Central Nervous System and Limb Anomalies in Case Reports of First-Trimester Statin Exposure

To the Editor: The cholesterol-lowering statin drugs are contraindicated in pregnancy[1]; therefore, few data exist regarding their safety in human gestation. We reviewed 178 cases of first-trimester statin exposure reported to the Food and Drug Administration (FDA) from 1987 through 2001 for patterns suggesting possible drug-related effects on embryogenesis. After the exclusion of cases involving first-trimester elective or spontaneous abortions (46 and 42 cases, respectively), pregnancy loss due to maternal illness (15), fetal genetic disorders (3), transient neonatal disorders (5), or loss to follow-up (15), 52 cases were considered evaluable Table 1

Among these cases, there were 20 reports of malformation, including 5 severe defects of the central nervous system (2 of which were holoprosencephaly) and 5 unilateral limb deficiencies; one patient had both of these malformations. The two simvastatin-exposed cases of limb deficiency were 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 VACTERL association (i.e., three or more of the following findings: vertebral, anal, cardiac, tracheal, esophageal, renal, and limb defects).

In all cases of adverse outcomes at birth, the associated statin was lipophilic. Cerivastatin, simvastatin, lovastatin, and atorvastatin all achieve embryoplacental concentrations similar to those of maternal plasma.[1] In studies in animals, lipophilic statins have been shown to have adverse reproductive effects in the axial skeleton, viscera, or central nervous system. No malformations were reported among 14 infants exposed to pravastatin; this statin is hydrophilic, has low tissue penetration, and has not caused reproductive toxic effects in animals.[1]

Holoprosencephaly and the VACTERL association have been linked to inhibition of cholesterol biosynthesis, down-regulation of the cholesterol-dependent sonic hedgehog morphogenetic pathway, or both.[3] , [4] These malformations as well as neural-tube and cardiac defects are also associated with maternal diabetes; thus, diabetes might confound the association between statin use and these malformations. However, maternal diabetes was identified in only 7 of 178 case reports and 1 of 20 cases of malformation (spina bifida).

It is thought that only a small proportion of adverse events are reported to the FDA[2]; however, reports are likely to be biased toward severe outcomes. The number of births after first-trimester exposures to statin are unknown. Table 1 presents both the number of reported exposures and the predicted number of exposures on the basis of prescription data and birth

rates. There would be no expected cases of most of the malformations listed in the table, even allowing for the imprecision of estimating exposures; yet three rare anomalies [3], [4], [5] are each observed twice in this small series.

Data from case series cannot be used to test hypotheses of teratogenicity. However, these findings support the need for controlled epidemiologic studies evaluating the potential teratogenic effects of individual drugs in this class.

Robin J. Edison, M.D., M.P.H.
Maximilian Muenke, M.D.
National Institutes of Health
Bethesda, MD 20892-1852
muenke@nih.gov

References

1. Physicians' desk reference. 55th ed. Montvale, N.J.: Medical Economics, 2001.
2. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. N Engl J Med 2002;346:539-540.
3. Muenke M, Beachy PA. Holoprosencephaly. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. Metabolic & molecular bases of inherited disease. 8th ed. Vol. 4. New York: McGraw-Hill, 2001:6203-30.
4. Kim J, Kim P, Hui CC. The VACTERL association: lessons from the Sonic hedgehog pathway. Clin Genet 2001;59:306-315.
5. McGuirk CK, Westgate M-N, Holmes LB. Limb deficiencies in newborn infants. Pediatrics 2001;108:e64-e64.

Table 1. Congenital Anomalies Associated with First-Trimester Statin Exposure.*

Case	Drug and Dose†	Exposure	Pregnancy Outcome	Comments	Approximate Prevalence of Isolated Malformations	Estimated Total Exposed Infants‡		Cases Isolated (Malformation Only)§	
						Reported	Calculated	Reported	Expected
		wk after last menstrual period							
Central nervous system anomalies									
1	Cerivastatin, 0.25 mg/day	0–8	Holoprosencephaly	Therapeutic abortion after prenatal diagnosis	1/16,000	11	600	2	0–1
2	Lovastatin, 40 mg/day	0–7	Holoprosencephaly (defective septum separating lateral cerebral ventricles, with cerebral dysfunction), atrial septal defect, aortic hypoplasia, death at 1 mo of age	Corrective cardiac surgery not performed because of poor overall prognosis; no concomitant medications or illness	Holoprosencephaly, 1/16,000; aortic hypoplasia, 1/50,000; atrial septal defect, 1/370	84	6,050		
3	Lovastatin, 40 mg/day	0–4.5	Aqueductal stenosis with hydrocephalus, concurrent limb deficiency (right banded, atretic thumb)	46,XX; no concomitant medications or illness	Aqueductal stenosis with hydrocephalus, 1–3/10,000; banded, atretic thumb, <1/50,000			1	1 (isolated aqueductal stenosis only)
4	Lovastatin, 20 mg/day	First trimester	Cervicothoracic-to-lumbar neural-tube defect, myelocele, duplication of spinal cord, cerebellar herniation with hydrocephalus; apparent agenesis of palate	46,XX; no concomitant medications or illness, duration of exposure reported inconsistently	Neural-tube defect, <1/10,000; palate agenesis, 1/10,000			1	0 (complex neural-tube defect)
5	Atorvastatin, dose unknown	Until pregnancy recognized	Spina bifida, right-arm abnormality	Type 1 diabetes	3/10,000 (approximate rate in diabetic pregnancy, year of case report [1999])	21	12,000	1	1 (neural-tube defect in all pregnancies)
Limb-deficiency anomalies									
6	Simvastatin, 20 mg/day	0–6	Right leg: fibula and tibia 9% shorter than left side, agenesis of one tarsal bone; right foot 16% shorter than left (reported at 4 yr of age)	Concomitant medications: aspirin, codeine, acetaminophen, propoxyphene during 1st mo of gestation	"Unclassifiable" complex lower-limb deficiency, 1/100,000	393	7,075	2 Complex lower-limb deficiencies reported with long-bone and foot involvement	0
7	Simvastatin, 10 mg/day	0–13	Left leg: femur 16% shorter than right side; foot: aplasia of metatarsals and phalanges 3, 4, and 5; additional VACTERL defects: left renal dysplasia, reversed laterality of aorta, disorganized lumbosacral vertebrae, single umbilical artery; additional findings: clitoral hypertrophy, vaginal and uterine agenesis	46,XX; concomitant medication: promegestone (10 days/mo), duration 0–13 wk	"Unclassifiable" complex lower limb deficiency, 1/100,000; four-component VACTERL, <1/50,000			2 VACTERL associations with more than three features	0

Home Page | Profile | Services
In the News | Contact Us | Useful Links
Frequently Asked Questions | Claim Questionnaires

---

340 Devon Court
Ridgewood NJ 07450-1810
Toll-Free 1-800-279-6996