

DRUGS, PREGNANCY, AND LACTATION

Antihyperlipidemic Agents

The large antihyperlipidemic class of drugs can be subdivided into bile acid sequestrants, HMG-CoA reductase inhibitors, fibric acid derivatives, ezetimibe, and niacin. With the possible exception of familial hypercholesterolemia, there appears to be no maternal benefit for the treatment of hyperlipidemia during gestation. Nearly all reported pregnancy exposures have occurred accidentally. If treatment is required, only bile acid sequestrants are considered compatible in pregnancy and lactation.

Ezetimibe (Zetia) also appears to be low risk in gestation, but not in lactation. Because most drug-induced adverse effects (about two-thirds) in nursing infants have been reported during the first month after birth, delaying treatment of a nursing mother until after this period appears to be best.

Cholestyramine has been used as a treatment for intrahepatic cholestasis of pregnancy and as an antidote for some types of diarrhea, chlordecone pesticide poisoning, and digitalis toxicity. Because bile acid sequestrants are not absorbed into the systemic circulation, they do not represent a direct risk to the embryo or fetus and are considered compatible with pregnancy (all are rated risk factor B) and lactation. However, the resins also bind fat-soluble vitamins in the gut, and deficiencies of these vitamins may result.

The six HMG-CoA reductase inhibitors (statins) are atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor, Altacor), pravastatin (Pravachol), rosuvastatin (Crestor), and simvastatin (Zocor). All are contraindicated in pregnancy (risk factor X). Case reports and surveillance studies have described healthy outcomes from a number of pregnancies inadvertently exposed in the first trimester and later. The largest number of cases (187) were reported with simvastatin, with 86 cases that could be evaluated: 74% had normal outcomes, 15% resulted in spontaneous abortion, 6% of cases demonstrated congenital anomalies, 4% of cases had effects related to prematurity, and 1% resulted in fetal death. Three of the five birth defect cases were not related to simvastatin because of the timing of exposure or the outcome was a known chromosome defect. The remaining two cases involved unilateral cleft lip and a clubfoot, neither of which appear to be attributable to simvastatin.

In contrast, a 2004 reference described 178 cases of first-trimester exposure to statins reported to the Food and Drug Administration. Among the 52 cases suitable for evaluation, there were 20 major malformations, some

thought to be consistent with inhibition of cholesterol biosynthesis. All 20 defects involved a lipophilic statin (atorvastatin, cerivastatin (Baycol), lovastatin, or simvastatin). No defects were reported with pravastatin, a hydrophilic agent with low tissue penetration that is not associated with animal developmental toxicity. These results are controversial, and controlled studies are needed to determine if there is a causal relationship. Because all statins are probably excreted into milk, women taking these drugs should not breast-feed.



BY GERALD G. BRIGGS, B. PHARM.

Among the fibric acid derivatives, only gemfibrozil (Lopid) has some human data. The other agent, fenofibrate (TriCor), has no human data. The animal data (developmental toxicity in two animal species at doses up to 10 times the human dose) for each drug suggest there may be a risk to the human embryo or

fetus. Thus, the safest course is to avoid these drugs in pregnancy (both are risk factor C). Although there are no data, the drugs are probably excreted into milk, and women on these agents should not breast-feed because of the potential toxicity, such as tumors, in their infants.

Ezetimibe (risk factor C) selectively inhibits the intestinal absorption of cholesterol and related phytosterols. At doses up to 10 times the human dose, the drug is teratogenic in rats but not in rabbits. Human pregnancy exposures have not been reported. If therapy during pregnancy is mandated, ezetimibe appears to be a better choice than statins. There are no data on use during lactation, but the drug is probably excreted into milk. Toxicity is a potential concern; nursing infants should be monitored for headache, diarrhea, arthralgia, pharyngitis, sinusitis, and other adverse effects observed in adults.

Niacin (nicotinic acid) is converted in vivo to niacinamide, the active form of vitamin B₃, an essential nutrient. But high doses (up to 2,000 mg/day) used for hyperlipidemia have not been studied in pregnancy. Because niacinamide is actively transported to the fetus, producing higher concentrations in the fetus and newborn than in the mother, niacin is best avoided during pregnancy and lactation.

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Pregnancy Concerns: What the Data Show

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — In the general ob.gyn. practice of Amy Meg Autry, M.D., visits with pregnant patients have evolved from giving equal time to examination and counseling to about 2% to examination and 98% to counseling.

