Pregnancy Outcomes after Maternal Exposure to Simvastatin and Lovastatin

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Received 4 August 2004; Revised 7 June 2005; Accepted 8 June 2005

BACKGROUND: Our objective was to determine the frequency of adverse outcomes after maternal exposure to simvastatin and/or lovastatin during pregnancy in postmarketing experience. **METHODS:** We reviewed the Merck & Co., Inc. (West Point, PA) pharmacovigilance database for reports of exposure to simvastatin or lovastatin during pregnancy. The reports were classified as prospective (reported prior to pregnancy outcome) or retrospective (reported after pregnancy outcome) and were evaluated for timing of exposure, outcome, congenital anomalies, and other events. Outcome rates were calculated for prospective pregnancies. **RESULTS:** We identified 477 reports (386 prospective and 91 retrospective) with 225 prospective outcomes reported: 154 live born infants, 49 elective abortions, 18 spontaneous abortions, and 4 fetal deaths. Six congenital anomalies were reported: chromosomal translocation, trisomy 18, hypospadias, duodenal atresia, cleft lip, and skin tag. The rate of congenital anomalies (congenital anomalies/live births plus fetal deaths) was 3.8%, which is similar to the background population rate (3.2%; relative ratio, 1.21; 95% 1-sided upper confidence interval [CI], 2.02). There were 13 retrospective reports describing a range of congenital anomalies. No specific pattern of anomalies was identified in either the prospective or retrospective reports. Rates for other outcomes were similar to background rates. **CONCLUSIONS:** Although the number of reports was relatively small, there was no evidence of a notable increase in congenital anomalies in women exposed to simvastatin or lovastatin versus the general population. Greater reporting of congenital abnormalities in the retrospective cohort is not unexpected and may reflect a reporting bias. Drugs should be used during pregnancy only if the benefits outweigh the risks. Simvastatin and lovastatin remain contraindicated during pregnancy. *Birth Defects Research (Part A) 73: 888–896, 2005.* © 2005 Wiley-Liss, Inc.

Key words: pregnancy; lovastatin; simvastatin; congenital anomaly; malformation/birth defects

INTRODUCTION

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also called statins, are widely used for the treatment of hyperlipidemia. Lovastatin (Mevacor; Merck & Co., Inc., West Point, PA), the first drug of this class, was introduced in 1987. Simvastatin (Zocor; Merck & Co., Inc.) was first approved in 1988, and other drugs of this class followed. Lovastatin and simvastatin are similar agents. They differ structurally only in that simvastatin has a side-chain methyl group that is not present in lovastatin. It has become the accepted standard of care that cholesterol should be aggressively lowered in at-risk patients, and statins are the presently recommended first-line therapy for that purpose (Maron et al., 2000). Because the benefits of treatment with statins are substantial, the National Cholesterol Education Program Expert Panel (2001) recently expanded its recommendations to include more intensive efforts to lower cholesterol in patients with multiple risk factors as a strategy for the primary prevention of coronary heart disease.

One potential implication of broader treatment guidelines for the use of statins is that these drugs will be

Presented at the 1st International Conference on Therapeutic Risk Management and the 19th International Conference on Pharmacoepidemiology, Philadelphia, Pennsylvania, 2003.
P.S. Pollack, K.E. Shields, D.M. Burnett, M.J. Osborne, and M.E. Stepanavage are salaried employees of Merck & Co., Inc. and possess stock and stock options in the company.
M.L. Cunningham has received consulting fees from Merck & Co., Inc.
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Published online 14 September 2005 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/bdra.20181

prescribed more frequently to women of childbearing potential. Until now, the use of statins in women of this age range has generally been limited to the small subset with familial hypercholesterolemia. As with any woman of childbearing age who is prescribed chronic medications, pregnancy may occur while she is receiving therapy.

