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SAFE PRESCRIBING PRACTICES IN PREGNANCY AND LACTATION

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ABSTRACT

Midwives and other health care providers face a dilemma when a pregnant woman develops a condition that usually is treated with a pharmacologic agent. Understanding of basic teratology associated with drugs as well as the FDA categorization of agents can assist professionals in recognizing which pharmaceuticals should be used or avoided. In addition to reviewing teratology, this article addresses the use of common drugs for the treatment of upper respiratory conditions, minor pain, gastrointestinal problems, psychiatric illnesses, and neurologic disorders. In each category, current evidence is presented pertaining to which agents should be recommended for pregnant women. J Midwifery Womens Health 2002;47:409–421

INTRODUCTION

How often do pregnant women take medication? One study of women in the United States reported that 62% received a non-dietary supplement medication during pregnancy. One fourth of the women received a narcotic-containing medication, and 13% received a psychotropic drug (1). Another study showed that mothers received an average of 3.1 non-vitamin medications during pregnancy (2). A recent study of French women showed that 99% received a prescription for at least one medication during pregnancy, with a mean of 13.6 medications per woman (3): 1.6% of the women received a medication in the U.S. Food and Drug Administration (FDA) X category (fetal risk outweighs benefits), and 59% of women had a prescription for drugs from the D category (fetal risk but benefits may be acceptable). When expressed as a percentage of exposed women, the most commonly prescribed classes of drugs were gastrointestinal drugs (69.4%), dermatologic drugs (63.0%), and analgesics (62.3%) (3). An accompanying commentary does point out that, for cultural reasons, the French have one of the highest prescribing levels in Europe.

Nevertheless, these rates of prescribed drug use during pregnancy are of concern due to the known and unknown effects of the medications on the developing fetus. In contrast, Czeizel (4), responding to the French study (3), noted that women may be unnecessarily frightened by some of the information they receive concerning medications, leading to unnecessary terminations. He cites a 1990 study in Hungary (5), which showed that about 70% of pregnant women took a medication and 1.7% received a possible human teratogen based on the Swedish classification.

The data outlined above illustrate the difficulties that health care providers for pregnant women face. During pregnancy, women continue to be affected by the usual illnesses that the non-pregnant population faces. In addition, there are multiple conditions, some of which directly result from the pregnancy or are worsened by it, that may require pharmacologic therapy. Thus, the health care provider must be aware of appropriate pharmacologic therapy for a variety of conditions and the potential impact on the pregnant or lactating women. In general, the clinician should ask what the appropriate treatment in the non-pregnant state would be. In most cases, the answer is the same for women who are pregnant (6). When several choices are available, as is often the case, the second principle is to choose pharmacologic agents by their relative safety for the patient and the fetus.

Prescribing medication for pregnant or lactating women requires knowledge of teratogenicity and fetal and neonatal effects that may be associated with the drugs under consideration (6). This article reviews the risks associated with treatment of several of the most common disorders seen in the pregnant population, including both prescription and over-the-counter medications for upper respiratory complaints, aches and pains, gastrointestinal problems, psychiatric illnesses, headaches, and seizures.

TERATOGENICITY OF DRUGS

Teratology is the study of abnormal development or the production of defects in the fetus (7). Little information was available about teratogenesis before 1950, when most defects were believed to be genetic in origin (8,9). Birth defects affect 2%–3% of neonates in the United States (10). Exogenous causes of birth defects, including drugs or chemical exposures, account for almost 10% of

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all birth defects. Thus, about 0.2%–0.3% of pregnancies are affected by teratogenic agents.

Exposure to agents during the first 2–3 weeks after conception is generally thought to have no effect or result in spontaneous loss (the "all-or-none" phenomenon). The period of susceptibility to teratogenic agents is classically thought to be from 3 to 8 weeks postconception (35–70 days after the last menstrual period) or to 10 weeks from the last menstrual period (11). Thus, the first trimester is the most critical time period for a teratogenic effect. After this, any effect will likely involve growth restriction or an effect on the nervous system and gonadal tissue. Overall growth continues throughout the remainder of the pregnancy and because the nervous system and gonads develop slower than other organ systems, they are vulnerable to teratogenic effects over a longer period of time.

Characterization of an agent as a human teratogen requires 1) documented exposure at a critical time in prenatal development, 2) consistent statistically significant findings by two or more epidemiologic studies (of high quality) that associate drug exposure with subsequent characteristic pattern of malformations, 3) careful delineation of clinical cases, and 4) rare environmental exposure associated with a rare defect.

Although not absolutely required, proof of teratogenicity ideally includes 1) teratogenicity in experimental animals, 2) an association that is biologically plausible, and 3) experimental proof that the agent acts in an unaltered state (12).

SAFETY OF DRUGS DURING PREGNANCY

To address teratogenicity and to discourage use of nonessential medication during pregnancy, the FDA introduced a drug classification system in 1979 (13,14). Several characteristics of the FDA classification system may lead to overly frightening perceptions by the public of drug dangers. For example, it has been known for some time that only about 20–30 commonly used drugs are proven teratogens, yet 7% of the more than 1,000 medications listed in the *Physicians' Desk Reference* are classified as category X (15,16). The definitions of the FDA pregnancy safety categories are listed in Table 1. All new medications are classified as category C because most products initially FDA approved to be both safe and efficacious have only animal data available on teratogenicity and teratogenicity in animals is common. This leads to an elevated impression of danger in drugs that have not been used for extensive periods of time. In addition, there are no FDA regulations requiring further study, seeking more data or performing human evaluations so that changes in classification are rare.

The Teratology Society, a multidisciplinary scientific society founded in 1960, suggested abandoning the FDA classification in 1994 (15). They further suggest use of a narrative-based system to summarize available data. The FDA has begun working on such a narrative-based system, and information is available online (http://www.fda.gov; search site for "pregnancy" and "labeling"). Briefly, the FDA began to ask a series of questions concerning the pregnancy labeling system that had been started in 1979. At a public hearing in September 1997, they asked whether health care providers relied on the system, is it useful, what is good or bad about it, and

TABLE 1
U.S. Food and Drug Administration Drug Risk Categories

Category A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
Category B: Either animal reproduction studies have not demonstrated fetal risk but no controlled studies in pregnant women have been reported, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters.)
Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) but no controlled studies in women have been reported, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Category D: Positive evidence of human fetal risk exists, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed for a life-threatening condition or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X: Studies in animals or human beings have demonstrated fetal abnormalities, or evidence exists of fetal risk based on human experience, or both, and the risk in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

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what are the problems and how can they be fixed? It has been thought that the system in place is used and appreciated for its simplicity. On the other hand, the simplicity is a problem when trying to apply it in clinical decision making, given the fact that the data behind the specific category assignments is not clearly evident.

In May 1999, a concept article that outlined a model for labeling and included suggested sections titled, "clinical management statement," "summary risk assessment," and "discussion of data" for both pregnancy and lactation was presented. Discussion of the new system is ongoing and includes the suggestion of establishing pregnancy registries to provide data about exposure during gestation. The final form of labeling that the FDA will approve is to date undetermined

Given the difficulty of ascertaining safety on the basis of FDA assigned categories, we suggest that providers become familiar with some of the Internet databases and Web sites with drug information to provide the most accurate and up-to-date information to patients. The three databases housed within the REPRORISK system are described in the Resources for Clinicians column in this issue and listed in Appendix A of this article. These commercially available databases have extensive up-to-date lists of teratogens and their known effects.

