Continued from previous page

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)

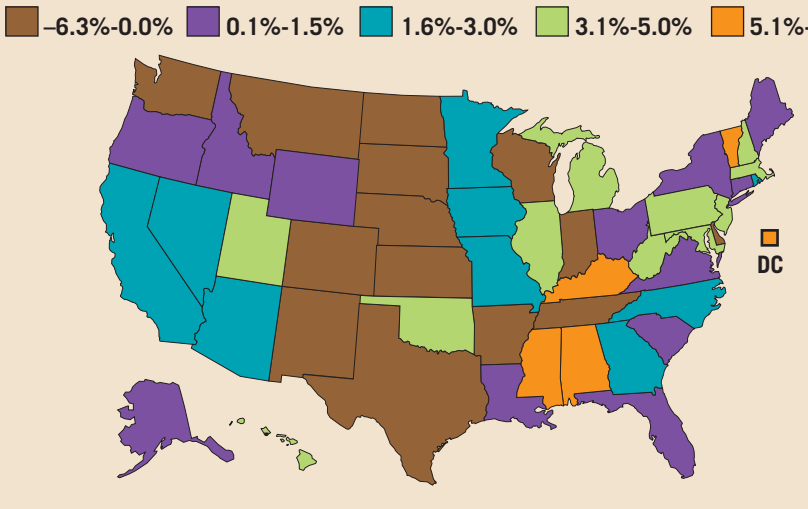
Corticosteroids

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

Elsevier Global Medical News