MOTHERISK ROUNDS

The Fetal Safety of Statins: A Systematic Review and Meta-Analysis

Judith Zarek, MSc, Gideon Koren, MD

The Motherisk Program, Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, Hospital for Sick Children, Toronto ON

Abstract

Although an initial case series suggested that use of statins in pregnancy carried teratogenic risk, a recent meta-analysis of controlled observational studies has failed to corroborate this. A large number of potentially beneficial uses of statins in pregnant women have prompted a new evaluation of the risk–benefit ratio of these agents in pregnancy.

Résumé

Bien qu'une série de cas initiale ait laissé entendre que l'utilisation de statines pendant la grossesse donnait lieu à des risques tératogènes, une récente méta-analyse d'études observationnelles comparatives n'est pas parvenue à corroborer de tels résultats. Puisque les statines comptent un grand nombre d'utilisations potentiellement bénéfiques chez les femmes enceintes, une nouvelle évaluation du rapport risques-avantages de ces agents pendant la grossesse a été mise en œuvre.

HMG-CoA reductase inhibitors (statins) are commonly prescribed for men and women with cardiovascular disease. Their safety during pregnancy has not been clearly determined. The Food and Drug Administration (FDA) in the United States has designated all statins category X, which means their use during pregnancy is contraindicated. This determination is based on the overarching concept that the benefits of statin therapy during pregnancy do not outweigh potential fetal risks of exposure.[1] The essential role of cholesterol during pregnancy, combined with teratogenic effects seen in some animal studies with lovastatin, has supported this contraindication. However, the use of statins has become exceedingly popular in both men and women; women are increasingly delaying pregnancy, and obesity and associated cardiovascular risks have increased.[1] With 50% of all pregnancies unplanned,[2] these factors substantially increase the likelihood that a woman who is planning pregnancy, or who finds herself pregnant, may be taking a statin. Furthermore, stopping statin therapy may have detrimental health effects for both the fetus and pregnant woman. Statins have been shown to have additional potential benefits not related to their cholesterol-lowering effects, as discussed below.[3–14] These new potential indications of statins may support their use during pregnancy for obstetrical complications.

Key Words: Statins, cholesterol, pregnancy, congenital malformations

ANIMAL STUDIES

Developmental studies with lovastatin administration in mice at doses 10 and 47 times the recommended maximum dosage showed no increased risk of congenital malformations, except for a slightly elevated incidence of skeletal malformations except at maternally toxic doses.[15] Similarly, in studies of the administration of simvastatin in pregnant rats, no evidence of teratogenicity was observed.[16–18] With atorvastatin, no teratogenic effects were observed in rats or rabbits.[19]

THE SCARE

In 2004, a series of case reports collected by the FDA and showing 31 fetal malformations among 70 spontaneously reported statin-exposed pregnancies was published in the New England Journal of Medicine.[20] This report was interpreted by many as providing proof of the fetal risks of the statins, justifying their rating by the FDA as category X drugs. Critics of this report noted that there was no unique pattern consistent with lipophilic statin use in the described malformations. Specifically, Smith–Lemli–Opitz syndrome, a known abnormality of

J Obstet Gynaecol Can 2014;36(5):506–509

cholesterol biosynthesis, was not identified in any of the case reports.[21] Critically, these spontaneous case reports were lacking a denominator of the total number of exposed cases to allow calculation of the increased risk. It is well known that retrospective reports of pregnancy drug exposure typically describe an up to five-fold increase in teratogenic risk because of over-reporting of adverse outcomes.[22]

This case series was followed by a number of cohort studies of statin exposure in pregnancy that failed to show an increase in teratogenic risk.[23–28] However, because of the limited number of studies, we felt it was important to combine them in a meta-analysis, thus increasing the overall statistical power to show risk in pregnancy.

SYSTEMATIC REVIEW AND META-ANALYSIS

In a recently published meta-analysis, we identified all studies published up to January 28, 2013, on pregnancy outcome following first trimester exposure to statins.[1] The inclusion criteria were:

1. retrospective or prospective controlled studies,
2. studies of pregnant women exposed to a statin, and
3. studies that included a control group of women unexposed to statins.

We reviewed the full text of a large number of published papers and found six studies that matched the inclusion criteria.[23–28] The earliest reported study was the only one to include disease-matched control subjects (hypercholesterolemic women). The remaining five studies included non-hypercholesterolemic control subjects. There was no increased risk of birth defects in the statin-exposed pregnancies compared with the control subjects (RR 1.15; 95% CI 0.75 to 1.76) (Figure 1). In contrast, the relative risk of miscarriage was increased in the statin-exposed group compared to control subjects (RR 1.35; 95% CI 1.04 to 1.75) (Figure 2). There was an increased rate of elective pregnancy terminations (RR 2.56; 95% CI 1.71 to 3.84).

NEW POTENTIAL REPRODUCTIVE INDICATIONS FOR STATINS

This lack of demonstrated increased risk of teratogenicity with use of statins further highlights the need to discuss the potential benefits of statin therapy in pregnant women or in women who might become pregnant. Potential uses include therapy that would benefit women with obstetrical complications, and this may shift the current view that the benefits of statin therapy during pregnancy do not outweigh potential risks of therapy.

One potential benefit is the use of statins for treating endometriosis, in which excessive angiogenesis and invasion of endometrial endothelial cells is associated with locally elevated inflammatory cytokines.[3–6] While current treatment for endometriosis is surgical, the use of statins is being investigated because of their anti-inflammatory effects. They have been shown to decrease endothelial cell invasion, inhibiting excessive cellular growth and decreasing the elevated levels of inflammatory cytokines in this condition.[3–6]

Another potential indication is the use of statins for treatment of women with polycystic ovary syndrome. These women exhibit biochemical evidence of chronic systemic inflammation, elevated serum androgen levels, and endothelial dysfunction in a variety of vascular beds.[7] In two randomized controlled studies, atorvastatin and simvastatin decreased circulating androgen concentrations compared with placebo, and simvastatin therapy resulted in lower androgen levels than the standard therapy with metformin.[8,9] In two additional randomized controlled trials, women exposed to simvastatin and atorvastatin exhibited lower levels of pro-inflammatory markers in addition to lower serum androgen levels than in control subjects.[10,11] Because of the FDA's category X classification, women with endometriosis and polycystic ovary syndrome who are planning a pregnancy are currently excluded from exploring statin therapy, despite its potential in treating these conditions.

Statins have also demonstrated potential efficacy in the treatment of recurrent pregnancy loss. In an animal model of recurrent pregnancy loss, pravastatin has been shown to decrease thrombus formation, to increase uterine blood flow and angiogenesis, and to rescue pregnancies in miscarriage-prone mice.[12]

Finally, statin therapy is currently being explored for treating preeclampsia. In animal models of preeclampsia, pravastatin decreased the anti-angiogenic protein soluble fms-like tyrosine kinase-1 (sFlt-1), increased placental growth factors and blood flow, reversed intrauterine growth restriction, and reduced hypertension and proteinuria.[13,14] Currently, a randomized double-blind placebo-controlled study is underway in the United Kingdom investigating pravastatin use in women with preeclampsia.[29] As well, a multicentre clinical trial is in progress in the United States to investigate the use of pravastatin for the prevention of preeclampsia.[30]

CONCLUSIONS

Our meta-analysis has suggested that statin exposure is not associated with a significant increase in birth defects compared with control subjects (RR 1.15). However, there