Periodically, the American Academy of Pediatrics (AAP) issues a policy statement about the transfer of drugs into breast milk and the safety of breastfeeding while taking these drugs. A statement on the transfer of drugs and chemicals into human milk was first published in 1983, with revisions in 1989, 1994, and most recently in 2001 (17). The AAP statement is based on a thorough review of the literature. Exposures are then placed in one of seven categories: 1) cytotoxic drugs that may interfere with cellular metabolism of the nursing infant, 2) drugs of abuse for which adverse effects on the infant during breastfeeding have been reported, 3) radioactive compounds that require temporary cessation of breast feeding, 4) drugs for which the effect on nursing infants is unknown but may be of concern, 5) drugs that have been associated with significant effects on some nursing infants and should be given to nursing mothers with caution, 6) maternal medication usually compatible with breastfeeding, and 7) food and environmental agents' effects on breastfeeding.

UPPER RESPIRATORY CONDITIONS

The common cold is the most frequent acute illness affecting humans (18). Most commonly, the cold is due to rhinoviruses (30%–40%), but colds can also be caused by coronaviruses, respiratory syncytial virus, adenovirus, parainfluenza virus, influenza virus, and others (19). Patients typically present with fatigue, malaise, rhinorrhea, nasal congestion, cough, and sore throat. Fever may be present and is usually low grade. Most symptoms last less than 2 weeks, although the cough may linger longer (20). Transmission is from a contagious individual's nose to their hand, from their hand to another's hand, and from there to the mucus membranes of the nose or eyes. Transmission can also be via fomites (19).

Treatment for the common cold is generally symptomatic. We advise trying to specifically treat the most bothersome symptoms with the most specific medications. This allows for limiting the number and dose of administered pharmacologic agents. Generally, the medications will include antihistamines, decongestants, and cough suppressants.

Several large studies have evaluated the use of antihistamines in pregnancy (21,22). It appears that the older sedating agents are safe in pregnancy. These agents have been studied in more depth than the recently introduced non-sedating medications within the antihistamine family. In the Collaborative Perinatal Project (21) chlorpheniramine (Chlor-Trimeton), diphenhydramine (Benadryl), trimethobenzamide (Tigan), methapyrilene, thonzylamine, pyrilamine, tripelennamine (PBZ-SR), phenyltoloxamine, and buclizine were not associated with an increased risk of malformations. There were 10 malformed infants among 65 women exposed to brompheniramine (Bromfed) during the first trimester, yielding a relative risk of 2.34 ($P < .05$). Their defects were mild, and the rates varied at the different participating institutions, making the clinical relationship to drug ingestion questionable despite the statistical significance. Furthermore, in the Boston Collaborative Drug Surveillance Program (22), only 5 of 172 brompheniramine (Bromfed)-exposed women delivered malformed infants, which was equal to the expected background rate of malformations seen in women unexposed to any teratogen. Triprolidine with pseudoephedrine (Actifed) and phenylpropanolamine with chlorpheniramine (Ornade) were found to be safe.

The newer non-sedating antihistamines, including cetirizine (Zyrtec), loratadine (Claritin), and fexofenadine (Allegra), have not been extensively studied. Cetirizine (Zyrtec) appeared safe in a study involving 39 exposed women (23). No human data are available for loratadine (Claritin) or fexofenadine (Allegra).

Administration of topical nasal decongestants or steroids appear safe in pregnancy. The safety of inhaled steroids was demonstrated in 229,101 Michigan Medicaid recipients where there were 395 newborns exposed to beclomethasone (24). Use of the topical nasal decongestant oxymetazoline (Afrin) and xylometazoline (Otrivin) was safe in the Boston Collaborative Program (22). The Collaborative Perinatal Project showed a higher rate of eye and ear malformations in infants exposed to phenylephrine (Neo-Synephrine), but it was not clear whether the exposures were topical or systemic, making this agent

a second choice at best (21). The commonly used newer topical nasal steroid preparations: beclomethasone (Vancenase, Beconase), budesonide (Rhinocort), dexamethasone (Decadron), flunisolide (Nasalide), and others have not been studied in large trials. Given little systemic absorption, all the nasal preparations noted above should be safe to use. The oral decongestants include pseudoephedrine (Sudafed) and phenylephrine (Codimal), and both appear safe.

The diagnosis and treatment of cough was recently reviewed (25). The primary cough and sore throat remedies are codeine and dextromethorphan, although many preparations also include the expectorant guaifenesin (glyceryl guaiacolate). All three of these agents appear safe in pregnancy. Cough syrups containing alcohol should be avoided during pregnancy.

In recommending prudent choices for the pregnant woman with the common cold, one theme would be to treat her specific symptoms rather than use a broad array of pharmacotherapy. Rhinorrhea and nasal congestion can be treated with pseudoephedrine (Sudafed) or a combination product like chlorpheniramine and pseudoephedrine. Cough can be treated with products containing dextromethorphan but not alcohol. Some women have very difficult-to-treat coughs, which can become debilitating by interfering with sleep and codeine can be very effective for them. Over-the-counter cold and cough preparations can contain varying combinations of antihistamines, analgesics, decongestants, and cough preparations. A partial list of common over-the-counter formulations with is shown in Appendix B.

Lactating women can achieve symptomatic relief from the common cold with the use of antihistamines, decongestants, and codeine, which are all generally considered safe during breastfeeding. Other reviews have found no problems with antihistamine use during lactation (26).

In contrast to colds, bacterial sinusitis and streptococcal infections should be treated with antibiotics. Distinguishing between a viral cold, streptococcal infection, and bacterial sinusitis can be difficult. Most patients with sinus infections do not have the classic symptoms of maxillary toothache, purulent nasal secretions on physical examination, history of colored nasal discharge, abnormal maxillary sinus transillumination, or a poor response to decongestants as those with sinusitis typically have (27,28). Ultimately, the caregiver will have to decide appropriate treatment based on clinical judgment and discussion with the patient. Appropriate antibiotic choices include cefuroxime axetil, clarithromycin, cefprozil, and amoxicillin/clavulanate (29).

Diagnosis of streptococcal infection can be aided by use of a rapid streptococcal antigen test or throat culture. In the presence of fever, purulent pharyngitis, and tender cervical lymph nodes, antibiotics can be prescribed immediately. The antibiotic of choice is penicillin G or, for the allergic patient, erythromycin, azithromycin, or a second-generation cephalosporin (29). The issue of use of cephalosporins in the patient with a reported penicillin allergy is controversial and has been recently reviewed (30). Three approaches to treatment of the penicillin-allergic patient are supported by different sets of literature. One approach is to avoid all antibiotics with a beta-lactam ring including cephalosporins. A second approach is to treat the patient as long as the allergy did not result in serious sequelae such as anaphylaxis or immediate hypersensitivity reaction. The third approach is to skin test for penicillin and to only treat those with negative tests. The latter strategy is probably best for patients with a history of a serious reaction and a current strong indication for prescribing a cephalosporin (30).

