MASTER CLASS

A Fairly Common Condition

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Nausea and vomiting in pregnancy are fairly common conditions. By themselves, they are neither life threatening nor threatening to the pregnancy, but they are nevertheless terribly uncomfortable, displeasing, and sometimes disabling.

Nausea and vomiting can often interfere with a patient's ability to perform household or workplace duties and can be destabilizing to a patient's life at a time when there otherwise is joy and happiness. Sometimes, nausea and vomiting can be so severe that they result in hospitalization and intravenous feeding.

For all these reasons, they cannot be overlooked.

Unfortunately, they are also mysterious. Nausea and vomiting in pregnancy are relatively uncommon in the populations of certain continents, such as Africa and Asia, but relatively common among North American women. They occur for varying lengths of time in some North American women and not at all in others. The causation, in short, is unclear and likely complicated. A number of hypotheses have been advanced, but none has been proved.

Despite the uncertainties, the frequency and effects of nausea and vomiting in pregnancy demand our attention. It therefore seems important to present a Master Class on the subject and to review the various treatments that have been tried and are available for patients who struggle with the condition.

Some of these approaches will work for our patients, and some will not. With these options before us, however, we can offer our patients the very best care.

Here to address the issue is Dr. Jennifer R. Niebyl, professor and chair of the department of obstetrics and gynecology at the University of Iowa Hospitals and Clinics, Iowa City.

Dr. Niebyl is an expert in the area of drugs and pregnancy and an expert in maternal-fetal medicine, with a special interest in nausea and vomiting in pregnancy. ■

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Nausea and Vomiting in Pregnancy

BY JENNIFER R. NIEBYL, M.D.

Nausea and vomiting are common in pregnancy and can have a significant negative effect on women's health. Approximately half of all pregnant women in the United States have nausea and vomiting in early pregnancy, and about 25% have nausea alone. Only about 25% of pregnant women are free of any such problem.

The problem presents across a broad spectrum of severity, with the most severe form being hyperemesis gravidarum, a condition characterized by persistent vomiting, weight loss greater than 5%, ketonuria, electrolyte abnormalities, hypokalemia, and dehydration; this condition usually results in the need for hospitalization, treatment with intravenous fluids, and even intravenous feeding. Approximately 1% of pregnant women have vomiting severe enough to require hospitalization.

Persistent mild nausea, however, can also be a significant problem worthy of attentive management. It is not just "morning sickness" for many of these women. Approximately 35% of women with nausea during pregnancy lose time from work, and 25% cannot function well at home throughout the day.

Nausea and vomiting can significantly impair their routines, can negatively affect their relationships with their husbands and children, and are sometimes cited as reasons for an otherwise undesired pregnancy termination.

Women who are suffering from nausea and vomiting in pregnancy frequently do not seek or receive specific therapy out of concern over safety, yet such fear is often based on misinformation and misperceptions regarding teratogenesis. Women have numerous safe and effective options, including therapy with vitamin B_6 and doxylamine, as well as ginger and other nonpharmacologic approaches, and treatment with various antiemetic drugs.

Etiology, Differential Diagnosis

Some patients can identify the triggers of their nausea and thus can avoid aggravating odors or foods. Dietary modifications include eating frequent and small meals; taking fluids between meals; eating primarily bland, dry, and high-protein foods; and avoiding fatty or spicy foods.

Discontinuing prenatal vitamin tablets containing iron also can help, as the iron can contribute to nausea. Women who are having trouble can switch to a multivitamin with no or low iron for the first trimester and can resume prenatal vitamins after 3 months, or they can switch to folic acid alone, which is all that is needed to prevent birth defects.

We must also consider other diagnoses that can cause nausea and vomiting in pregnancy, from gastroenteritis, pancreatitis, appendicitis, and other gastrointestinal disorders, to gastrourologic problems such as pyelonephritis and various metabolic disorders.

There are sometimes clues that the nausea and vomiting cannot be attributed to the pregnancy alone: Fever, abdominal pain, and headache, for instance, result from something other than the pregnancy, as do serious changes in liver enzymes, bilirubin, and amylase or lipase.

Nausea and vomiting that begin later in the pregnancy also cannot be attributed to the pregnancy itself. The problem has an early onset, usually starting at the time of the missed menstrual period. It is fully manifested by 10 weeks of gestation, and—although it usually improves as the pregnancy progresses further—the problem may persist until the placenta is delivered.

