What precautions should we use with statins for women of childbearing age?

Chaitany Patel, MD, Lisa Edgerton, PharmD
New Hanover Regional Medical Center, Wilmington, North Carolina
Donna Flake, MSLS, MSAS
Coastal Area Health Education Center, Wilmington, NC

EVIDENCE-BASED ANSWER

Statins are contraindicated for women who are pregnant or breastfeeding. Data evaluating statin use for women of childbearing age is limited; however, they may be used cautiously with adequate contraception. Pravastatin may be preferred based on its low tissue-penetration properties. Cholesterol-lowering with simvastatin 40 mg/d did not disrupt menstrual cycles or effect luteal phase duration (strength of recommendation: **C**).

CLINICAL COMMENTARY

Use statins only as a last resort for women of childbearing age

I try to follow the USPSTF recommendations and not screen women aged <45 years without coronary artery disease risk factors for hyperlipidemia. When a woman of any age needs treatment, my first-line therapy is lifestyle modification. Given the risks of statin drugs to the developing fetus, women with childbearing potential should give fully informed consent and be offered reliable contraception before stating statin therapy.

Before reading this review, I had not been aware of the serious effects of statin medications on the developing fetus. In conversations with my colleagues, I found that the adverse effects of statins during pregnancy are not readily known. Such information needs to be more widely disseminated.

Ariel Smits, MD
Department of Family Medicine, Oregon Health & Science University, Portland

Evidence summary

Hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly called statins, have been on the market since the late 1980s. Statins are primarily used to treat hypercholesterolemia, and in recent years have been shown to reduce the risks of coronary events, stroke, and cardiovascular mortality.[1]

Use of statins is contraindicated during pregnancy based on pre-marketing animal studies showing developmental toxicities in animal fetuses; consequently they are pregnancy category X.[2] To date, no controlled studies demonstrate teratogenic effects in humans; however, numerous case reports have documented congenital anomalies, including vertebral, anal, cardiac, tracheal, esophageal, renal, and limb deficiency (VACTERL association), intrauterine growth retardation (IUGR), and demise in fetuses exposed during pregnancy, especially in the first trimester. It is thought that adverse events are under-reported and likely biased toward severe outcomes, thereby limiting actual reported exposures. Despite this limitation, the likelihood of observing specific anomalies has been predicted based upon prescription data and birth rates. The overall birth prevalence of any isolated lower-limb defect or VACTERL anomaly is estimated as 1:100,000 and ranges from 1:50,000 for simvastatin (Zocor) to 1:500,000 for lovastatin (Mevacor).[3] These congenital

FAST TRACK

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anomaly frequencies do not exceed general population rates.

One study suggests that short-term use of simvastatin does not affect menstruation or ovulation of premenopausal women. This double-blind, randomized, placebo-controlled trial enrolled 86 normally cycling women. Mean age of women completing the study was 35. Simvastatin 40 mg/d was studied for cholesterol effects and female reproductive effects. Urinary luteinizing hormone (LH) and pregnanediol glucuronide (PDG), a progesterone metabolite, were assessed to determine if treatment with simvastatin adversely affects luteal function. Simvastatin lowered low-density lipoprotein (LDL) cholesterol by 34.3% ($P<.001$). Normal luteal phase duration and peak were confirmed by urinary PDG and LH levels. This study demonstrated that treatment with simvastatin for 4 months had no significant clinical changes on reproductive gonadal function compared with placebo.[4]

Although ovulation may not be affected by simvastatin, do statins provide a reward worth the risk of other adverse effects? A recent meta-analysis evaluated the benefits of lipid-lowering medication in trials of at least 1 year duration that included women. Total and coronary heart disease (CHD) mortality, nonfatal myocardial infarction, revascularization, and total CHD events were assessed among women with and without cardiovascular disease (CVD). Ten trials included statins. Of the 5 studies that reported age, the average was 61 years. For women without CVD, lipid-lowering treatment was not shown to affect total or CHD mortality. For women with known CVD, hyperlipidemia treatment did not affect total mortality, but was shown effective in reducing CHD events, CHD mortality, nonfatal myocardial infarction, and revascularization; the relative risk of CHD events for statin users was 0.80 (95% confidence interval [CI], 0.71–0.91). The number of women needed to treat (NNT) to prevent an initial CHD event was 140. For secondary prevention, the NNT to prevent 1 CHD event was 26. Since women of child-bearing potential have lower probability of CHD events compared to the older women studied in this meta-analysis, the expected benefit for younger women is likely to be substantially lower.[5]

Consider initial pregnancy tests and inform all women of childbearing age of the possibility of fetal injury before starting statin therapy.[2] Highly lipophilic statins—such as simvastatin, atorvastatin (Lipitor), and lovastatin—achieve embryoplacental concentrations similar to those of maternal plasma. For this reason, if statin therapy is needed, these agents should be avoided. Pravastatin (Pravachol) is the most hydrophilic statin and has no reports of abnormal pregnancy outcomes, even in animal research.[3]

Recommendations from others

The National Cholesterol Education Program Expert Panel and the American Heart Association make no specific recommendations regarding precautions with statin use for women of childbearing age who require treatment for hypercholesterolemia or coronary heart disease.[6,7] The American College of Obstetrics and Gynecologists makes no distinction regarding recommendations for pharmacological treatment of hyperlipidemia for women aged 20 to 45 years.[8]

The US Preventive Services Task Force makes no recommendations on treatment with statins; they only address screening for hypercholesterolemia.[9] The Food and Drug Administration has given statin agents a pregnancy category of X (risks involved in use of the drug by pregnant women clearly outweigh potential benefits).

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