ANALGESICS

Analgesics are another group of medications commonly used during pregnancy. Generally, the analgesics fall into three broad categories: the non-steroidal anti-inflammatory agents (which includes aspirin), acetaminophen, and the opioids.

Acetylsalicylic acid (Aspirin) acts by creating an irreversible inhibition of the enzymes responsible for prostaglandin synthesis, specifically those prostaglandins (Thromboxane A) that cause platelet aggregation and vasoconstriction. In more than 5,100 pregnancies in which aspirin was used during the first 16 weeks of pregnancy, no detectable increase in fetal malformations was seen (31). More recently, several reports have suggested that there is an association between maternal aspirin use and an increase in the incidence of fetal gastroschisis (32,33). In one study, aspirin was found to have an increased relative risk of 4.7-fold (CI 1.2–18.1) (32), whereas another found an increased relative risk of 3.33-fold over background (CI 1.05–9.80) for gastroschisis (33). Earlier studies had made similar suggestions, increasing the chance that this is not a spurious finding (34,35). Thus, women should not use regular doses of aspirin ($>$150 mg/day) during pregnancy.

Aspirin has been considered for prevention of preeclampsia and intrauterine growth restriction in women at high risk for developing these conditions. It is now clear that low-dose aspirin (60–100 mg) does not decrease the incidence of preeclampsia or intrauterine growth restriction in women at risk (36–38). Some have stated that higher doses may be needed because the positive effect on vasculature reactivity and platelet aggregation will only be evident when increases in maternal bleeding time can be documented (39). However, maternal serum thromboxane concentrations did not predict outcome in a large National Institutes of Health trial (40). Low-dose aspirin has also been used to improve the outcomes of women with antiphospholipid

antibody syndrome (APAS). Criteria necessary to diagnose APAS require both clinical (pregnancy losses or thrombosis) and presence of specific autoimmune antibodies (eg, lupus anticoagulant and others) (41). At least one study showed little benefit of aspirin in improving pregnancy outcome of women with APAS (42).

In general, the lower doses of aspirin (60–100 mg) are believed to be safe from significant maternal or fetal problems. Their utility as a preventive or treatment modality is open to question. Higher doses should be avoided because of an increased risk of abruption and other bleeding problems and the increased risk of gastroschisis. Because high doses of aspirin should not be used because of concerns about inducing placental abruption and the lower doses of 60–100 mg that would be safe are too low for an analgesic effect, during pregnancy, aspirin should be reserved for women with APAS

The World Health Organization (WHO) Working Group on Human Lactation has classified the salicylates as unsafe for use by nursing women (43). The American Academy of Pediatrics Committee on Drugs advises caution with use during lactation (17). In both cases, concern is due to the potential of slow accumulation of elevated levels in the neonate leading to bleeding problems. One case of metabolic acidosis has been reported as well (17).

Acetaminophen is used more frequently than aspirin during pregnancy (44). In recommended doses, it is considered a safe medication. No increase in congenital abnormalities was seen with maternal use in the Collaborative Perinatal Project (21) or another large study of more than 690 first-trimester exposures (22). Use of acetaminophen is also considered safe during lactation by the American Academy of Pediatrics and the WHO (17,43).

The classic nonsteroidal antiinflammatory agents (NSAIDs) include indomethacin (Indocin), which unlike aspirin, causes a reversible inhibition of cyclooxygenase. The medication is used as a tocolytic and to treat the pain of degenerating leiomyomas when necessary, yet it can also cause constriction of the fetal ductus arteriosus in doses as low as 1 mg/kg orally (45). The effect increases with gestational age (46), and use of indomethacin (Indocin) is not recommended after 32 weeks' gestation. In addition, indomethacin can cause profound adverse effects on fetal renal function, leading to decreased urine output and frank oligohydramnios (47,48). If indomethacin is given for a prolonged period, oligohydramnios can lead to pulmonary hypoplasia and neonatal death. In general, we do not recommend use for more than 2 days beyond the first trimester. Similar but more limited information is available for ibuprofen (Advil). Both indomethacin and ibuprofen are considered compatible with breastfeeding (17).

Many opioid or narcotic analgesics are available, including codeine, meperidine (Demerol), and oxycodone (Percocet). None have been shown to cause malformations (13,21,49), but there are concerns about the potential of neonatal withdrawal or neonatal respiratory depression when used in the last weeks to hours before delivery (50). The lactating mother should look for signs of neurologic depression if she is taking multiple doses of narcotics, but they are considered compatible with breastfeeding by the American Academy of Pediatrics (17).

TREATMENT OF GASTROINTESTINAL PROBLEMS

Gastrointestinal problems are extremely common in pregnancy and include nausea, vomiting, hyperemesis gravidarum, gastroesophageal reflux, intrahepatic cholestasis of pregnancy, and inflammatory bowel disease. The presentation of several serious disorders may be altered or overlooked during pregnancy and include appendicitis, cholecystitis, pancreatitis, hepatitis, and carcinoma of the gastrointestinal tract.

Nausea and Vomiting of Pregnancy

Nausea and vomiting, often referred to as "morning sickness," occurs in 70%–85% of pregnancies (51). The symptoms can range from mild to debilitating. In extreme cases, the morning sickness progresses to hyperemesis gravidarum, which is diagnosed when the client has persistent vomiting that leads to fluid and electrolyte abnormalities and at least a 5%–10% weight loss from prepregnancy weight.

Non-pharmacologic therapy has been used successfully to eliminate nausea and vomiting of pregnancy. Two recent publications have evaluated acupressure or acustimulation at the Neiguan point (P6). The P6 point is located on the surface of the forearm about 4–5 cm above the wrist (52). In a study from Sweden, 60 women were randomized to receive pressure at P6, pressure at another point, or no treatment. In the experimental group, a band was used to apply pressure at P6; a similar band applied pressure at a point on the upper side of the wrist in the second group. Women with nausea and vomiting not receiving other treatment could take part in the study. The bands were worn for 2 weeks, with removal only during showering. Significant differences were found in ratings of nausea with a reduction in the P6 group versus the no-treatment group. There was some initial effect in the group receiving pressure at the non-P6 point, which disappeared in the second week.

Another study used a device that provided an electrical stimulus similar to a transcutaneous nerve stimulator at the P6 site (53). Only women less than 11 weeks' pregnant were included in the study. No control group

was studied, but the 41 patients taking part reported the therapy to be highly effective in providing significant or complete relief. These recent studies confirm earlier works supporting acupressure in reducing nausea (54), although possibly not as effective in decreasing the frequency of vomiting (55). A recent trial of acupuncture using a control group that received sham treatment showed no benefit of the acupuncture over the sham treatment (56), whereas a second trial of deep versus superficial acupuncture at P6 did show benefit (57). No risks have been reported to the fetus from these treatment modalities. Several studies have shown benefit of ginger (58–60) in reducing nausea and vomiting. No clear risks have been seen with ginger supplementation including capsule form.

