MOTHERISK *UPDATE*

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Use of lipid-lowering agents (statins) during pregnancy

ABSTRACT

QUESTION A 34-year-old patient of mine is taking a "statin" for hyperlipidemia. She is planning pregnancy and is worried about the safety of the drug. How should I advise her?

ANSWER Limited evidence from animal and human studies indicates that statins should not be taken during pregnancy. If a patient is inadvertently exposed during pregnancy, however, termination does not appear to be medically indicated.

RÉSUMÉ

QUESTION Une de mes patientes prend des «statines» contre l'hyperlipidémie. Elle planifie une grossesse et s'inquiète à propos de la sécurité de ce médicament. Comment puis-je la conseiller?

RÉPONSE Des données scientifiques limitées, tirées d'études chez les animaux et les humains, indiquent que les statines ne devraient pas être prises durant la grossesse. Si une patiente était exposée à ce médicament par inadvertance pendant qu'elle est enceinte, il n'est cependant pas indiqué sur le plan médical de mettre un terme à la grossesse.

"Statins," β-hydroxy-β-methyglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, have been widely used for treatment of hyperlipidemia and for reducing morbidity and mortality in coronary artery disease (CAD).[1-5] Current recommendations suggest discontinuing the medication before conception,[6] especially since stopping therapy for the relatively short duration of pregnancy is believed to have little effect on long-term outcome.[7] If a patient becomes pregnant while taking the medication, there are no clear guidelines to follow.

Pharmacology of HMG-CoA reductase inhibitors

The HMG-CoA reductase inhibitors currently marketed for clinical use include atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin (cerivastatin was withdrawn from the market because of reports of fatal rhabdomyolysis; it will not be discussed further). These medications reduce the intracellular concentration of cholesterol and result in an increase in the activity of low-density lipoprotein cholesterol (LDL-c) receptors that enhances the uptake and catabolism of LDL-c.[8] Clinical trials have shown that all the statins significantly improve various lipid parameters including LDL-c, high-density lipoprotein cholesterol, and triglycerides.[9,10] More importantly, summarized results of both angiographic and clinical trials have shown that aggressively lowering LDL-c by at least 25% with statin therapy can delay progression of CAD and decrease the incidence of nonfatal myocardial infarction and death from CAD.[9,11]

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at (416) 813-7562; they will be addressed in future Motherisk Updates. Published Motherisk Updates are available on the College of Family Physicians of Canada website (**www.cfpc.ca**). Some articles are published in *The Motherisk Newsletter* and on the Motherisk website (**www.motherisk.org**) also.

Effects of maternal hypercholesterolemia on a fetus

A growing body of evidence suggests that maternal hypercholesterolemia is associated with

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development of fetal atherosclerosis. Napoli et al[12] found that fetal aortas from hypercholesterolemic mothers (mean plasma cholesterol 292 mg/dL before pregnancy and 385 mg/dL during pregnancy) contain a significantly higher number of fatty streak lesions and are larger than fetal aortas from mothers with normal cholesterol levels (total plasma cholesterol <185 to 200 mg/dL, depending on age).

This difference was even found for mothers who were hypercholesterolemic only during pregnancy. The authors also discovered that the lesions got significantly larger with advancing age beyond 1 year and that the rate of progression was faster in children of hypercholesterolemic mothers. The difference in the rate could not be attributed to the children's cholesterol levels because they were found to be normal. The findings of these studies have been confirmed in animal models.[13,14]

Interventions to reduce cholesterol and lipid oxidation, including cholestyramine and vitamin E therapy, significantly reduce lesions at birth.[14,15] These findings suggest the importance of maternal cholesterol levels in the pathogenesis of atherosclerosis in children, but their clinical importance is still unknown.

Fetal toxicity associated with statins

Atorvastatin (Lipitor). No teratogenic effects of atorvastatin were seen in rats and rabbits, even at maternally toxic doses, although fetal body weight was lower than normal.[15] Another study in rats showed that atorvastatin at maternally toxic doses resulted in a 45% lower survival rate of the offspring, decreased body weight, and abnormal neonatal development.[16]

No data on human pregnancies have been published. We located eight cases in our Motherisk database of statin use during the first trimester of pregnancy. Among these cases, there were two spontaneous abortions, one premature neonatal death (at 24 weeks' gestation), one elective abortion, two normal outcomes, and two patients lost to follow up. Given the limited information available, atorvastatin should be avoided during pregnancy.

