Nausea and Vomiting of Pregnancy

JEFFREY D. QUINLAN, LCDR, MC, USN, Naval Hospital, Jacksonville, Florida
D. ASHLEY HILL, M.D., Florida Hospital, Orlando, Florida

Nausea and vomiting of pregnancy, commonly known as “morning sickness,” affects approximately 80 percent of pregnant women. Although several theories have been proposed, the exact cause remains unclear. Recent research has implicated Helicobacter pylori as one possible cause. Nausea and vomiting of pregnancy is generally a mild, self-limited condition that may be controlled with conservative measures. A small percentage of pregnant women have a more profound course, with the most severe form being hyperemesis gravidarum. Unlike morning sickness, hyperemesis gravidarum may have negative implications for maternal and fetal health. Physicians should carefully evaluate patients with nonresolving or worsening symptoms to rule out the most common pregnancy-related and nonpregnancy-related causes of severe vomiting. Once pathologic causes have been ruled out, treatment is individualized. Initial treatment should be conservative and should involve dietary changes, emotional support, and perhaps alternative therapy such as ginger or acupressure. Women with more complicated nausea and vomiting of pregnancy also may need pharmacologic therapy. Several medications, including pyridoxine and doxylamine, have been shown to be safe and effective treatments. Pregnant women who have severe vomiting may require hospitalization, orally or intravenously administered corticosteroid therapy, and total parenteral nutrition. (Am Fam Physician 2003;68:121-8. Copyright© 2003 American Academy of Family Physicians.)

Few data support the theory that psychologic factors are responsible for nausea and vomiting of pregnancy. The roles of human chorionic gonadotropin and estrogen are controversial.
Gastrointestinal tract dysfunction also has been suggested as a cause of nausea and vomiting of pregnancy. In one study in which progesterone was prescribed to nonpregnant women, resultant nausea and vomiting suggested that delayed gastric motility caused by progesterone may be responsible for the condition. Another study reviewed many potential gastrointestinal causes of nausea and vomiting of pregnancy, including abnormalities of gastric electrical rhythm (gastric dysrhythmias).

Many reports have suggested that hormones may cause nausea and vomiting of pregnancy and hyperemesis gravidarum. In one comparative study, women with nausea and vomiting of pregnancy were found to have elevated levels of human chorionic gonadotropin (hCG); however, another study did not support this finding. Some studies have shown elevated estrogen levels in women with this condition; others have not. Hence, the roles of hCG and estrogen remain controversial. Many pregnant women with hyperemesis have suppressed thyrotropin-stimulating hormone (TSH) levels. Work is ongoing to elucidate the interaction of hCG and TSH in pregnant women with hyperemesis.

A recent study suggested that chronic infection with Helicobacter pylori may play a role in hyperemesis gravidarum. In this study, 61.8 percent of pregnant women with hyperemesis were found to be positive for the *H. pylori* genome, compared with 27.6 percent of pregnant women without hyperemesis.

### Differential Diagnosis and Evaluation

A thorough history and a complete physical examination are important in the evaluation of pregnant women who present with persistent vomiting. Nausea and vomiting in early pregnancy is usually a self-limited condition. When the condition is more severe, potentially serious causes need to be ruled out (Table 1). If nausea and vomiting begin after nine weeks of gestation, other causes should be investigated.

If the findings of the history and physical examination suggest a specific cause, testing is directed toward confirming that cause. For example, the findings may suggest pyelonephritis, a common condition in pregnancy. Ultrasonography may be helpful in ruling out gallbladder, liver, and kidney disorders. In addition to hyperemesis gravidarum, pregnancy-related causes of persistent vomiting include acute fatty liver and preeclampsia. Nonpregnancy-related causes include gastrointestinal, genitourinary, metabolic, and neurologic disorders.