In any case, a patient who has not had any nausea in the first 3 months of her pregnancy and begins experiencing nausea and headache at 16 weeks of gestation is probably having a migraine headache.

Many believe that nausea and vomiting are related to the presence of human chorionic gonadotropin (HCG), because HCG can stimulate the ovaries to produce estrogen, and estrogen can contribute to nausea. Indeed, the start, peak, and resolution of nausea and vomiting in pregnancy correlate closely with the curve of HCG concentration. Nausea and vomiting are also more common in patients with multiple gestations and hydatidiform moles, obstetric situations in which HCG is high.

Hormonal influences do not explain, however, why some women have problems with nausea and others do not.

Over the years, some have believed that the problem is psychological, but I and many others strongly discount this belief. Any psychological problems these women have are not a cause of their nausea and vomiting, but rather are an effect.

Gastrointestinal dysmotility and *Helicobacter pylori* infection have been cited as other possible associations. *H. pylori* seropositivity has been associated with hyperemesis or serious nausea and vomiting, but data are conflicting and investigators have not studied whether the problem resolves after treatment for the infection. Ulcer disease should register as a possibility in any differential diagnosis, particularly if the woman has pain, but whether it is more broadly causative of the nausea and vomiting of pregnancy is uncertain.

There is also some evidence that the nausea and vomiting of pregnancy may be related to vitamin B_6 deficiency, and indeed, a significant number of women respond to vitamin B_6 supplementation. Overall, however, the etiology of nausea and vomiting in pregnancy are unknown.

Vitamin-Based Therapy and Doxylamine

Vitamin B_6 is a good initial therapy for women whose nausea and vomiting cannot be managed with dietary change. It has been more widely tested for safety and efficacy than has any other vitamin-based therapy for the problem, and it is inexpensive and widely available.

In a study from our group conducted many years ago, pregnant patients with nausea and vomiting were randomized to 3 days of vitamin B_6 or a placebo at a dosage of 25 mg three times a day. Half of the patients stopped vomiting, and most patients with severe nausea reported a diminution to mild or moderate nausea. Several years later, another group of investigators used 10 mg of vitamin B_6 three times a day in a larger, randomized, placebo-controlled study. After 5 days of therapy, they also documented a significant decrease in nausea.

A once-a-day, extended-release formulation of vitamin B_6 (PremesisRx) is a good first-line option. It delivers 75 mg of vitamin B_6 over 24 hours—which is easier than taking 25 mg three times a day—and contains some vitamin B_{12}, calcium carbonate, and 1 mg of folic acid. (The level of folic acid makes the formulation a prescription therapy.)

If vitamin B_6 alone is not successful, the antihistamine doxylamine can be added in a combination similar to the formulation that was available in Bendectin from 1956 to 1983. It is estimated that Bendectin was used by more than 30 million women during this time period and, at one point, by approximately 40% of pregnant women.

Although no other agent given in pregnancy has more conclusive safety data with regard to the incidence of birth defects (more than 6,000 patients exposed to the combination have been compared with more than 6,000 controls), Bendectin was removed from the U.S. market in 1983 by the manufacturer because of lawsuits that alleged a teratogenic effect.

The combination has been continually available in Canada as Diclectin (a sustained-release formulation), and interestingly, there are significantly fewer hospitalizations for nausea and vomiting in pregnancy in Canada than in the United States.

A version of the combination can be created by combining vitamin B_6 with the over-the-counter sleep aid Unisom SleepTabs, which contains 25 mg of doxylamine per tablet. The dose of doxylamine in Bendectin was 10 mg, and two

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Key Points

- ► Vitamin B_6 and doxylamine should be first-line therapy for nausea and vomiting in pregnancy.
- ► No antiemetic has been found to have any teratogenic risk.
- ► Some alternative remedies, such as ginger and acupuncture, have been shown to be effective.

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tablets were recommended at night, so one full tablet of Unisom can be taken at night, along with a half tablet in the morning and a half-tablet in the afternoon if some nausea persists and, of course, 25 mg of vitamin B_6 at each of these times of the day.

The combination of vitamin B_6 and doxylamine can bring fast and dramatic relief for many patients, leading to significant improvements in the quality of their lives. There is always concern for obstetricians that a mother will claim that a child's birth defect was caused by a drug prescribed during the first trimester, but this is unlikely to happen with the combination of vitamin B_6 and doxylamine because legal precedents already hold that the drug does not cause birth defects.