Statins are contraindicated during pregnancy, and in the United States all statins are labeled as FDA Pregnancy Category X. The rationale for Category X labeling is based on the findings of studies conducted in rats and rabbits that were performed as part of the original preclinical safety assessment of lovastatin prior to its approval in 1987. Although no developmental anomalies were induced by lovastatin in rabbits (Merck & Co., Inc., unpublished data), evidence of fetal anomalies (predominantly skeletal defects) was found in rats at a maternally toxic dose of 800 mg/kg/day (Minsker et al., 1983). Because cholesterol and its precursors are essential components of cell membranes, and cholesterol is a precursor for steroid hormone synthesis, these experimental findings were considered to be indicative of a pharmacological basis for developmental toxicity. For example, the inborn error in cholesterol metabolism that causes the human disorder Smith-Lemli-Opitz (SLO) syndrome results in numerous developmental malformations (Porter, 2002). Additionally, cholesterol is now known to play a role in the posttranslational modification of signaling proteins, such as mammalian Sonic hedgehog, that are critical to normal fetal development. Interference with this signaling pathway can lead to cyclopia and holoprosencephaly (Porter et al., 1996; Roessler et al., 1996; Cooper et al., 1998).

However, various studies found that other statins were not teratogenic in animals (Tanase and Hirose, 1987; Tanase et al., 1987; Wise et al., 1990; Dostal et al., 1994; Henck et al., 1998; von Keutz and Schluter, 1998), challenging the assumption that inhibition of HMG-CoA reductase per se is teratogenic. Lovastatin induces an intense inflammatory response in the maternal nonglandular stomach, a structure that is unique to the rodent, leading to maternal weight loss and other adverse signs that impact negatively on the developing embryo. Studies were designed to avoid the development of this inflammatory gastric lesion during gestation and thus prevent maternal toxicity in early pregnancy while providing the same level of systemic lovastatin exposure to the developing embryo/fetus as in the original studies. Unlike traditional safety assessment studies in which the drug of interest is administered approximately 1 week after the animals are mated, in a study by Lankas et al. (2004) treatment with lovastatin was initiated 2 weeks prior to mating to temporally separate maternal toxicity from fetal development. Under these experimental conditions, no adverse fetal effects in lovastatin-treated rats relative to control animals were seen, indicating that the skeletal abnormalities produced by high doses of lovastatin were due to toxic effects of lovastatin on the mother and not to a primary teratogenic effect (Lankas et al., 2004). Other investigators have been unable to demonstrate that inhibition of HMG-CoA reductase by lovastatin (Incardona et al., 1998) or any other HMG-CoA reductase inhibitor (Muenke and Beachy, 2001) adversely affects Sonic hedgehog signaling. On the basis of their experimental findings, Incardona et al. (1998) concluded that there appears to be no mechanistic basis for associating treatment with HMG-CoA reductase inhibitors with the development of holoprosencephaly.

Limited data are available regarding pregnancy outcomes in humans when there has been maternal exposure to statins. Clinical studies of statins during pregnancy are not feasible, since drugs should be used during pregnancy only if the potential benefits outweigh the potential risks. Although the use of these drugs is contraindicated during pregnancy, inadvertent exposure may occur, particularly in the early weeks of gestation, prior to pregnancy detection. Merck & Co., Inc. receives postmarketing reports involving exposure during pregnancy for its marketed statins, simvastatin (Zocor) and lovastatin (Mevacor). Postmarketing surveillance includes a systematic follow-up of these reports.

Our objective was to review and analyze information regarding pregnancy outcomes that involve maternal exposure to simvastatin and/or lovastatin from cases reported to Merck & Co., Inc. as part of routine postmarketing pharmacovigilance. This cumulative review describes 15 years of postmarketing experience and updates an earlier report on data through 1995 (Manson et al., 1996).

MATERIALS AND METHODS

We reviewed all reports entered into Merck & Co., Inc.'s pharmacovigilance Worldwide Adverse Experience System (WAES) database through 31 December 2002 that recorded exposure to simvastatin and/or lovastatin during pregnancy. The WAES database contains study reports of serious adverse events from clinical trials and postmarketing studies, as well as all spontaneous postmarketing reports related to product use from any source, including health care professionals, patients, and regulatory agencies. Individual case reports identified from the literature are also included. Adverse event reports are entered into the WAES database regardless of whether the reporter or a Merck & Co., Inc. physician believes that a causal relationship exists between the drug and the adverse event. The spontaneous reporting system is a voluntary system of adverse event reporting for the purpose of generating early warning signals. The data are not necessarily complete and may include reports with unsubstantiated diagnoses and incomplete information.

