternal side effects, possible fetal risks (oral cleft, hypospadias, and other malformations), and uncertain efficacy, corticosteroids are reserved for treatment of refractory NVP or HG after the first trimester.[49,54] If the benefit of treatment is thought to outweigh the risk, the recommended dosage is methylprednisolone 16 mg IV every 8 hours for 48-72 hours. Methylprednisolone can be stopped abruptly if there is no response, and tapered over 2 weeks in women who experience symptom relief.[33] After IV therapy, women can follow an oral prednisone taper regimen.

Conclusion

Nausea and vomiting of pregnancy is a prevalent condition with major clinical impact for many women. After ruling out other possible causes of the N/V, HCPs can offer patients multiple therapeutic options such as dietary approaches, OTC/CAM therapies, and pharmacotherapeutic options to improve their QOL and the overall pregnancy experience. A period of time may be needed to fine-tune the therapeutic intervention that works best for each woman.

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A. https://healthmonix.com/npwh/courses/home/details/406

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