Pyridoxine (vitamin B6) is a water-soluble vitamin, which has been shown to reduce nausea and vomiting in pregnancy (61). In two randomized, double-blind placebo-controlled trials, oral pyridoxine 10 or 25 mg was given every 8 hours for 3–5 days with significant relief (62,63). No substantive evidence exists linking pyridoxine with teratogenic risk. Pyridoxine was a component of Bendectin (with dicyclomine and doxylamine), which was voluntarily withdrawn from the market in 1984. Bendectin was the only FDA-approved drug for nausea and vomiting of pregnancy. The manufacturer removed the medication after several large legal settlements against the manufacturer following false allegations that the drug was teratogenic (64).

When dietary manipulations and/or the nonpharmacologic treatments outlined above fail, pharmacologic treatment can be necessary for quality of life or to avoid serious medical complications. Generally, the agents used fall into one of three categories: antihistaminic, antidopaminergic, and other. Doxylamine (Unisom) is an antihistamine and was also a component of Bendectin. Usually taken as 25 mg orally at bedtime, the dose can be split into 12.5 mg taken twice a day. Pyridoxine can be added, effectively recreating the components of Bendectin. Doxylamine is safe in the first trimester. Dimenhydrinate (Dramamine) is usually taken 50–100 mg orally every 4 hours. It can be administered intramuscularly or intravenously as well. Diphenhydramine (Benadryl) is given as 50 mg orally three to four times per day. Both the latter medications appeared safe in the Collaborative Perinatal Project (24). Other medications that appear safe include meclizine (Antivert) 20–50 mg orally per day, hydroxyzine (Vistaril, Atarax) 25–100 mg orally three to four times per day, and promethazine (Phenergan) 12.5–25 mg orally every 4–6 hours.

Among the antidopaminergic agents, prochlorperazine (Compazine) 5–10 mg orally every 3–4 hours and metoclopramide (Reglan), which can be given 5–10 mg orally up to four times per day, can reduce nausea and vomiting and appear safe. Other agents include trimethobenzamide hydrochloride (Tigan) and ondansetron hydrochloride (Zofran). Although they can be effective, trimethobenzamide can have several serious side effects, and it is not clear that ondansetron offers a benefit over other therapies like promethazine (65). Ondansetron is also extremely expensive.

Several medications can be administered as rectal suppositories for the patient who cannot tolerate them orally. This includes promethazine (Phenergan), chlorpromazine (Thorazine), and prochlorperazine (Compazine). Medications effective for treatment of nausea and vomiting during pregnancy are summarized in Table 2.

Gastroesophageal Reflux

Gastroesophageal reflux (heartburn) can occur alone or in combination with nausea and vomiting. A wide variety of treatments appear both efficacious and safe. Antacids that contain aluminum, calcium, and magnesium salts can be used to neutralize stomach acids. Because they can bind with other medications and vitamins, they should be taken an hour apart from other medications. The histamine-2 receptor antagonists are also safe and include cimetidine (Tagamet), famotidine (Pepcid), and ranitidine (Zantac).

Intrahepatic Cholestasis

Intrahepatic cholestasis of pregnancy is one of the few gastrointestinal disorders that adversely affect both maternal and fetal well-being. Although not completely understood, multiple factors interact along with a genetic predisposition to alter the membrane composition of the bile ducts and hepatocytes. Serum bile acids (chenodeoxycholic acid, deoxycholic acid, and cholic acid) are increased. These acids are deposited in the skin and probably cause the extreme pruritus. Pruritus without accompanying rash on the arms, legs, and trunk typically begins after 20 weeks and progresses until delivery. This is accompanied by increases in liver function enzymes and conjugated bilirubin. Both symptoms and laboratory abnormalities rapidly resolve after delivery.

Intrahepatic cholestasis is associated with an increased risk of spontaneous preterm delivery, fetal distress with meconium staining of amniotic fluid, and fetal death. In the past, cholestyramine resin (Questran) was the only treatment of choice. Cholestyramine is a nonabsorbable anion-exchange resin that binds bile acids, thereby preventing reentry into the bloodstream via the enterohepatic circulation. Divided doses of 8–20 g/day were used. However, the results were often disappointing, doing little to relieve maternal symptoms while being difficult for the patient to take. Women who take cholestyramine should also take vitamin K throughout the remainder of pregnancy because cholestyramine binds

TABLE 2
Drugs Commonly Used for Management of Nausea and Vomiting in Pregnancy

Generic Name	*Trade Name®*	*Dosage*
Anticholinergics		
Dicyclomine	Bentyl	20 mg PO or IM qid
Doxylamine and Pyridoxine	Bendectin	Doxylamine 12.5 mg po bid and 25 mg po at night Pyridoxine 25 mg bid
Doxylamine	Unisom	25 mg PO 30 minutes before bed
Dimenhydrinate	Dramamine	50–100 mg PO q4° 50 mg IM or IV q3–4°
Diphenhydramine	Benadryl	50 mg PO q6–8° 20–50 mg IM or IV q2–3°
Droperidol	Inapsine	Individualized with dose adjustments needed (usual dose 1 mg/h)
Haloperidol	Haldol	1–5 mg PO bid 1–5 mg IM q12°
Metoclopramide	Reglan	5–10 mg PO qid 5–20 mg IM or IV qid
Miscellaneous		
Trimethobenzamide Hydrochloride	Tigan	250 mg PO or PR q6–8°
Ondansetron	Zofran	8 mg PO or IV q8°
Vitamins		
Pyridoxine	Vitamin B_6	10–25 mg PO tid
Dopamine Antagonists		
Chlorpromazine	Thorazine	10–25 mg PO q4–6° 25 mg PR q12° 25–50 mg IM q3–4°
Perphenazine	Trilafon	2–4 mg PO q4–6° 5 mg IM once
Prochlorperazine	Compazine	5–10 mg PO or IM q3–4° 10 mg PR q4–6°

this vitamin and can lead to vitamin K deficiency. There is now some evidence that ursodeoxycholic acid (UDCA), also called ursodiol (Actigall), a minor, naturally occurring hydrophilic bile salt, both reduces maternal pruritus and improves biochemical abnormalities without obvious adverse effects on the newborn (66–68). Evidence is accumulating from controlled clinical trials that UDCA is safe. When intrahepatic cholestasis is diagnosed, UDCA coupled with close maternal fetal surveillance is indicated.

Inflammatory Bowel Disease

Inflammatory bowel disease includes ulcerative colitis and Crohn's disease. Sulfasalazine (Azulfidine), composed of 5-aminosalicylic acid and sulfapyridine, is used for the treatment of both. Mesalamine (Asacol) is used for the treatment of ulcerative colitis. No increased risks of malformations have been reported with either mesalamine or sulfasalazine, in large part due to poor absorption from the gastrointestinal tract. Although azathioprine (Imuran) has been used widely in renal transplant patients since the 1970s and is largely believed to be safe, there is not as much experience with azathioprine when used for inflammatory bowel disease (IBD). Generally, if a woman with IBD conceives on azathioprine and the drug plays an important role in remission, it should be continued. A Swedish Pregnancy Registry reported no increased risk over baseline in 33 women treated with azathioprine during pregnancy (69). There is less information on 6-mercaptopurine, and this should be reserved for refractory cases. Use of either azathioprine or 6-mercaptopurine should involve consultation with other specialists.