### Maternal and Fetal Outcomes

Women with uncomplicated nausea and vomiting of pregnancy (“morning sickness”) have been noted to have improved pregnancy outcomes, including fewer miscarriages, preterm deliveries, and stillbirths, as well as fewer instances of fetal low birth weight, growth retardation, and mortality. In contrast, hyperemesis gravidarum has been associated with increases in maternal adverse effects, including splenic avulsion, esophageal rup-

---

**TABLE 1**

**Differential Diagnosis of Persistent Vomiting in Pregnancy**

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Metabolic disorders</th>
<th>Neurologic disorders</th>
<th>Pregnancy-related conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenteritis</td>
<td>Diabetic ketoacidosis</td>
<td>Pseudotumor cerebri</td>
<td>Nausea and vomiting of pregnancy*</td>
</tr>
<tr>
<td>Biliary tract disease</td>
<td>Porphyria</td>
<td>Vestibular lesions</td>
<td>Acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Addison's disease</td>
<td>Migraine headaches</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>Hyperthyroidism</td>
<td>Central nervous system tumors</td>
<td>Drug toxicity or intolerance</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicitis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Genitourinary tract disorders

<table>
<thead>
<tr>
<th>Pyelonephritis</th>
<th>Uremia</th>
<th>Degenerating uterine leiomyoma</th>
<th>Torsion</th>
<th>Kidney stones</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Metabolic disorders</th>
<th>Neurologic disorders</th>
<th>Pregnancy-related conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Pseudotumor cerebri</td>
<td>Nausea and vomiting of pregnancy*</td>
</tr>
<tr>
<td>Porphyria</td>
<td>Vestibular lesions</td>
<td>Acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>Addison's disease</td>
<td>Migraine headaches</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Central nervous system tumors</td>
<td>Drug toxicity or intolerance</td>
</tr>
</tbody>
</table>

* — Including hyperemesis gravidarum.

ture, Mallory-Weiss tears, pneumothorax, peripheral neuropathy, and preeclampsia, as well as increases in fetal growth restriction and mortality.\textsuperscript{13-15}

Treatment

The management of nausea and vomiting of pregnancy depends on the severity of the symptoms. Treatment measures range from dietary changes to more aggressive approaches involving antiemetic medications, hospitalization, or even total parenteral nutrition (TPN). We prefer to start with dietary changes and then add medications as necessary. A Cochrane review of various nonpharmacologic and pharmacologic treatments for nausea and vomiting of pregnancy and hyperemesis gravidarum was recently published.\textsuperscript{16} [Evidence level B, systematic review of variable-quality randomized controlled trials (RCTs)]

**NONPHARMACOLOGIC THERAPY**

*Dietary Measures.* Initial treatment of women with mild nausea and vomiting of pregnancy (i.e., morning sickness) should include dietary changes. Affected pregnant women should be instructed to eat frequent, small meals and to avoid smells and food textures that cause nausea. Solid foods should be bland tasting, high in carbohydrates, and low in fat. Salty foods (e.g., salted crackers, potato chips) usually can be tolerated early in the morning, and sour and tart liquids (e.g., lemonade) often are tolerated better than water. Family members should be informed that pregnant women with nausea and vomiting of pregnancy may need to alter mealtimes and other home routines.

*Emotional Support.* Although nausea and vomiting of pregnancy and hyperemesis gravidarum are not strongly associated with psychologic illness, some women may become depressed or exhibit other affective changes. It is important that these women receive appropriate support from family members and medical and nursing staff. Consultation is indicated if a pregnant woman is depressed, domestic violence is suspected, or evidence of substance abuse or psychiatric illness exists.

*Acupressure.* Several studies\textsuperscript{17,18} have suggested acupressure as a treatment for nausea. The most common location for acupressure is the pericardium 6 or Neiguan point, which is located three fingerbreadths above the wrist on the volar surface. Various commercial products for relieving motion sickness (e.g., Sea-Band, ReliefBand) apply pressure to this area. One review\textsuperscript{19} of data from seven trials involving Neiguan point acupressure indicated that these products are helpful for controlling morning sickness in early pregnancy; however, a recent study\textsuperscript{20} demonstrated no benefit for acupressure in pregnant women. Further data are necessary to determine whether acupressure is a viable treatment for nausea and vomiting of pregnancy. However, acupressure is a nonpharmacologic intervention without known adverse side effects. Some physicians may wish to offer it to their patients.

