

## MOTHERISK ROUNDS

# Risks of Statin Use During Pregnancy: A Systematic Review

Aleksey Kazmin, MD, Facundo Garcia-Bournissen, MD, Gideon Koren, MD, FCRCP

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

## Abstract

Although statins have been identified as potential teratogens on the basis of theoretical considerations and small case series, the available evidence is far from conclusive. In fact, epidemiological data collected to date suggest that statins are not major teratogens. The actual risk for an exposed pregnancy seems to be small, if present at all, and does not by itself warrant termination of pregnancy. Nevertheless, given the scarcity of available data, it is still advisable to avoid use of these drugs in patients who are planning pregnancy in order to reduce the risks as much as possible.

## Résumé

Bien que les statines aient été identifiées comme de possibles agents tératogènes en vertu de considérations théoriques et de séries de cas de faible envergure, les données disponibles sont loin d'être concluantes. En fait, les données épidémiologiques recueillies à ce jour semblent indiquer que les statines ne constituent pas des agents tératogènes majeurs. Le risque réel dans le cas d'une grossesse y ayant été exposée semble être faible, s'il existe même, et ne justifie pas à lui seul le recours à l'interruption de grossesse. Quoiqu'il en soit, compte tenu de la rareté des données disponibles, il est toujours conseillé d'éviter d'avoir recours à ces médicaments chez les patientes qui planifient une grossesse, et ce, afin de réduire les risques au maximum.

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## INTRODUCTION

Drugs of the class known as statins (e.g., lovastatin, simvastatin) are used successfully in the treatment of hypercholesterolemia.<sup>1</sup> They interrupt cholesterol synthesis in the liver through inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme-A reductase, leading to a decrease in plasma cholesterol levels. They also increase the expression of low-density lipoprotein receptors in hepatocytes, leading to reductions in circulating LDL-cholesterol. The reduction of plasma cholesterol and LDL-cholesterol levels induced by these drugs results in significant reductions in cardiovascular risk by reducing atherosclerosis in all major arterial trees. Statins are amongst the most extensively investigated and prescribed pharmaceutical agents in current clinical use.<sup>1</sup>

## STATINS IN PREGNANCY

### Animal Data

Animal studies have produced conflicting evidence on the potential teratogenicity of statins. Studies in rats and rabbits failed to show a teratogenic effect of simvastatin.<sup>2</sup> However, skeletal malformations were observed with other structurally related HMG-CoA reductase inhibitors (lovastatin and active metabolites, cerivastatin, fluvastatin) in similar animal models.<sup>3</sup> Theoretical concerns over a potential impairment in gonadal steroidogenesis by the decrease of cholesterol availability have never been supported by conclusive evidence in animals.<sup>3</sup>

Studies in rats and rabbits have provided evidence that atorvastatin has developmental toxicity, but only at doses that induced maternal toxicity.<sup>4</sup> Rats and rabbits (given 300 mg/day and 100 mg/day of atorvastatin, respectively) had smaller pups and reduced litter size but also reduced maternal body weight and food consumption. No malformations were observed.<sup>4</sup> Evidence of fetal anomalies (predominantly skeletal defects: vertebrae, sternum, fused ribs, incomplete ossification) was found in rats treated with a HMG-CoA reductase inhibitor, mevinolin, at the high dose of 800 mg/kg/day, which also produced significant maternal toxicity.<sup>5</sup> The relevance of the mevinolin-induced malformations in the context of treatment with other statins in clinical use is not clear.

During the first trimester of pregnancy the placenta enables the development of the embryo and the fetus. HMG-CoA reductase activity is required for normal placental development in mammals and for the biosynthesis of hormones important for the maintenance of pregnancy.<sup>6-8</sup> Inhibition of HMG-CoA reductase by statins may disrupt membrane synthesis, cellular proliferation and growth, metabolism and protein glycosylation that are crucial for normal development of the embryo and the placenta.<sup>9,10</sup> One study<sup>11</sup> suggested that simvastatin can adversely affect placental formation, leading to failure of the implantation process and deleterious effects on the growth potential of the placenta. Impaired implantation and function of the placenta in the first trimester of pregnancy can be responsible for the higher abortion rate observed in animals exposed to statins during pregnancy.<sup>11</sup>

On the basis of the limited animal data, the FDA in the United States assigned statins to pregnancy category X. The FDA cited the lack of study data relating to the effects on a pregnant women and/or the fetus (as opposed to the existence of evidence of harm) as the main reason for this decision.<sup>12,13</sup>