Reports involving oral exposure to simvastatin and/or lovastatin during pregnancy were classified as prospective or retrospective according to the information contained in the report at the time it was received by the manufacturer. Prospective reports are reports received after exposure occurred but prior to knowledge of pregnancy outcome, whereas retrospective reports are those received only after the outcome of the pregnancy is known. Routine postmarketing surveillance at Merck & Co., Inc. includes systematic attempts to obtain further information about the events that are reported, and efforts are made to obtain follow-up at the end of each pregnancy. However, reporting is voluntary, and further information can be obtained only if the reporter is willing to provide additional data.

All reports were evaluated for timing of exposure, dose, and outcome. We estimated the time of exposure according to the number of weeks of gestation from the first day of the last menstrual period, with the first trimester defined as weeks 0–13, the second trimester as

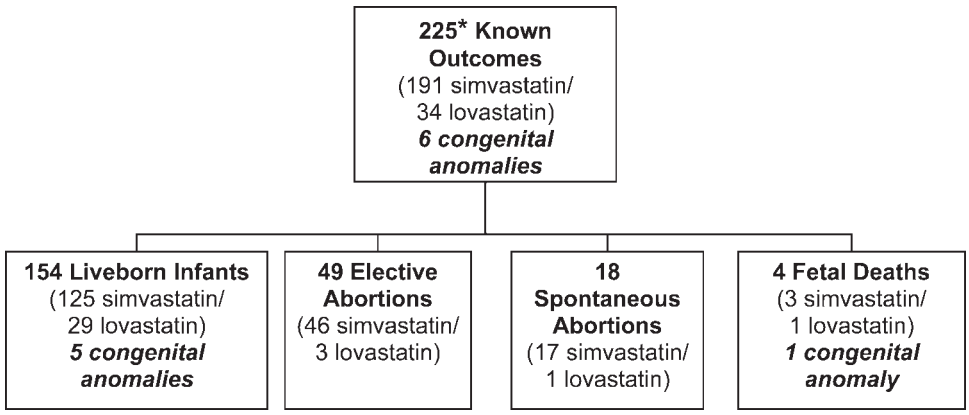

Figure 1. Prospective reports: pregnancy outcomes. All 6 prospectively reported congenital anomalies involved maternal exposure to simvastatin. *Includes 2 reports of twin gestation.

weeks 14–27, and the third trimester as week 28 until term. Reports involving exposure to both simvastatin and lovastatin were arbitrarily classified as exposure to simvastatin.

Pregnancy outcomes included elective abortions, spontaneous abortions (death of conceptuses <20 weeks from the first day of the last menstrual period) (March of Dimes, 2004a), fetal deaths (or stillbirth; death of conceptuses ≥20 weeks from the last menstrual period) (March of Dimes, 2004b), or live births (birth of a viable neonate). Neonatal deaths and other adverse neonatal outcomes were also included. Congenital anomalies were classified according to the guidelines published by the Metropolitan Atlanta Congenital Defects Program (MACDP) of the Centers for Disease Control and Prevention (CDC) (CDC, 1988). Reports of congenital anomalies were reviewed by a dysmorphologist (M.L.C.).

Statistical Analysis

Outcome rates were calculated for prospectively reported pregnancies with denominators chosen to conform to the published population rates used as comparators (Alberman, 1992; Honein et al., 1999; Ventura et al., 2000; CDC, 2001). The incidence of congenital anomalies was calculated for prospective reports using the number of reported anomalies in live births and fetal deaths as the numerator, and the total number of reported live births and fetal deaths as the denominator, in a manner similar to MACDP methodology (CDC, 1988). Confidence intervals (CIs) were calculated using the method of Haenszel W, Loveland D, and Sirken MG (Lilienfeld and Stolley, 1994) for Poisson-distributed variables. The ratio of the rate of anomalies in the statin-exposed group and the background population (Honein et al., 1999) was calculated, and the CIs around this ratio were estimated using Fieller's theorem (Finney, 1964). A 1-sided CI was considered appropriate because there was no expectation of a beneficial statin effect on pregnancy outcome.

Outcome rates were not calculated for retrospective reports, because the total number of exposed pregnancies (denominator) was not known. Adverse pregnancy outcomes, particularly congenital anomalies, are also likely to be disproportionately represented among retrospective reports (Mitchell, 1994).