*Ginger.* A popular alternative treatment for morning sickness, ginger has been used in teas, preserves, ginger ale, and capsule form. One European study\textsuperscript{21} demonstrated that ginger powder (1 g per day) was more effective than placebo in reducing the symptoms of hyperemesis gravidarum. There have been no published reports of fetal anomalies associated with the use of ginger. However, one investigator\textsuperscript{22} warned that ginger root contains thromboxane synthetase inhibitor, which may interfere with testosterone receptor binding in the fetus. Other investigators\textsuperscript{23} noted that although safety data are lacking, people in many cultures use ginger as a spice; the amounts used are similar to those commonly prescribed for the treatment of nausea and vomiting of pregnancy.
Pyridoxine (Vitamin B₆) and Doxylamine. Pyridoxine can be used as a single agent or in conjunction with doxylamine. One small study demonstrated that vitamin B₆ in a dosage of 25 mg taken orally every eight hours (75 mg per day) was more effective than placebo for controlling nausea and vomiting in pregnant women.24 [Evidence level A, RCT] In pharmacologic doses, vitamin B₆ has not been found to be teratogenic. A single 25-mg doxylamine (Unisom) tablet taken at night can be used alone or in combination with pyridoxine (25 mg three times daily).

In the 1970s, a medication combining pyridoxine and doxylamine (Bendectin) commonly was used to treat women with nausea and vomiting of pregnancy. Although multiple studies showed no increased risk of birth defects, the manufacturer voluntarily withdrew Bendectin from the market in 1983 because of litigation. Pyridoxine-doxylamine is still the only medication that the U.S. Food and Drug Administration has specifically labeled for the treatment of nausea and vomiting of pregnancy.

Antiemetics. If the previously discussed therapies are unsuccessful, a trial of antiemetics is warranted. The phenothiazines prochlorperazine (Compazine) and chlorpromazine (Thorazine) have been shown to reduce nausea and vomiting of pregnancy compared with placebo.25 A reasonable regimen is prochlorperazine administered rectally in a dosage of 25 mg every 12 hours (50 mg per day) or promethazine (Phenergan) given orally or rectally in a dosage of 25 mg every four hours (150 mg per day).

If treatment with prochlorperazine or promethazine is unsuccessful, some physicians try other antiemetics, such as trimethobenzamide (Tigan) or ondansetron (Zofran). In a small study26 of intravenous therapy in women with hyperemesis gravidarum, no increased benefit was demonstrated for ondansetron over promethazine. Although one study27 of 315 pregnant women demonstrated a slightly increased risk of birth defects when phenothiazines were given during the first trimester, a larger study28 showed no association with fetal malformations.

Women with severe nausea and vomiting of pregnancy or hyperemesis gravidarum may benefit from droperidol (Inapsine) and diphenhydramine (Benadryl). One study29 found that continuous intravenous administration of both droperidol and diphenhydramine resulted in significantly shorter hospitalizations and fewer readmissions compared with a variety of other inpatient antiemetic therapies.

Antihistamines and Anticholinergics. Meclizine (Antivert), dimenhydrinate (Dramamine), and diphenhydramine have been used to control nausea and vomiting during pregnancy. All

**The Authors**

JEFFREY D. QUINLAN, LCDR, MC, USN, is program director of the family practice residency program at Naval Hospital, Jacksonville, Fla. After graduating from the University of Pittsburgh School of Medicine, Dr. Quinlan completed a family medicine residency at Naval Hospital, Camp Pendleton, Calif., and an obstetrics fellowship at Florida Hospital, Orlando.

