CASE  Pregnant patient seeks medication for her NVP
A 23-year-old G1P0 woman at 9 weeks’ gestation presents to your office with nausea and vomiting that is interfering with work. She has tried many changes in her daily habits. She has tried eating small, frequent meals; snacking on nuts and crackers; using lemon-scented products; and avoiding coffee and strong odors. Following an evaluation you diagnose nausea and vomiting of pregnancy (NVP). She asks, “Is there a medication for my nausea that is safe for my baby?”

Nausea with or without vomiting is a common problem for pregnant women between 6 and 14 weeks of gestation. In one study, nausea with or without vomiting was reported by 69% of patients and resulted in pharmacologic treatment in 15%. In a Cochrane review of NVP, investigators analyzed 37 trials involving treatments such as acupressure, acustimulation, acupuncture, ginger, chamomile, lemon oil, vitamin B6, and antiemetic medications. The authors concluded, “There is a lack of high-quality evidence to support any particular intervention.”

Clinicians are challenged to effectively treat the symptoms of NVP and simultaneously to minimize the risk that the fetus will be exposed to a teratogen during the first trimester, a vulnerable period in organ development.

In this editorial, I briefly review nonpharmacologic options for NVP, but focus on current pharmacologic treatments. Of those available to ObGyns, what is the best first-choice treatment given recent and accumulated data regarding associated congenital anomalies?

Nonpharmacologic treatment
Although the authors of the Cochrane review did not identify high-quality evidence to support nonpharmacologic interventions, results of multiple randomized trials have demonstrated that ginger is effective in reducing pregnancy-associated nausea and vomiting. Ginger treatment is recommended at doses of 250 mg in capsules or syrup four times daily.

First-line pharmacologic treatment: Doxylamine plus pyridoxine
The US Food and Drug Administration (FDA) has approved the combination of doxylamine plus pyridoxine (vitamin B6) in a delayed-release formulation for treatment of NVP (Diclegis). Doxylamine is an antihistamine that blocks H1-receptor sites in the chemoreceptor trigger zone. It also diminishes vestibular stimulation and depresses labyrinthine activity through central anticholinergic
activity. Its elimination half-life is 10 to 12 hours (Lexicomp). Each tablet contains doxylamine 10 mg and pyridoxine 10 mg. The starting dose is 2 tablets at bedtime.

If the woman has persistent symptoms, a third tablet is added, to be taken in the morning. If symptoms continue, a fourth tablet is recommended to be taken in the afternoon. In a large, randomized clinical trial, doxylamine-pyridoxine treatment reduced nausea, vomiting, and retching and improved perceived quality of life compared with placebo. The FDA assigned doxylamine-pyridoxine pregnancy category A because of the extensive evidence that it does not cause an increase in fetal malformations.

If the delayed-release doxylamine-pyridoxine formulation (Diclegis) is not available to the patient, alternative formulations of doxylamine and pyridoxine can be prescribed. Pyridoxine is widely available over the counter as 25-mg tablets, and one tablet can be prescribed two or three times daily. Doxylamine is available as a chewable prescription medicine in 5-mg tablets (Aldex AN) and two tablets can be prescribed two or three times daily. Doxylamine is also available as a 25-mg over-the-counter tablet in Unisom SleepTabs. One-half tablet can be prescribed two or three times daily. The patient should be alerted that Unisom SleepGels contain diphenhydramine, not doxylamine.

**Second-line pharmacologic treatment: Metoclopramide**

Metoclopramide is a dopamine antagonist. It enhances upper gastrointestinal motility, accelerates gastric emptying, and increases lower esophageal sphincter tone. At higher doses it blocks serotonin receptors in the chemoreceptor trigger zone. Its elimination half-life is 5 to 6 hours (Lexicomp). There are no large, randomized, placebo-controlled trials of oral metoclopramide for the treatment of nausea and vomiting of early pregnancy.

I am recommending metoclopramide as a second-line treatment for NVP because it appears to be effective and is not known to be associated with an increased risk of congenital malformations. Metoclopramide is widely used to prevent and treat intraoperative and postoperative nausea associated with cesarean delivery. In addition, intravenous (IV) metoclopramide is commonly used to treat women hospitalized with hyperemesis gravidarum. Results of randomized clinical trials demonstrate that when used to treat hyperemesis gravidarum, IV metoclopramide (10 mg every 8 hours) has similar efficacy to IV ondansetron (4 mg every 8 hours) and IV promethazine (25 mg every 8 hours). When using metoclopramide as an oral treatment for NVP, 10 mg every 8 hours is a commonly recommended regimen.