PSYCHIATRIC ILLNESS AND DEPRESSION

Psychiatric illnesses are very common in the childbearing years. Major depression and schizophrenia occur in approximately 15% and 8%–10% of the general population respectively (70,71).

Depression

Many medications are available to treat depression. Tricyclic antidepressants have traditionally been used, and amitriptyline (Elavil) and imipramine (Tofranil) have been frequent choices. Pooled data from more than 300,000 births with 414 first-trimester exposures found no significant risk of congenital malformations (72). The

Michigan Medicaid data also show no association between tricyclic antidepressant exposure and birth defects. The American Academy of Pediatrics classifies amitriptyline (Elavil) and imipramine (Tofranil) as drugs whose effects on the nursing infant are unknown but may be of concern (17). Yet, neither amitriptyline (Elavil) nor imipramine (Tofranil) nor their metabolites have been detected in the serum of breastfeeding infants whose mothers are taking these drugs (73,74).

The selective serotonin reuptake inhibitors (SSRIs) are another frequently used class of antidepressants that includes sertraline (Zoloft), paroxetine (Paxil), and fluoxetine (Prozac). Multiple studies have evaluated fluoxetine (Prozac) and show no clear evidence that this agent causes birth defects. This includes a study of 128 women treated with fluoxetine (Prozac) versus other agents (75), the Michigan Medicaid data with more than 140 newborns exposed in utero, and more than 796 first-trimester exposures (76). A larger long-term study compared 55 children whose mothers received fluoxetine (Prozac) during pregnancy with 80 children whose mothers took a tricyclic during pregnancy and 84 controls. No differences were found on global IQ, language development, or behavioral development in children followed to preschool (77). The SSRIs are also classified as drugs whose effects on the nursing infant are unknown but may be of concern by the American Academy of Pediatrics (17). We would agree with a recent review (78): "In nursing women taking these drugs [antidepressants], breast-feeding is possible. The infant should be carefully monitored for any clinical side effects and, whenever observed, nursing should be discontinued."

Bupropion (Wellbutrin), a combined SSRI and dopaminergic agent, has recently gained much attention because of its antidepressant effects and excellent side effect profile as well as its adjunctive role in smoking cessation. GlaxoSmithKline is currently gathering data in an international pregnancy registry (79). A case report on breastfeeding while on bupropion (Wellbutrin) showed that, although bupropion (Wellbutrin) accumulates in human breast milk in concentrations much higher than maternal plasma, neither bupropion (Wellbutrin) nor its metabolites were detected in the infants' plasma (80).

Extract of *Hypericum perforatum* (St. John's wort) is being touted as an "alternative" antidepressant. Given lack of data on use in pregnancy and lack of FDA control over contents of nutritional supplements, the use of St. John's wort is not recommended during pregnancy. Furthermore, a recent large randomized, double-blinded, placebo-controlled clinical trial with 200 participants with major depression concluded that St. John's wort was not effective for treatment of major depression (81).

Although amphetamines (and other related psychostimulants which are prescribed for depression or taken recreationally) have not been shown to increase congenital malformations (82), there is concern about the potential for long-term developmental problems. Use in pregnancy should be discouraged. The American Academy of Pediatrics (17) considers amphetamines to be contraindicated during breastfeeding.

Bipolar Disorders

The mood stabilizers, specifically lithium (Lithobid), valproic acid (Depakote), and carbamazepine (Tegretol), all raise concerns about teratogenicity. Recent studies of lithium (Lithobid) are more reassuring than earlier reports linking this medication to markedly increased risks of congenital abnormalities (Ebstein's anomaly in particular) (71). Although no toxic effects have been seen in infants exposed to lithium (Lithobid) via breast milk, the American Academy of Pediatrics considers lithium (Lithobid) to be contraindicated during breastfeeding (17). Given this discrepant information, women using lithium who plan to become pregnant will have to decide what course to take in consultation with a perinatal specialist. Preconception counseling should be recommended for women taking these medications if possible.

Both valproic acid (Depakote) and carbamazepine (Tegretol) are teratogens that cause an increased risk of neural tube defects. Carbamazepine (Tegretol) is also associated with other anomalies (71). In many cases, the pregnant woman will already be on a medication for her psychiatric diagnosis at the time of conception or diagnosis of pregnancy. These women will need counseling about the potential adverse effects of the medication and encouragement to continue to use the drug. Appropriate prenatal testing such as serum screening and ultrasound should be obtained. For the women with new onset psychiatric disease, treatment should occur in consultation with a psychiatrist and perinatologist to determine appropriate pharmacologic management during pregnancy. For the women on a known teratogenic agent, consultation should be obtained to allow for discussion of the risks and benefits of the medication, provision of appropriate antenatal testing, and termination if desired. However, both drugs are compatible with breastfeeding (17).

NEUROLOGIC DISORDERS

Epilepsy

Epilepsy constitutes the most common neurologic disorder in pregnancy (83). About 1% of reproductive-age women in the United States, or more than 1 million women, have seizure disorders (84). One of every 250 fetuses is exposed to an antiepileptic drug (85). Because of concerns about teratogenicity, an international consensus guideline suggested that physicians consider weaning

women off their antiepileptic drugs before conception if they have been seizure-free for more than 2 years. Ideally, the patient should be on the fewest medications and at the lowest dose needed to control the seizures (86).

The commonly used "old-line" antiepileptic drugs include phenytoin (Dilantin), carbamazepine (Tegretol), phenobarbital, and valproic acid (Depakote). These medications all have a risk of causing teratogenic effects. Women taking these medications during pregnancy should have regular consultation from an obstetrician or perinatologist and neurologist in concert. However, they are all compatible with breastfeeding. We suggest that ultrasounds and serum screening (for maternal serum alpha-fetoprotein to detect neural tube defects) be offered to all women taking these medications. Although a normal outcome cannot be guaranteed, most neonates do not have malformations even if their mothers used an antiepileptic drug. There are several newer antiepileptic drugs, including felbamate (Felbatol), gabapentin (Neurontin), and lamotrigine (Lamictal). To date, there is not enough data to make any recommendations.

Headaches

Headaches and/or migraines are common in pregnancy. Migraines alone occur in 18% of women (87). Migraine headaches often improve after the first trimester; thus, many women may be able to manage their headaches with nonpharmacologic means such as ice, massage, and biofeedback (88–90). If pharmacologic relief is needed, first steps can include acetaminophen with or without codeine, codeine and other opiates, or nonsteroidal anti-inflammatory drugs in limited doses, depending on the gestational age (91).

The serotonin receptor agonists are a common class of medications used to treat migraines. The best studied of the group is sumatriptan (Imitrex). The most extensive data comes from the Glaxo Wellcome Pregnancy Registry and a study of 96 women (92). Although both are reassuring, these are still fairly limited data. Even less information is available for other selective serotonin receptor agonists such as naratriptan (Amerge), zolmitriptan, or rizatriptan (Maxalt).

