are similar to those of other common respiratory diseases, making a specific diagnosis of SARS poses difficulties to medical professionals. Our enhanced real-time (ERT) polymerase-chain-reaction (PCR) method (first presented in June 2003 at a symposium on SARS[1]) has been designed for the detection of SARS-CoV with high sensitivity and easy-to-interpret results.[2] The power of the ERT technique has now been extensively explored with the development of ERT-based diagnostic tests for various infectious diseases, including avian influenza and foot-and-mouth disease.

Since the first report of ERT results for SARS,[2] the ERT technique has been modified to increase its sensitivity for the detection of SARS-CoV by at least 10 times (Fig. 1). This improved sensitivity has been achieved by combining the reverse-transcriptase (RT) and PCR steps into a single step (described in Supplementary Appendix 1, available with the full text of this letter at www.nejm.org). In addition, the procedural change makes the diagnostic procedure more convenient. These salient features of one-step RT-PCR have thus far been overlooked by other researchers in this field. Because the single RT-PCR step and the subsequent real-time PCR step require only 35 cycles, the detection of SARS-CoV by the modified ERT technique yields results quickly and with higher sensitivity than regular real-time PCR assays reported to date.

As noted by the World Health Organization with respect to the shortcomings commonly seen in available diagnostic tests for SARS,[3] it is important to unify a molecular test for SARS that can provide sensitive, reliable, and accurate results. Currently, many research groups claim that their methods are accurate, but the way in which they evaluate accuracy is not clearly described.[4] The usefulness of an accurate test that lacks sensitivity has yet to be determined. Unless a unified molecular test for SARS with high sensitivity and reliability is available, we may face the risk of false negative test results, which would allow infected patients to slip into the community and avoid control measures set up to isolate carriers.

Over a year after the start of the 2003 SARS outbreak, many people are still struggling to recover from the physiological and psychological scars inflicted at that time. Identifying potential SARS-CoV carriers by a method with high sensitivity and reliability and as early as possible is crucial to avoid a repetition of the 2003 outbreak.

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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-

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

Table 1. (Continued.)

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							
8	Lovastatin, 10 mg/day	6–11	Left arm: aplasia of radius and thumb, shortened ulna; additional VACTERL defects: left arthrogryposis, thoracic scoliosis, fusion of ribs on left, butterfly vertebrae in thoracic and lumbar region, esophageal stricture, anal atresia, renal dysplasia; additional findings: hemihypertrophy of entire left side, craniofacial anomalies (including asymmetric ears, ptosis of eyelids, high arched palate), torticollis	Concomitant medications: dextroamphetamine for wk 6–11 of gestation; 46,XX; negative for Fanconi's anemia	Five-component VACTERL, <1/500,000	84	6,050		
9	Atorvastatin, 10 mg/day	0–9	Limb-reduction deficiency; transverse deficiency of otherwise normal radius and ulna superior to wrist structures, with aplasia of all distal structures	10–15 cigarettes/day, otherwise no concomitant medications or illness	Transverse deficiency in distal third of forearm, absence of all metacarpal and phalangeal structures, no bony abnormalities above truncation, estimated 1/1,000,000	21	12,000	1 Transverse deficiency of distal forearm	0
3	Lovastatin, 40 mg/day	0–4.5	As described above (Case 3): banded, atretic thumb with aqueductal stenosis	As described above (Case 3)	Banded, atretic thumb, <1/50,000; aqueductal stenosis with hydrocephalus, 1–3/10,000	84	6,050	1 Banded, atretic thumb	0

* The patient in Case 3 had both central nervous system and limb defects and is therefore listed twice. Eleven additional cases involving structural anomalies were as follows: simvastatin: cleft lip with intrauterine growth restriction, cleft lip (prospective report), polydactyly (prospective report), duodenal atresia (prospective report), hypospadias (prospective report), clubfoot, and "major abnormalities" not otherwise specified (therapeutic abortion); atorvastatin: cleft palate and esophageal atresia; lovastatin: microtia with absent auditory canal, and "severe deformity" not otherwise specified. Thirty-two other outcomes were as follows: intrauterine growth restriction (4, all simvastatin), intrauterine fetal death (3, simvastatin; 2, lovastatin), and healthy infants (including preterm births) (23). VACTERL denotes vertebral, anal, cardiac, tracheal, esophageal, renal, and limb defects.

† The number of reports that could be evaluated and the total number submitted are as follows: atorvastatin (Lipitor), 7 and 21, respectively; cerivastatin (Baycol, withdrawn from the market in 2001), 1 and 11; lovastatin (Mevacor), 15 and 28; and simvastatin (Zocor), 25 and 102. Information for other drugs (not shown) is as follows: pravastatin (Pravachol), 3 and 14; the 3 outcomes that could be evaluated were normal; estimated number of births, 5000; and fluvastatin (Lescol), 1 and 2; the 1 outcome that could be evaluated was normal; estimated number of births, 1500.

‡ The following method was used for the estimation of exposures. The smaller number (the reported value) equals the number of exposures reported to the FDA plus any additional exposures (according to information from the manufacturers) that did not require an FDA report (e.g., normal outcome). We then calculated a predicted number of births after statin exposure. The algorithm used incorporated sex- and age-specific prescribing data for each drug. Age-specific birth rates were used to yield an approximate total number of births potentially exposed to each agent through 2001. Assumptions include full compliance with the dispensed medication, discontinuation of the drug before conception in the estimated 50 percent of pregnancies that are planned, and comparability with the general population for age-specific birth rates. No adjustment was made downward to reflect the likelihood that long-term statin users would limit their family size over time rather than remain at continual age-specific risk of pregnancy throughout the duration of their drug exposure.

§ The reported numbers reflect only those adverse birth outcomes included in the FDA data base, which is generally considered to underrepresent actual events.[2] They are not true "observed" numbers, such as those that would be available if ascertainment were complete. Expected numbers are derived from predicted birth numbers and population background rates; they refer to a theoretical number of population events rather than an expected number of reports to the FDA.

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[3-5] 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.

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