The FDA has assigned metoclopramide to pregnancy category B, which indicates that there is no evidence of fetal risk. Studies from Israel and Denmark show that metoclopramide is not associated with an increased risk of congenital malformations. In the study from Israel, among 3,458 infants born to women who had filled a prescription for metoclopramide during the first trimester of pregnancy, there was no increase in major congenital malformations, low birth weight, preterm delivery, or perinatal death. In the study from Denmark, among 28,486 infants born to mothers who had filled a prescription for metoclopramide during the first trimester there was no increase in major congenital malformations or any of 20 individual categories of malformations, including neural tube defects, transposition of the great vessels, ventricular septal defect, atrial septal defect, tetralogy of Fallot, coarctation of the aorta, cleft lip or palate, anorectal atresia/
stenosis, or limb reduction. The results of these two large studies are reassuring that metoclopramide is not associated with an increased risk of congenital malformations.

Metoclopramide can cause tardive dyskinesia, a serious movement disorder that may be irreversible with discontinuation of the drug. This risk increases with dose and length of treatment. The FDA recommends that clinicians avoid the use of metoclopramide for more than 12 weeks.

Third-line pharmacologic treatment: Ondansetron
In the United States ondansetron is commonly used to treat NVP. The drug is a selective 5-HT₃ antagonist that blocks serotonin action in the central nervous system chemoreceptor trigger zone. The elimination half-life of ondansetron is 3 to 6 hours (Lexicomp).

The frequent use of ondansetron may be due, in part, to the perception that it is a very effective antiemetic. For example, in one small clinical trial, ondansetron 4 mg every 8 hours was reported to be superior to a combination of pyridoxine 25 mg every 8 hours plus doxylamine 12.5 mg every 8 hours. (Note that the pyridoxine and doxylamine tablets used in this trial were not in a combination delayed-release formulation.) I am recommending ondansetron as a third-line treatment for NVP because, although it is effective, it may be associated with an increased risk of fetal cardiac anomalies.

Is ondansetron associated with cardiac malformations?
The FDA has assigned ondansetron to pregnancy category B; however, there is concern that it may be associated with congenital heart defects. In a recent study of 1,349 infants born to Swedish women who had filled a prescription for ondansetron in early pregnancy, a significantly increased risk of cardiovascular defect (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.04–2.14) and cardiac septum defect (OR, 2.05; 95% CI, 1.19–3.28) was reported. The cardiovascular anomalies were mostly atrial septal or ventricular septal defects.

In a second study, reported as an abstract, authors analyzed congenital malformations in 1,248 infants born to Danish women who filled a prescription for ondansetron in early pregnancy. These authors also found an increased risk of a congenital heart malformation (OR, 2.0; 95% CI, 1.3–3.1).

A US case-control study showed an association between ondansetron use and cleft palate. The Swedish and Danish studies reported above did not find an association between ondansetron use and cleft palate.

The FDA issued a warning in June 2012 that at a dose of 32 mg, administered intravenously, ondansetron may prolong the QT interval and result in a potentially fatal heart arrhythmia, torsades de pointes. In the announcement the FDA did not alter the recommendations for oral dosing because there is no strong evidence that oral dosing is associated with clinically significant arrhythmias. Authors of a recent systematic review concluded that IV administration of large doses of ondansetron may cause cardiac arrhythmias, especially in patients with cardiac disease and those taking other drugs that prolong the QT interval, but that a single oral dose of ondansetron does not have a significant risk of causing an arrhythmia.

Health Canada has advised that many commonly prescribed medications increase serotonin activity. When multiple drugs that each increase serotonin activity are prescribed in combination, the risk of serotonin syndrome is increased. Serotonin syndrome results in hyperthermia, agitation, tachycardia, and muscle twitching and can be fatal. Ondansetron was specifically mentioned in the Health Canada warning, but a search of the literature revealed very few reported cases of ondansetron being implicated in the serotonin syndrome.

My bottom-line recommendations
NVP is a common obstetric problem. When oral pharmacologic therapy is indicated, first-line treatment should be with the FDA-approved combination of doxylamine-pyridoxine because it is both effective and associated with no known increased risk of congenital malformations. An effective second-line agent is metoclopramide. Based on very limited data, metoclopramide appears effective and is not associated with an increased risk of congenital malformations. However, it is not FDA approved for treatment of NVP. Ondansetron appears to be effective but its use in early pregnancy may be associated with congenital anomalies. Consequently, ondansetron should not be used to treat NVP unless first- and second-line treatments have been ineffective to treat the patient’s symptoms.

Dr. Barbieri reports no financial relationships relevant to this article.

References