D. ASHLEY HILL, M.D., is associate director of the Department of Obstetrics and Gynecology at Florida Hospital's family practice residency program, Orlando. Dr. Hill received his medical degree from the University of South Florida College of Medicine, Tampa, where he also completed a residency in obstetrics and gynecology.

Address correspondence to Jeffrey D. Quinlan, LCDR, MC, USN, Associate Program Director, Family Practice Residency Program, Naval Hospital, 2080 Child St., Jacksonville, FL 32214 (e-mail: jdquinlan@yahoo.com; jdquinlan@sar.med.navy.mil). Reprints are not available from the authors.
have been shown to be more effective than placebo. Although meclizine was previously thought to be teratogenic, studies have demonstrated its safety during pregnancy. One study found an association between diphenhydramine and cleft lip and palate, but a subsequent study did not support this finding.

Motility Drugs. Metoclopramide (Reglan) acts by increasing pressure at the lower esophageal sphincter, as well as speeding transit through the stomach. This drug has been shown to be more effective than placebo in the treatment of hyperemesis gravidarum. Metoclopramide has not been associated with an increased incidence of congenital malformations.

Corticosteroids. A randomized, double-blind, controlled study found no hospital readmissions for recurrent vomiting in women with hyperemesis gravidarum who were treated with orally administered methylprednisolone (Medrol), compared with five readmissions in those who received oral promethazine therapy. The authors of the study suggested that methylprednisolone, in a dosage of 16 mg three times daily (48 mg per day) followed by tapering over two weeks, is a worthwhile treatment for women with refractory hyperemesis gravidarum.

Of note, these and other authors have found that almost all women with hyperemesis gravidarum can tolerate oral corticosteroid therapy. We have used the two-week tapering regimen in pregnant women who have been refractory to standard antiemetic therapy and have noted a subjective decrease in hospitalization rates and readmissions.

Corticosteroid therapy generally is considered safe during pregnancy. However, a recent meta-analysis demonstrated a marginally increased risk of major malformation and a 3.4-fold increased risk of oral cleft in infants exposed to corticosteroids in the first trimester.

Pharmacologic treatments for nausea and vomiting of pregnancy and hyperemesis gravidarum are summarized in Table 2.

TABLE 2
Pharmacologic Therapy for Nausea and Vomiting of Pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage*</th>
<th>Pregnancy category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridoxine (Vitamin B₆)†</td>
<td>25 mg orally three times daily</td>
<td>A‡</td>
</tr>
<tr>
<td>Doxylamine (Unisom)†</td>
<td>25 mg orally once daily</td>
<td>§</td>
</tr>
<tr>
<td>Antiemetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine (Thorazine)</td>
<td>10 to 25 mg orally two to four times daily</td>
<td>C</td>
</tr>
<tr>
<td>Promethazine (Phenergan)</td>
<td>12.5 to 25 mg orally every four to six hours</td>
<td>C</td>
</tr>
<tr>
<td>Trimethobenzamide (Tigan)</td>
<td>250 mg orally three or four times daily</td>
<td>C</td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>8 mg orally two or three times daily</td>
<td>B</td>
</tr>
<tr>
<td>Droperidol (Inapsine)</td>
<td>0.5 to 2 mg IV or IM every three or four hours</td>
<td>C</td>
</tr>
<tr>
<td>Antihistamines and anticholinergics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine (Benadryl)</td>
<td>25 to 50 mg orally every four to eight hours</td>
<td>B</td>
</tr>
<tr>
<td>Meclizine (Antivert)</td>
<td>25 mg orally every four to six hours</td>
<td>B</td>
</tr>
<tr>
<td>Dimenhydrinate (Dramamine)</td>
<td>50 to 100 mg orally every four to six hours</td>
<td>B</td>
</tr>
<tr>
<td>Motility drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide (Reglan)</td>
<td>5 to 10 mg orally three times daily</td>
<td>B</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone (Medrol)</td>
<td>16 mg orally three times daily; then taper</td>
<td>C</td>
</tr>
</tbody>
</table>

IV = intravenously; IM = intramuscularly.