Several other classes of medications are used to treat headaches, specifically migraines. This includes the antidepressants already discussed; beta-blockers (including atenolol, metoprolol, and propranolol); and calcium channel blockers (including diltiazem, nifedipine, and verapamil). We believe that the latter two classes are safe in pregnancy and lactation. Ergotamine/caffeine combinations (Cafergot) are contraindicated during pregnancy secondary to the potential of ergot to cause uterine contractions.

CONCLUSION

Clearly, medical disorders requiring use of pharmacologic agents are common in pregnancy. Although many medications are safe during pregnancy and lactation, knowledge of each specific agent is necessary. Medications that pose a risk during pregnancy do not necessarily pose a risk during breastfeeding. Specific knowledge will allow proper treatment and avoid unnecessary maternal anxiety and undue risk (11).

REFERENCES

1. Brocklebank JC, Ray WA, Federspiel CF, Schaffner W. Drug prescribing during pregnancy. A controlled study of Tennessee Medicaid recipients. Am J Obstet Gynecol 1978;132:235–44.

2. Piper JM, Baum C, Kennedy DL. Prescription drug use before and during pregnancy in a Medicaid population. Am J Obstet Gynecol 1987; 57:148–56.

3. Lacroix I, Damase-Michel C, Lapeyre-Mestre M, Montastruc JL. Prescription of drugs during pregnancy in France. Lancet 2000;356: 1735–6.

4. Czeizel AE. Drug use during pregnancy. Lancet 2001;357:800.

5. Czeizel AE, Rácz J. Evaluation of drug intake during pregnancy in the Hungarian Case-Control Surveillance of Congenital Anomalies. Teratology 1990;42:505–12.

6. Yankowitz J. Use of medications in pregnancy: general principles, teratology, and current developments. In: Yankowitz J, Niebyl JR, editors. Drug therapy in pregnancy. Baltimore (MD): Lippincott Williams & Wilkins, 2001.

7. Sever LE, Mortensen ME. Teratology and the epidemiology of birth defects: occupational and environmental perspectives. In: Gabbe SG, Niebyl JR, Simpson JL, editors. Obstetrics: normal and problem pregnancies, 3rd ed. New York: Churchill Livingston, 1996.

8. Hanson JW. Human teratology. In: Rimoin DL, Connor JM, Pyeritz RE, editors. Principles and practice of medical genetics, 3rd ed. New York: Churchill Livingstone, 1996.

9. Jones KL. Effects of therapeutic, diagnostic, and environmental agents. In: Creasy RK, Resnik R, editors. Maternal-fetal medicine: principles and practice, 3rd ed. Philadelphia (PA): WB Saunders Co, 1994.

10. Aase JM. Diagnostic dysmorphology. New York: Plenum Medical Book Company, 1990.

11. McMahon MJ, Katz VL. Clinical teratology. In: Kuller JA, Chescheir NC, Cefalo RC, editors. Prenatal diagnosis and reproductive genetics. Baltimore (MD): Mosby-Year Book, Inc., 1996.

12. Shepard TH. "Proof" of human teratogenicity. Teratology 1994;50: 97–8.

13. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation, 4th ed. Baltimore (MD): Williams & Wilkins, 1994.

14. Teratology Society Public Affairs Committee. FDA classification of drugs for teratogenic risk. Teratology 1994;49:446–7.

15. Teratology Society Public Affairs Committee. FDA classification of drugs for teratogenic risk. Teratology 1994;49:446–7.

16. Friedman JM. Report of the Teratology Society Public Affairs Committee Symposium on FDA Classification of Drugs. Teratology 1993; 48:5–6.

17. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. Pediatr 2001;108:776–89. http://www.aap.org/policy/0063.html.

18. Ely JW. Treatment of upper respiratory complaints in pregnancy. In: Yankowitz J, Niebyl JR, editors. Drug therapy in pregnancy. Baltimore (MD): Lippincott Williams & Wilkins, 2001.

19. Lorber B. The common cold. J Gen Intern Med 1996;11:229–36.

20. Gwaltney JM Jr. The common cold. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases, 4th ed. New York: Churchill Livingstone 1995:561–6.

21. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton (MA): Publishing Sciences Group, Inc., 1977.

22. Aselton P, Jick H, Milunsky A, Hunter JR, Stergachis A. First trimester drug use and congenital disorders. Obstet Gynecol 1985;65: 451–5.

23. Einarson A, Bailey B, Jung G, Spizzirri D, Baillie M, Koren G. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. Ann Allergy Asthma Immunol 1997;78:183–6.

24. Briggs GG, Freeman RK, Yaffee SJ. Drugs in pregnancy and lactation, 5th ed. Baltimore (MD): Williams & Wilkins, 1998.

25. Irwin RS, Madison JM. Primary care: the diagnosis and treatment of cough. N Engl J Med 2000;343:1715–21.

26. Lione A, Scialli AR. The developmental toxicity of the H1 histamine antagonists. Reprod Toxicol 1996;10:247–55.

27. Williams JW Simel DL. Does this patient have sinusitis? Diagnosing acute sinusitis by history and physical examination. J Am Med Assoc 1993;270:1242–6.

28. Williams JW Jr, Simel DL, Roberts L, Samsa GP. Clinical evaluation for sinusitis. Making the diagnosis by history and physical examination. Ann Intern Med 1992;117:705–10.

29. Gilbert DN, Moellering RC Jr, Sande MA. The Sanford guide to antimicrobial therapy, 28th ed. Vienna (VA): Antimicrobial Therapy, Inc., 1998.

30. Kelkar PS, Li JT-C. Cephalosporin allergy. N Engl J Med 2001; 345:804–9.

31. Slone D, Heinonen OP, Kaufman DW, et al. Aspirin and congenital malformations. Lancet 1976;1:1373–5.

32. Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJR. Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology 1996;54:84–92.

33. Martinez-Frias ML, Rodriguez-Pinilla E, Prieto L. Prenatal exposure to salicylates and gastroschisis: a case-control study. Teratology 1997;56:241–3.

34. Drongowski RA, Smith RK Jr, Coran AG, Klein MD. Contribution of demographic and environmental factors to the etiology of gastroschisis: a hypothesis. Fetal Diagn Ther 1991;6:14–27.

35. Werler MM, Mitchell AA. First trimester maternal medication use in relation to gastroschisis. Teratology 1992;45:361–7.

36. Duley L, Henderson-Smart D, Knight M, King J. Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. BMJ 2001;322:329–33.

37. Heyborne KD. Preeclampsia prevention: lessons from the low-dose aspirin therapy trials. Am J Obstet Gynecol 2000;183:523–8.

38. Sibai BM. Prevention of preeclampsia: a big disappointment. Am J Obstet Gynecol 1998;179:1275–8.

39. Dumont A, Flahault A, Beaufils M, Verdy E, Uzan S. Effect of aspirin in pregnant women is dependent on increase in bleeding time. Am J Obstet Gynecol 1999;180:135–40.