Fluvastatin (Lescol). Manufacturer's data showed no evidence of teratogenicity in rats or rabbits given high doses of fluvastatin. The same researchers showed, however, that high doses of fluvastatin resulted in maternal mortality secondary to cardiomyopathy, weight loss, decreased neonatal weight gain, and an increased incidence of stillbirths and neonatal deaths.[17,18]

Sandoz Pharmaceuticals (manufacturer of Lescol) reported on five human pregnancies.[19] There were two normal outcomes, one ectopic pregnancy, one spontaneous abortion, and one unknown outcome. Duration and timing of drug exposure were not mentioned. An additional report described a 28-year-old woman taking medications, including fluvastatin during her first trimester, who delivered a normal, full-term, healthy infant. Given the evidence to date (ie, maternal mortality in animal models), however, fluvastatin should be avoided during pregnancy.

Lovastatin (eg, Mevacor). Administration of lovastatin to pregnant rats at doses of 800 mg/kg daily resulted in decreased maternal weight gain, fetal skeletal malformations (including vertebrae and ribs), and gastroschisis.[19] No drug-induced changes were seen in rabbits or mice given lovastatin at doses nine to 50 times the maximum recommended dose for humans.[20]

A postmarketing surveillance study[7] reported on 48 cases with known outcome of women using lovastatin during pregnancy. There were three (6.3%) spontaneous abortions, one (2.1%) stillbirth, four (8.3%) infants with congenital anomalies (atrial or ventricular septal defects, cerebral dysfunction, VATER complex, spina bifida, and holoprosencephaly), 39 (81.2%) normal outcomes, and one case of pedal edema. Based on the timing of exposure and diversity of malformations, there is likely no causal relationship between taking the drug and congenital anomalies.[7]

Pravastatin (Pravachol). High doses of pravastatin administered to rats and rabbits had no teratogenic effects.[21,22] No data on human use of pravastatin during pregnancy have been published. The manufacturer, Bristol-Myers Squibb, has, however, received 26 case reports of exposure during pregnancy. Among these, 11 were exposed during the first trimester, and all had normal pregnancy outcomes (personal communication from Bristol-Myers Squibb Canada, November 12, 1996). Animal data and known human exposures indicate that pravastatin does not increase the risk of major congenital anomalies.

Simvastatin (Zocor). Animal studies using both rats and rabbits demonstrated no teratogenic effect of high doses of simvastatin.[23,24] Toxic doses, however, resulted in maternal weight loss and an increased resorption rate in rabbits.[25] In contrast, high doses resulted in decreased mean fetal body weight and maternal weight gain in rats.[25,26] Postmarketing surveillance data are available on 86 cases with known pregnancy outcome following exposure to simvastatin.[7] Among these cases, there were 13 (15.1%) spontaneous abortions, one (1.2%) fetal death, five (5.8%) congenital anomalies (polydactyly, unilateral cleft lip, balanic hypospadia, trisomy 18, and clubfoot), three (3.5%) miscellaneous adverse outcomes

possibly related to prematurity, and 64 (74%) normal outcomes. Based on animal and human data, exposure to simvastatin during pregnancy does not appear to increase the risk of congenital malformations.

Conclusion

Results of animal studies indicate that many statins are associated with adverse fetal outcomes at maternally toxic doses. The limited human data suggest that statins are not major human teratogens.[7] Thus, if women are inadvertently exposed to statins before recognition of pregnancy, they can be reassured that their fetuses do not appear to be at increased risk.

Nonetheless, it seems reasonable to follow the current recommendation of discontinuing the medication immediately upon recognition of pregnancy or before conception if pregnancy is planned.[6,19,21,27,28] With new evidence to suggest that maternal hypercholesterolemia has a detrimental effect on a developing fetus, this recommendation might change, particularly as results of further studies of statins and other agents, such as vitamin E, during pregnancy become available.

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