*—These regimens usually are administered only as needed.
†—Although some research supports the effectiveness and safety of combination pyridoxine-doxylamine (Bendectin), the manufacturer voluntarily withdrew the medication from the U.S. market in 1983 after isolated studies raised questions about potential teratogenicity. The product remains available in Canada under the trade name Diclectin (10 mg of pyridoxine and 10 mg of doxylamine in a delayed-release tablet). Diclectin typically is prescribed in a dosage of two tablets at night for mild symptoms and in a dosage of up to two tablets three times daily (six tablets per day) for more severe symptoms.
‡—The pregnancy category for doxylamine relates to its use as a vitamin supplement.
§—According to the Physicians’ Desk Reference for Nonprescription Drugs and Dietary Supplements, doxylamine should not be taken by pregnant women or women who are nursing a baby; however, some research supports its efficacy and safety.

Information from references 16, 23, 35, 36, and 37.
Nausea and Vomiting of Pregnancy

Nausea and vomiting in a pregnant woman

Rule out nonpregnancy causes (see Table 1).

Positive findings (i.e., nonpregnancy cause identified)

- Treat or refer as appropriate.

Negative findings

Dietary changes and emotional support

No resolution

Options: pyridoxine (vitamin B₆), doxylamine (Unisom),* acupressure, ginger

Resolution

Routine prenatal care

No resolution

Check ketone and electrolyte levels.

Abnormal

Options: intravenous fluids, hospitalization, antiemetics, antihistamines, anticholinergics, corticosteroids

No resolution

Consider total parenteral nutrition. Obtain maternal-fetal medicine consultation.

Resolution

Routine prenatal care

Normal

Options: antiemetics, antihistamines, anticholinergics, corticosteroids

No resolution

Routine prenatal care

Resolution

Routine prenatal care

*—According to the Physicians’ Desk Reference for Nonprescription Drugs and Dietary Supplements,* doxylamine should not be taken by pregnant women or women who are nursing a baby; however, some research supports its efficacy and safety.

FIGURE 1. Algorithm for the suggested evaluation and management of women with nausea and vomiting of pregnancy.
OTHER TREATMENTS

Intravenous Fluids. Pregnant women who, despite the previously discussed treatments, are unable to keep down liquids will probably require intravenous fluids. Normal saline or lactated Ringer’s solution is the mainstay of intravenous fluid therapy. Many physicians use solutions that contain dextrose; however, it may be advisable to give thiamine (vitamin B<sub>1</sub>) first, because of the theoretic risk of Wernicke’s encephalopathy.

Intravenous fluid may provide relief from nausea and vomiting, but many pregnant women also require an antiemetic administered orally, rectally, or by infusion with the fluid. Depending on the severity of the symptoms, intravenous fluid therapy may be given in the hospital or at home by a visiting nurse.

Enteral or Parenteral Nutrition. Enteral tube feeding and TPN are last-resort treatments for pregnant women who continue to vomit and lose weight despite aggressive treatment with any or all of the previously discussed modalities. Few studies have evaluated enteral nutrition, although all seven women in one small study tolerated feedings using an 8-French Dobbhoff nasogastric tube and infusion rates of up to 100 mL per hour.

TPN is administered through a central venous catheter. Its content is determined by the pregnant woman’s daily caloric requirements and any existing electrolyte abnormalities. Consultation with a perinatologist experienced in parenteral nutrition, as well as a gastroenterologist or inpatient parenteral nutrition service, may be prudent. Both TPN and central venous access can result in significant complications, including sepsis.

An algorithm for the suggested evaluation and management of women with nausea and vomiting of pregnancy is provided in Figure 1.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Medical Department of the U.S. Navy or the U.S. Naval Service at large.

REFERENCES