40. Hauth J, Sibai B, Caritis S, VanDorsten P, Lindheimer M, Klebanoff M, et al. Maternal serum thromboxane B2 concentrations do not predict improved outcomes in high-risk pregnancies in a low-dose aspirin trial. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medical Units. Am J Obstet Gynecol 1998;179:1193–9.

41. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette J-C, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309–11.

42. Pattison NS, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, McDougall J. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. Am J Obstet Gynecol 2000;183:1008–12.

43. The WHO Working Group, Bennet PN, editor. Drugs and human lactation. New York: Elsevier, 1988.

44. Rayburn W, Wible-Kant J, Bledsoe P. Changing trends in drug use during pregnancy. J Reprod Med 1982;27:569–75.

45. Arishima K, Yamamoto M, Takizawa T, Ueda Y, Kusanagi M, Eguchi Y. Onset of the constrictive effect of indomethacin on the ductus arteriosus in fetal rats. Acta Anat 1991;142:231–5.

46. Moise K. Effect of advancing gestational age on the frequency of fetal ductal constriction in association with maternal indomethacin use. Am J Obstet Gynecol 1993;168:1350–3.

47. Hickok DE, Hollenback KA, Reilley SF, Nyberg DA. The association between decreased amniotic fluid volume and treatment with nonsteroidal anti-inflammatory agents for preterm labor. Am J Obstet Gynecol 1989;160:1525–31.

48. Bivins HA, Newman RB, Fyfe DA, Campbell BA, Stramm SL. Randomized trial of oral indomethacin and terbutaline sulfate for the long-term suppression of preterm labor. Am J Obstet Gynecol 1993;169: 1065–70.

49. Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. Eur J Epidemiol 1992;8:757–60.

50. Khan K, Chang J. Neonatal abstinence syndrome due to codeine. Arch Dis Child Fetal Neonatal Ed 1997;76:59–60.

51. Jewell D, Young G. Interventions for nausea in early pregnancy (Cochrane Review). Oxford, The Cochrane Library, Issue 4. Update Software, 2001.

52. Werntoft E, Dykes A-K. Effect of acupressure on nausea and vomiting during pregnancy. J Reprod Med 2001;46:835–9.

53. Slotnick NR. Safe, successful nausea suppression in early pregnancy with P-6 acustimulation. J Reprod Med 2001;46:811–4.

54. De Aloysio D, Penacchioni P. Morning sickness control in early pregnancy by Neiguan point acupressure. Obstet Gynecol 1992;80: 852–4.

55. Belluomini J, Litt RC, Lee KA, Katz M. Acupressure for nausea and vomiting of pregnancy: a randomized, blinded study. Obstet Gynecol 1994;84:245–8.

56. Knight B, Mudge C, Openshaw S, White A, Hart A. Effect of acupuncture on nausea of pregnancy: a randomized, controlled trial. Obstet Gynecol 2001;97:184–8.

57. Carlsson CP, Axemo P, Bodin A, Carstensen H, Ehrenroth B, Madegard-Lind I, Navander C. Manual acupuncture reduces hyperemesis gravidarum: placebo-controlled, randomized, single-blind, crossover study. J Pain Sympt Manage 2000;20:273–9.

58. Murphy PA. Alternative therapies for nausea an vomiting of pregnancy. Obstet Gynecol 1998;91:149–55.

59. Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol 1990;38:19–24.

60. Vutyavanich T, Kraisarin T, Ruangsri R. Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial. Obstet Gynecol 2001;97:577–82.

61. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. (Cochrane Review) In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.

62. Sahakian V, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. Obstet Gynecol 1991;78:33–6.

63. Vutyavanich T, Wongtrangan S, Ruangsri R. Pyridoxine for nausea and vomiting of pregnancy: a randomized double-blind placebo-controlled trial. Am J Obstet Gynecol 1995;173:881–4.

64. McMahon MJ. Drug therapy for the treatment of gastrointestinal disorders in pregnancy and lactation. In: Yankowitz J, Niebyl JR, editors. Drug therapy in pregnancy. Baltimore (MD): Lippincott Williams & Wilkins, 2001.

65. Sullivan CA, Johnson CA, Roach H, Martin RW, Stewart DK, Morrison JC. A pilot study of intravenous ondansetron for hyperemesis gravidarum. Am J Obstet Gynecol 1996;174:1565–8.

66. Palma J, Reyes H, Ribalta J, Iglesias J, Gonzalez MC, Hernandez I, et al. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. Hepatology 1992;15:1043–7.

67. Davies MH, da Silva RCMA, Jones SR, Weaver JB, et al. Fetal mortality associated with cholestasis of pregnancy and the potential benefit of therapy with ursodeoxycholic acid. Gut 1995;37:580–4.

68. Brites D, Rodrigues CMP, Oliveira N, da Conceicao Cardos M, et al. Correction of maternal serum bile acid profile during ursodeoxycholic acid therapy in cholestasis of pregnancy. J Hepatol 1998;28:91–8.

69. Kallen B. Session 10: drug treatment of rheumatic diseases during pregnancy. The teratogenicity of antirheumatic drugs—what is the evidence? Scand J Rheumatol 1998;27(Suppl 107):119–24.

70. American College of Obstetricians and Gynecologists. Depression in women. ACOG technical bulletin no. 182. Washington (DC): American College of Obstetricians and Gynecologists, 1992.

71. Allaire AD, Kuller JA. Psychotropic drugs in pregnancy and lactation. In: Yankowitz J, Niebyl J, editors. Drug therapy in pregnancy, 3rd ed. New York: Lippincott Williams & Wilkins, 2001.

72. Altshuler LL, Cohen L, Szuba M, Burt VK, Gitlin M, Mintz J. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996;153:592–606.

73. Bader TF, Newman K. Amitriptyline in human breast milk and the nursing infants serum. Am J Psychiatry 1980;137:855–6.

74. Sovner R, Orsulak PJ. Excretion of imipramine and desipramine in human breast milk. Am J Psychiatry 1979;136:451–2.

75. Pastuszack A, Schick-Boschetto B, Zuber C, Feldkamp M, Pinelli M, Sihn S, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). J Am Med Assoc 1993;269:2246–8.

76. Goldstein DJ, Corbin LA, Sundell KL. Effects of first-trimester fluoxetine exposure on the newborn. N Engl J Med 1997;89:713–8.

77. Nulman I, Rovert J, Stewart DE, Wolpin J, Gardner HA, Theis JGW, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997;336:258–62.

78. Arnon J, Shechtman S, Ornoy A. The use of psychiatric drugs in pregnancy and lactation. Isr J Psych Rel Sci 2000;37:205–22.

79. The Bupropion Pregnancy Registry, Interim report, September 1, 1997, through Feb 28, 2001, GlaxoSmithKline, 1011 Ashes Drive, Wilmington, NC 28405, 1-800-336-2176.

80. Briggs GG, Samson JH, Ambrose PJ, Schroeder DH. Excretion of bupropion in breast milk. Ann Pharmacother 1993;27:431–3.

81. Shelton RC, Keller MB, Gelenberg A, Dunner DL, Hirshfield R, Thase ME, et al. Effectiveness of St. John's wort in major depression. J Am Med Assoc 2001;285:1978–86.