### Human Data

We reviewed medical publication databases (PubMed, EMBASE, OvidMedicine) for all studies addressing the effect of HMG-CoA reductase inhibitors (statins) on pregnancy. Very few (and conflicting) clinical and laboratory

data are available regarding inadvertent exposure to statins in human pregnancy.<sup>14</sup>

The FDA identified 178 spontaneous reports of exposure to statins during pregnancy between 1987 and 2001, including 52 cases of exposure in the first trimester. Among these cases, there were 20 reports of malformations, including four severe defects involving the central nervous system and five unilateral limb deficiencies. The two simvastatin-exposed cases of limb deficiency described complex lower-limb anomalies, including both long-bone shortening and aplasia or hypoplasia of the foot structures. The infant in one of these cases and a lovastatin-exposed infant also had rare forms of the vertebral-anal-cardiac-tracheal-esophageal-renal-limb association.<sup>3,15</sup> However, conclusions based on data obtained from spontaneous case reports have to be drawn with care, given the significant reporting bias in spontaneous retrospective reporting processes. Pregnancies that result in the birth of a malformed child are several times more likely to be reported than pregnancies with a healthy outcome.<sup>16</sup>

A report of the Merck pharmacological vigilance database for exposure to simvastatin or lovastatin during pregnancy identified 477 reports of exposure, 225 of which had a documented outcome: 154 were live born infants, 49 were elective abortions, 18 were spontaneous abortions, and four were fetal deaths. Six congenital anomalies were reported: one chromosomal translocation, one trisomy 18, one hypospadias, one duodenal atresia, one cleft lip, and one skin tag. The rate of congenital anomalies was 3.8%, which is similar to the 3% background population rate. No specific patterns of anomalies were identified. Although the number of reports was relatively small, there was no evidence of an increase in congenital anomalies in children born to women exposed to simvastatin or lovastatin compared with the general population.<sup>17</sup>

An epidemiological study conducted in Quebec also failed to find evidence to support the potential teratogenicity of statins. In this study, three groups of women were analyzed: women who received a statin during the first trimester of pregnancy (group A), women who received a fibrate or nicotinic acid in the first trimester of pregnancy (group B) and women who received a statin in the period between one year before conception and one month before conception (group C). The rate of congenital anomalies in group A was 3/64 (4.69%; 95% CI 1.00, 13.69), the rate in group B was 3/14 (21.43%; 95% CI 4.41, 62.57) and 7/67 in group C (10.45%; 95% CI 4.19, 21.53).<sup>18</sup> The differences between the three groups were not statistically significant, suggesting that statin exposure during the first trimester of pregnancy did not increase the risk for malformations.

### ABBREVIATIONS

CI	confidence intervals
FDA	Food and Drug Administration
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme-A
LDL	low-density lipoprotein

A recent prospective cohort study conducted by Taguchi et al. at The Motherisk Program also did not observe any malformation patterns in infants from mothers exposed to a statin during the first trimester of pregnancy. There was no significant difference in the rate of major malformations between cases (1/45) and controls (3/45) ( $P = 0.38$ ).<sup>19</sup>

## DISCUSSION

Even though the available body of data regarding exposure to statins during pregnancy is relatively small, there is no evidence to date of an increase in congenital anomalies in the children of women exposed to these drugs during pregnancy.

Although the paucity of human data does not support the unrestricted use of simvastatin during pregnancy, there is no evidence to suggest that accidental exposures are associated with an increased risk of malformations. Nonetheless, it still seems reasonable to follow the current recommendation of discontinuing the medication immediately upon recognition of pregnancy or before conception if pregnancy is planned. Statins should be used during pregnancy only if the benefits clearly outweigh the risks. If a woman becomes pregnant while taking this drug, discontinuation of therapy should be discussed and the woman should be informed about potential hazards to the fetus. Long-term treatment of hypercholesterolemia would not be significantly impaired by temporary discontinuation of these medications during pregnancy. After pregnancy, it is considered safe for the woman to resume taking the medication.

## CONCLUSION

Although the information available to date is not conclusive, overall it suggests that statins are unlikely to be major teratogens. Nevertheless, until more data are available, statins should be avoided during pregnancy, and pregnant women exposed to cholesterol-lowering drugs should be monitored closely.

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