RESULTS

There were 477 reports of exposure of pregnant women to either simvastatin or lovastatin as of 31 December 2002. Of these, 386 were prospective reports and 91 were retrospective reports. There were 2 reports involving exposure to both simvastatin and lovastatin (1 prospective and 1 retrospective). Both reports were counted as simvastatin exposures.

Prospective Reports

The prospective reports included 319 cases of exposure to simvastatin, and 67 reports of exposure to lovastatin. The majority of reports were postmarketing reports, although 20 reports involving exposure to simvastatin were from clinical studies. There were no reports of exposure to lovastatin from clinical trials. Maternal age was reported in 291 cases, in which the mean age was 32 ± 6 years and the median age was 32 years. Prospectively reported cases were received, on average, at ~10 weeks gestation with a range of 17–277 days from the last menstrual period (based on the 141 prospective reports for which these data were available).

Pregnancy outcomes were reported in 225 (58%) of the prospective cases (Fig. 1). Congenital anomalies were reported in 5 live born infants and 1 stillborn infant, and all of these cases involved maternal exposure to simvastatin. There were no prospectively reported congenital anomalies in association with maternal exposure to lovastatin.

Table 1 compares the outcome rates for the prospectively reported pregnancies with published population background rates (Alberman, 1992; Honein et al., 1999; Ventura et al., 2000; CDC, 2001). Pregnancy outcomes in the exposed group were similar to what would be expected in the population as a whole. There were 4 reports of fetal death. Although the rate of fetal death was higher than the population background rate, there was no apparent pattern that would suggest a relationship to maternal therapy with simvastatin or lovastatin. Fetal deaths included 1 at 6

Table 1
Prospective Reports: Pregnancy Outcomes

Outcome	*n*	Denominator	% Of Reports	U.S. background rate (%)[a]
Elective abortion	49	225[b]	21.7	22
Spontaneous abortion	18	176[c]	10.2	10–20
Fetal death	4	158[d]	2.5	0.7
Live births	154	225[b]	68.4	62
Congenital anomalies	6	158[d]	3.8	3.15

[a]Ref. Alberman (1992); Honein et al. (1999); Ventura et al. (2000); CDC (2001).
[b]Total number of pregnancy outcomes.
[c]Total number of spontaneous abortions + livebirths + fetal deaths.
[d]Total number of live births + fetal deaths.

months of gestation (no additional information available), 1 at 40 weeks with no congenital anomalies (cause unknown), 1 case in which the reporter attributed fetal death to a nuchal cord, and 1 stillborn infant with trisomy 18 (Table 2).

The timing of exposure by trimester was known for 224 of the 225 prospective reports with known outcomes. First-trimester exposure was reported in 150 of the 154 live births, and the gestational weeks of exposure were reported in 136 of these cases. Therapy was initiated in the second trimester in only 4 cases (3 for simvastatin and one for lovastatin). In 88% of the cases (119/136), simvastatin or lovastatin was being used at the time of the last menstrual period, which suggests that most exposures occurred inadvertently prior to the recognition of pregnancy. In most cases (122/136, 90%) the drug was discontinued during the first trimester, presumably after the woman discovered that she was pregnant.

There was no apparent correlation between the specific timing of exposure during the first trimester and a congenital anomaly as an outcome. Timing of exposure by gestational week was known for 107 of the 125 prospectively reported simvastatin live births, including all 5 live born infants who were reported to have congenital anomalies (Fig. 2). Details of the prospectively reported congenital anomalies are shown in Table 2. Of the 6 cases, 5 involved live born infants. The sixth case involved a fetal death that occurred in 1 conceptus of a dizygotic twin who was later found to have trisomy 18 associated with multiple malformations. The surviving twin was born at 37 weeks and had no reported anomalies. No congenital anomalies were identified in the prospective reports of elective or spontaneous abortions.

The rate of congenital anomalies (6/158; 3.8%; 95% CI, 1.4, 8.2) is similar to the that of the overall U.S. population (3.15%) reported by the MACDP of the CDC (Honein et al., 1999). The relative ratio of these 2 rates is 1.21 with a 95% 1-sided upper CI of 2.02, which suggests that there is no evidence of a notable increase in congenital anomalies in women exposed to simvastatin or lovastatin versus the general population.