82. Milkovich L, Van den Berg BJ. Effects of antenatal exposure to anorectic drug. Am J Obstet Gynecol 1977;129:637–42.

83. ACOG Educational Bulletin. December 1996: No. 231.

84. The North American Pregnancy and Epilepsy Registry. A North American Registry for Epilepsy and Pregnancy, a unique public/private partnership of health surveillance. Epilepsia 1998;39:793–8.

85. Lindhout D, Omizigt JGC. Teratogenic effects of antiepileptic drugs: implications for the management of epilepsy in women of childbearing age. Epilepsia 1994;35(Suppl 4):S19–S28.

86. Delgado-Escueta AV, Janz D. Consensus guidelines: preconceptional counseling, management, and care of the pregnant woman with epilepsy. Neurology 1992;42(Suppl 5):149–60.

87. Silberstein SD. Headaches, pregnancy, and lactation. In: Yankowitz J, Niebyl J, editors. Drug therapy in pregnancy, 3rd ed. New York: Lippincott Williams & Wilkins, 2001.

88. Silberstein SD. Migraine and pregnancy. Neurol Clin 1997;15:209–31.

89. Silberstein SD. Appropriate use of abortive medication in headache treatment. Pain Manage 1991;4:22–8.

90. Silberstein SD. Headaches and women: treatment of the pregnant and lactating migraineur. Headache 1993;33:533–40.

91. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Eng J Med 1998;338:1128–37.

92. Shuhaiber S, Pastuszak A, Schick B, Matsui D, Spivey G, Brochu J, et al. Pregnancy outcome following first trimester exposure to sumatriptan. Neurology 1998;51:581–3.

APPENDIX A
Web Sites for Information About Drug Use in Pregnancy and Lactation

Site Name	*Address*	*Description*
Reprotox	http://www.reprotox.org/	An information system on environmental hazards to human reproduction and development
University of Washington, Teratogen Information Services	http://depts.washington.edu/terisweb/	Information about TERIS, Shepard's catalog of teratogenic agents, and other resources
Perinatology.Com	http://www.perinatology.com/exposures/druglist.htm	Summary of information about drugs in pregnancy and lactation
RxList: The internet drug index	http://www.rxlist.com/	Information about drug treatment
Organization of Teratology Information Services	http://www.otispregnancy.org/links.htm	Contains a variety of links to other sources
American Academy of Pediatrics	http://www.aap.org/default.htm	Information about drugs and lactation
Breastfeeding.com	http://www.breastfeeding.com/	Information about lactation and drugs in addition to a wide variety of breastfeeding information
UNICEF Baby friendly initiative	http://www.babyfriendly.org.uk/	Variety of information

APPENDIX B
Combination Over-the-Counter Cold and Cough Preparations

Trade Name	*Antihistamine*	*Decongestant*	*Cough remedy*	*Analgesic*
Actifed Cold & Allergy	TR	PS		
Actifed Cold & Sinus	CH	PS		AC
Benylin Adult Formula Cough Suppressant			DM	
Benylin Cough Suppressant Expectorant			GU, DM	
Benylin Multisystem		PS	GU, DM	
Comtrex Day-Night	CH	PS	DM	AC
Contac Day Cold/Flu		PS	DM	AC
Contac Night Cold & Flu	DI	PS		AC
Coricidin HBP Flu Maximum Strength	CH		DM	AC
Coricidin HBP Cough & Cold	CH		DM	
Coricidin HBP Nighttime Cold & Cough	DI			AC
Dimetapp Elixir	BR	PS		
Dristan Sinus		PS		IB
Dristan Cold	CH	PH		AC
Drixoral Cold & Allergy	BR	PS		
Drixoral Cold & Flu	BR	PS		AC
Drixoral Allergy/Sinus	BR	PS		AC
Novahistine Elixir	CH	PH		
Novahistine DMX*		PS	GU, DM	
Robitussin			GU	
Robitussin Cold & Cough		PS	GU, DM	
Robitussin Cold, Cough & Flu		PS	GU, DM	AC
Robitussin Severe Congestion (has propylene glycol)		PS	GU	
Robitussin DM			GU, DM	
Robitussin PE (has propylene glycol)		PS	GU	
Robitussin Cough Suppressant			DM	
Robitussin Cough & Cold (has propylene glycol)		PS	DM	
Robitussin Night-Time Cold (has propylene glycol)	DO	PS	DM	AC
Sinarest	CH	PS		AC
Sinarest No Drowsiness		PS		AC
Sine-Off Sinus	CH	PS		AC
Sinutab Non-Drying		PS	GU	
Sinutab Sinus Allergy	CH	PS		AC
Sinutab Sinus		PS		AC
Sudafed (12 or 24 hour)		PS		
Sudafed Cold & Allergy	CH	PS		
Sudafed Cold & Cough		PS	GU, DM	AC
Sudafed Non-Drying		PS	GU	
Sudafed Severe Cold		PS	DM	AC
Sudafed Sinus		PS		AC
Tavist or Tavist Allergy	CL			
TheraFlu Flu and Cold	CH	PS		AC
TheraFlu Flu, Cold & Cough	CH	PS	DM	AC
TheraFlu Night Time	CH	PS	DM	AC
TheraFlu Flu, Cold, Chest Congestion, and Cough		PS	GU, DM	AC
TheraFlu Flu, Cold, Cough, Non-Drowsy		PS	DM	AC
Triaminic AM Cough & Decongestant		PS	DM	
Triaminic AM Decongestant		PS		
Triaminic Sore Throat		PS	DM	AC
Tylenol Cold No Drowsiness		PS	DM	AC
Tylenol Cold Multisymptom	CH	PS	DM	AC
Tylenol Cold Severe Congestion Multisymptom		PS	GU, DM	AC
Tylenol Cough Multi-symptom*			DM	
Tylenol Cough Multi-symptom w/decongestant		PS	DM	AC
Tylenol Flu No Drowsiness		PS	DM	AC
Tylenol Flu Night Time	DI	PS		AC

APPENDIX B
Continued

Trade Name	*Antihistamine*	*Decongestant*	*Cough remedy*	*Analgesic*
Tylenol Severe Allergy	DI			AC
Tylenol Allergy Sinus Night Time	DI	PS		AC
Tylenol Allergy Sinus	CH	PS		AC
Tylenol Sinus		PS		AC
Vicks 44 Cough*			DM	
Vicks 44D Cough & Head Congestion*		PS	DM	
Vicks 44E Cough & Chest Congestion*			GU, DM	
Vicks 44M Cough, Cold & Flu*	CH	PS	DM	AC
Vicks DayQuil		PS	DM	AC
Vicks Nyquil Adult Nighttime Cold/Flu	DO	PS	DM	AC
Vicks Nyquil*	DO	PS	DM	AC

*Contains alcohol.

Antihistamines:
BR = dexbrompheniramine
CH = chlorpheniramine
CL = clemastine
DI = diphenhydramine
DO = doxylamine
TR = triprolidine

Decongestants:
PH = phenylephrine
PS = pseudophedrine.

Cough Preparations:
DM = dextromethorphan
GU = guaifenesin.

Analgesics:
AC = acetaminophen
IB = ibuprofen