Dr. Autry of the University of California, San Francisco, researched answers to some of women's most common safety concerns regarding pregnancy and offered an overview of her findings at a meeting on antepartum and intrapartum management sponsored by the university:

► **Fish.** While eating fish can be good for maternal cardiovascular health and fetal growth and development, fish accumulate methyl mercury in their muscles from industrial pollution, which may cause neurotoxic symptoms in neonates that resemble cerebral palsy.

Only one retrospective study has found severe neurotoxic effects in children born to Japanese women who ate a steady diet of fish with high levels of mercury, even though the mothers showed minimal or no effects of mercury ingestion. Three other studies found neurologic effects in Japanese adults who ate a similar toxic-fish diet or Iraqi adults who ate grain that had been pretreated with mercury.

Two prospective studies produced conflicting results. In one, a diet high in whale blubber was associated with delays in attention, memory, and small-motor function in serial testing of children through age 6 in the Faeroe Islands of Norway. A separate study of residents of the Seychelles Islands who ate 12 meals of fish per week found that they had mercury levels 10-20 times higher than average levels in U.S. residents, yet this exposure produced no long-term neurologic effects. Other prospective studies are ongoing.

A 2004 joint advisory for consumers issued by the Environmental Protection Agency and the Food and Drug Administration recommended that pregnant women not eat shark, swordfish, king mackerel, or tilefish, because they are high in mercury. The advisory emphasized the positive benefits of fish and stated that pregnant women may eat up to 12 ounces (two average meals) per week of fish low in mercury, such as salmon, shrimp, pollack, and catfish. Canned light tuna has less mercury than albacore tuna. For local fish, consult local and tribal advisories that apply to your area, or limit ingestion to 6 ounces per week.

► **Cheese and hot dogs.** One third of an estimated 1,500 cases of listeriosis each year in the United States are in pregnant women. They are more susceptible to the infection due to compromised immune systems. One in five pregnant women

with listeriosis experiences a spontaneous abortion or stillbirth.

Although cases of listeriosis in pregnancy are rare and sporadic, it's prudent to avoid high-risk foods such as hot dogs or luncheon meats, unless they've been reheated to steaming. Avoid soft cheeses, refrigerated patés or meat spreads, unpasteurized milk, and raw or undercooked meats.

► **Caffeine.** No data substantiate concerns about adverse pregnancy effects caused by light to moderate caffeine consumption.

Many studies that suggested caffeine may raise the risk for low birth weight, spontaneous abortion, congenital anomalies, or conception delays are poorly designed and demonstrate study bias, she said. Most of these studies were con-

founded by an association between caffeine intake and cigarette smoking.

All attempts to find a link between cancer and hair dye have washed out. Dye if you want to.

► **Alcohol.** Multiple small studies show deleterious effects of drinking even small amounts of alcohol during pregnancy. A 2002

study that followed children from birth to age 6, for example, found persistently smaller head circumferences, height, and weight in children of women who had less than one drink per day. A 2001 study found more aggressive behavior in children of mothers who had one drink per week during pregnancy.

► **Hot tubs.** Animal data suggest that maternal hyperthermia (a body temperature of 102° F) may lead to first-trimester spontaneous abortion or neural tube defects. A very poorly designed study in human subjects, which was published in 2003, found a higher rate of first-trimester losses in women who used a hot tub more than weekly within 4 weeks of their last menstrual period. A 2005 metaanalysis of 42 studies suggested an 86% increase in risk for neural tube defects if the mother used a hot tub, sauna, or electric blanket and developed a fever.

On average, a pregnant woman's core body temperature will reach 102° F after 15 minutes of soaking in 102° F water or 10 minutes in 106° F water.

Skip hot tubs in the first trimester, and limit soaking times or water temperature after that, Dr. Autry advised.

► **Exercise.** Getting hot from exercise is okay; there's no evidence that hyperthermia from exercise is teratogenic, she said. Even exercise at high altitudes appears safe.

Exercise helps prevent gestational diabetes and decreases the risk for postpartum depression. Avoid standing still, supine activities, sports that cause falling or heavy contact, and scuba diving, which can cause decompression sickness in the fetus.

► **Hair dye.** All attempts to find an association between hair dye and teratogenic effects or cancer have washed out. Dye if you want to, Dr. Autry said. ■