Adverse experiences other than congenital anomalies are also entered into the WAES database, although they are inconsistently reported. Prospectively reported neonatal events that are not considered congenital anomalies by MACDP included prematurity ($n = 5$, including 1 with intrauterine growth restriction [IUGR]), respiratory or fetal distress ($n = 4$), jaundice ($n = 3$), hypoglycemia ($n = 2$), patent ductus arteriosus at 31 weeks of gestation ($n = 1$), transient systolic murmur ($n = 1$), and hydrocele ($n = 1$). There was also 1 report describing a newborn with stiff-

Table 2
Prospective Reports: Congenital Anomalies ($n = 6$)

Simvastatin therapy (dose, mg)	Maternal age	GW[a] exposure	Outcome	Anomaly	Comment
10	30	3–4	Male live birth 2970 g	Postaxial polydactyly (reported as skin tag)[b,c]	Pea-sized spherical outgrowth, resolved with treatment; premature labor
10	27	2–6	Male live birth 3460 g	Balanic hypospadias[c]	Normal renal ultrasound; maternal exposure to alpidem, fluoxetine
10	30	0–7	Fetal death 22 GW	Trisomy 18/multiple anomalies[c]	Twin gestation; 1 normal male born by Cesarean section at 37 weeks
20	28	0–8	Female live birth 36 GW	Duodenal atresia	Delivery by Cesarean section; maternal exposure to cephalexin
20	40	0–12	Female live birth 35 GW 1480 g	Cleft lip[c]	Intrauterine growth restriction; maternal exposure to diltiazem, aspirin
20	34	3–5	Male live birth	Balanced translocation chromosomes I and II	Baby reported to look and behave normally; maternal hypertension with exposure to bendroflumethazide

[a]GW = gestational weeks.
[b]Reporter's use of the term of "skin tag" differs from authors' interpretation of the information in the case report.
[c]Discussed in Manson et al. (1996).

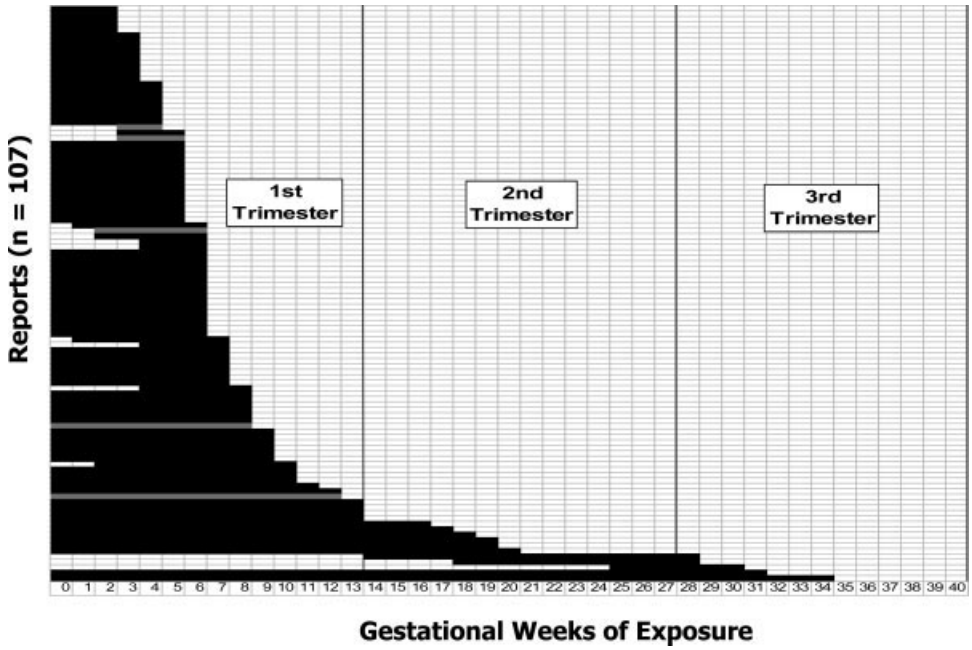

Figure 2. Simvastatin prospective live births: timing of exposure. The onset and duration of exposure to simvastatin is illustrated for all prospective cases for which the number of weeks of exposure was reported. Each row represents a single pregnancy. The reported period of exposure is shown for each case as a black bar (normal outcome) or gray bar (congenital anomaly).

ness, probable epileptic seizures, and subsequent poor development (none of which are classified as congenital anomalies by the CDC). The findings were initially reported as possible "hyperekplexia," but this case was not classified as a congenital anomaly because follow-up information indicated that the diagnosis was uncertain.