Interestingly, some studies have suggested that women who have taken multivitamins containing vitamin B_6 before pregnancy have less nausea and vomiting.

Nonpharmacologic Approaches

Ginger ale has been a traditional remedy for nausea in various populations, and among pregnant women with nausea and vomiting, ginger is the alternative therapy with the strongest evidence base. The data on ginger have accumulated to the point at which concerns about its possible adverse effects have largely dissipated, which makes it worthy of consideration as a second-line agent.

Two small, randomized, double-blind trials used 250-mg ground ginger capsules or placebo four times a day, one in 70 outpatients with nausea and vomiting and one in women who were hospitalized with hyperemesis gravidarum. Investigators of both trials reported significantly reduced nausea and reductions in vomiting among the women in the ginger groups (Obstet. Gynecol. 2001;97:577-82; Eur. J. Obstet. Gynecol. Reprod. Biol. 1990;38:19-24).

Among more recent randomized trials was one of approximately 300 women that compared ginger with vitamin B_6. Women who received identical-looking capsules three times a day of 25 mg vitamin B_6 or 350 mg ginger had similar levels of improvement in nausea and vomiting at 1 week, 2 weeks, and 3 weeks.

There were no differences in fetal outcome or congenital anomalies; the only difference was that the women taking ginger reported more heartburn and belching (Obstet. Gynecol. 2004;103:639-45).

In a literature review, a group of Italian investigators identified six double-blind, randomized, controlled trials with a total of 675 participants that met criteria for methodological quality for the evaluation of efficacy. Of these six trials, four demonstrated the superiority of ginger over placebo, and two demonstrated the equivalence of ginger with vitamin B_6.

To review safety, the investigators looked at an observational cohort study involving 187 women as well as at the randomized trials. The studies showed no significant side effects and no adverse effects on pregnancy outcome (Obstet. Gynecol. 2005;105:849).

Acupuncture is another therapy worthy of consideration and one that can be added to the treatment regimen at any time. It has now been studied in two randomized trials in pregnant women who had nausea and vomiting, and although the results do not demonstrate broad efficacy, the findings together suggest that the therapy can be worth a try (Obstet. Gynecol. 2001:97;184-8; J. Pain Symptom Manage. 2000:20;273-9).

Nerve stimulation of the P6 acupuncture point also appears to decrease the nausea and vomiting of pregnancy for some women, whereas acupressure with devices like the Sea-Band or the Bioband appears to be less effective.

Antiemetic Drugs

Ginger and vitamin B_6—alone or in combination with doxylamine—do not work for everyone. In unsuccessful cases, we can move on to try other antihistamines and, if necessary, to consider the four other categories of antiemetic drugs: phenothiazines, prokinetic agents, serotonin ($5\text{-}HT_3$) antagonists, and corticosteroids.

With the exception of doxylamine, which is a Food and Drug Administration category A drug, none are FDA approved for use in pregnancy. The drugs are underutilized, however, largely because of misperceptions of teratogenic risk.

In a supplement to the American Journal of Obstetrics and Gynecology on nausea and vomiting in pregnancy, Dr. L.A. Magee and associates reported on an evidence-based review of the safety and effectiveness of available antiemetics. They concluded that many medications, particularly the antihistamines and phenothiazines, are safe and effective for the treatment of varying degrees of nausea and vomiting (Am. J. Obstet. Gynecol. 2002:186;S256-61).

In the same supplement, Dr. Gideon Koren addressed the issue of perceived versus true risk of medications for nausea and vomiting, and presents an algorithm for management that includes a hierarchical use of antiemetic drugs based on the strength of evidence of fetal safety (Am. J. Obstet. Gynecol. 2002:186;S248-52).

Although few studies have compared the antihistamines for nausea and vomiting in pregnancy, sedation seems to be a main difference among the various drugs, with some—such as diphenhydramine (Benadryl)—sedating more than others. In addition to doxylamine and diphenhydramine, we can consider using dimenhydrinate (Dramamine), meclizine (Antivert), hydroxyzine (Vistaril, Atarax), and cetirizine (Zyrtec).

If the antihistamines as a class are not effective, the phenothiazines are a good choice. Promethazine (Phenergan) is widely used for nausea and vomiting in pregnancy, and prochlorperazine (Compazine) and chlorpromazine (Thorazine) are other options.