Retrospective Reports

Although outcome rates cannot be calculated from retrospective data, retrospective reports may be useful for identifying events of interest or clusters of related congenital anomalies. There were 91 retrospective reports of maternal exposure, including 52 reports of exposure to simvastatin (with 53 outcomes due to 1 twin birth) and 38 reports of exposure to lovastatin. Thirteen congenital anomalies were reported in 8 live births, 1 spontaneous abortion, and 4 elective abortions (Table 3). The timing of exposure was not reported in one case, and the remaining 12 cases involved first-trimester exposures. No specific pattern of anomalies was identified. Three reports contained minimal information and no further information could be obtained. There were 5 reports of infants with isolated anomalies, and 5 reports of infants with multiple anomalies. Of interest, because of the potential link with abnormalities in cholesterol metabolism, was 1 report of a preterm infant (34 weeks of gestation) with a left-hand skin tag, a banded nonfunctional thumb, and skull defects reported as holoprosencephaly. However, magnetic resonance imaging (MRI) showed hydrocephalus. There were no reported MRI findings to support a diagnosis of holoprosencephaly.

In addition to the reports involving congenital anomalies, retrospectively reported infant adverse event reports included 1 preterm (31 weeks) large-for-date infant with respiratory distress and metabolic disorder (mother had diabetes); 1 preterm (32 weeks) infant with IUGR who died on day 3 (mother had preeclampsia); 1 preterm (35 weeks) infant with IUGR, bilateral hydrocele, and severe jaundice; 1 other infant with jaundice; 1 small-for-gestational-age infant; 1 with pedal edema; and a normal newborn who was later readmitted for vomiting. One full-term healthy infant was reported as normal; however, the information given indicated short length (length [46 cm] in the fifth to 10th percentile, weight in the 25th percentile, and head circumference in the 25–50th percentile). Two reports regarding children included a 4-year-old with dental problems (caries) and a 6-year-old with attention deficit disorder, petit mal seizures, and developmental delay (slow speech development, learning problems, and underdeveloped fine motor skills and muscle control).

DISCUSSION

The key findings of this review are that 1) in prospectively reported pregnancies involving maternal exposure to simvastatin and/or lovastatin, the overall incidence of congenital anomalies (6/158 or 3.8%) was similar to the 3.15% incidence of overall birth defects reported by the MACDP (Honein et al., 1999), and 2) no specific pattern of congenital anomalies was identified for either prospectively or retrospectively reported pregnancies. Specifically, no patterns of anomalies known to be associated with reduced cholesterol biosynthesis, such as those seen in the human genetic disorder SLO syndrome, were reported. These data suggest that the reported anomalies are likely to represent chance occurrences of events seen in the back-

Table 3
Retrospective Reports: Congenital Anomalies (n = 13)