Possible adverse side effects of the phenothiazines include sedation, hypotension, dry mouth, and extrapyramidal symptoms. Compazine tablets are placed inside the cheek—a formulation that is helpful for women with moderate and severe nausea—and are generally well tolerated, with less drowsiness and sedation than the antihistamines.

The phenothiazine droperidol (Inapsine) was popular for some time, but there were reports of cardiac deaths and, in 2001, the FDA issued a black box warning stating that all patients need a 12-lead ECG before, during, and after administration. This drug has, consequently, fallen out of favor.

Metoclopramide (Reglan) can help some women when other drugs have failed. It is a prokinetic agent, increasing upper gastrointestinal motility and lower esophageal sphincter tone. A review of Medicaid data showed no increased risk of birth defects in 303 newborns in Michigan born to mothers who had ingested this drug.

The serotonin (5-HT3) antagonist ondansetron (Zofran) has been one of the most heavily marketed drugs for postoperative nausea and vomiting, and from the start many women and their obstetricians used the drug as a first-line or near-first-line antiemetic choice for nausea and vomiting in pregnancy, despite its high cost and the relative paucity of information on its use in pregnancy.

Several years of use and studies of several hundred patients have increased the comfort level related to ondansetron use. In general, this drug and the serotonin antagonists dolasetron (Anzemet) and granisetron (Kytril) are now felt to be safe. All are FDA category B drugs.

Zofran comes in an oral disintegrating tablet that, like Compazine, is useful in patients who have difficulty swallowing or who do not feel they are able to drink. In a randomized trial, Zofran was compared with Phenergan and was found to have similar efficacy, but with less sedation.

Corticosteroids may not be as beneficial as many first thought—there are now conflicting data about their effectiveness—and some studies have suggested an increased risk of cleft lip and palate when these agents are used before 10 weeks' gestation. The drugs are recommended, therefore, only after 10 weeks' gestation and in cases in which other medications have failed.

Neither I nor any member of my family has any financial connections with the pharmaceutical industry. ■

Treatments for Nausea/Vomiting

Vitamin B_6
PremesisRx

Antihistamines
Doxylamine (Unisom)
Dimenhydrinate (Dramamine)
Diphenhydramine (Benadryl)
Meclizine (Antivert)
Hydroxyzine (Vistaril, Atarax)
Cetirizine (Zyrtec)

Phenothiazines
Promethazine (Phenergan)
Prochlorperazine (Compazine)
Chlorpromazine (Thorazine)

Prokinetic Agent
Metoclopramide (Reglan)

5-HT_3 Receptor Antagonists
Ondansetron (Zofran)
Dolasetron (Anzemet)
Granisetron (Kytril)

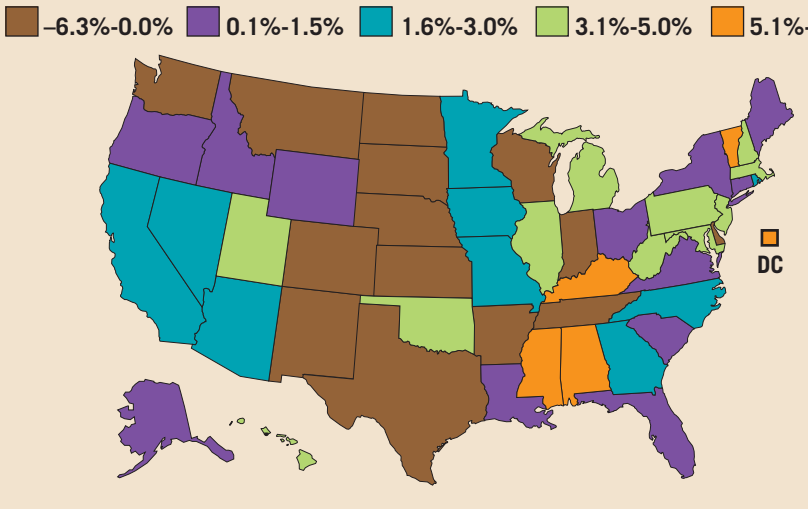
Corticosteroids

Acupuncture

Ginger

DATA WATCH

Percent Change of Live Births to Mothers Under 20 Years Old



Note: Based on 2005 and preliminary 2006 data.
Source: Centers for Disease Control and Prevention

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