Therapy (mg)	Maternal age	Exposure (gestational weeks)	Outcome	Anomaly	Comment
Minimal information					
Lovastatin NR	NR[a]	NR	Live birth	"Severe deformity"	No further information
Simvastatin NR	NR	1st trimester	Elective abortion	"Major abnormalities"	No further information
Simvastatin 20	24	0–9	Spontaneous abortion	Suspected triploidy	Not confirmed, no karyotyping performed
Isolated anomalies					
Simvastatin 10	37	2–6	Female, live birth, 2900 g	Unilateral cleft lip	No cleft palate reported
Lovastatin 20	NR	1st trimester	Elective abortion	Spina bifida[d]	46XX karyotype
Lovastatin 4 tablets (mg NR)	NR	0–8	Live birth	Deformed right ear; no auditory canal (microtia)	Maternal exposure to caffeine, pseudoephedrine, acetaminophen, Demulen
Simvastatin 20	NR	0–4	Female, live birth	Right lower limb aplasia of 1 tarsal bone, foot hypoplasia, equal shortening of the fibula and tibia (intercalary deficiency)	Maternal exposure to aspirin, codeine, acetaminophen, dextropropoxyphene
Simvastatin 10	33	1st trimester	Live birth	Clubfoot[d]	Maternal exposure to indapamide
Multiple anomalies					
Lovastatin 20	24	0–18	Elective abortion	Large thoracolumbar open neural tube defect, duplication of spinal cord, cleft palate	(Literature report, Hayes et al., 1995)
Lovastatin 40	22	0–5	Live birth, 3400 g	Ventricular septal defect, atrial septal defect, aortic hypoplasia[b,d]	Secondary cerebral dysfunction with abnormal EEG; infant died on day 32
Lovastatin 10	32	6–11	Female, live birth	Esophageal stricture, butterfly vertebrae, low-set eyes, phocomelia, high arched palate, hypoplastic nipples, deformed pectoralis muscle, left radial club hand, asymmetry of the ears, eyelid ptosis, torticollis, hemangioma, hypertrophy of left shoulder girdle with general hyperplasia of left side of body. (features consistent with VATER association with other abnormalities)[c,d]	Maternal exposure to dextroamphetamine (literature report, Ghidini et al., 1992)
Simvastatin 10	37	2–12	Elective abortion	Rhizomelic (femoral, intercalary) shortening; aplasia of metatarsals and toes 3–5, right-sided aortic arch, disorganized lumbosacral vertebrae, left renal dysplasia, left ureterocele, single umbilical artery, clitoromegaly, uterine and vaginal agenesis (features of VATER association with other abnormalities)	46XX karyotype
Lovastatin 40	26	0–4	Female, live birth, 34 GW, 1877 g	Rudimentary right thumb, left hand skin tag, skull defects. MRI revealed hydrocephalus and aqueductal stenosis (reported as holoprosencephaly).[d]	46XX karyotype, maternal gestational hypertension

[a]NR = not reported; GW = gestational weeks; MRI = magnetic resonance imaging; EEG, electroencephalogram.
[b]Initially reported as a cerebral ventricular septal defect and that terminology has been used by others in their description of this case (Edison and Muenke, 2004a, b). Based on follow-up information, it became clear that this was, in actuality, a cardiac defect. (Edison and Muenke, 2005).
[c]VATER = Vertebral defects, anal atresia, tracheoesophageal fistula, esophageal atresia, radial limb reduction and renal defect.
[d]Discussed in Manson et al. (1996).

ground population, and are unlikely to be related to maternal exposure to simvastatin or lovastatin.[1]

Given the ethical constraints on conducting controlled clinical studies to assess drug safety during pregnancy, postmarketing surveillance can be a useful tool for evaluating the effects of drugs on pregnancy outcomes. The disadvantage is that information received from postmarketing surveillance reports may be incomplete, and neither the total number of adverse pregnancy outcomes (numerator) nor the total population of exposed pregnancies (denominator) can be estimated. However, if only prospectively reported cases of exposure during pregnancy are considered, then the rates of these outcomes can be calculated and compared with rates seen in the general population. Prospective reports are less likely to be influenced by reporting bias and are more likely to reflect pregnancy outcomes in the exposed population as a whole.

Of the 6 prospective reports of congenital anomalies, 2 involved chromosomal abnormalities and three involved relatively common congenital defects (hypospadias, postaxial polydactyly, and cleft lip). Although postaxial polydactyly is a feature of SLO, isolated postaxial polydactyly is a common anomaly that occurs at an approximate frequency of 1:1300 white births and 1:140 African-American births (Watson and Hennrikus, 1997). Cleft lip and/or palate are seen commonly in the general population (1: 1000 Caucasian live births in the United States) (Wyszynski et al., 1996). Although cleft palate is a common feature of SLO (Porter, 2002), to our knowledge isolated cleft lip has not been described (OMIM, 2004). The sixth report involved duodenal atresia, which is a rare anomaly that has no apparent potential link to cholesterol biosynthesis.

All prospective reports of congenital anomalies involved exposure to simvastatin. This is likely a chance occurrence due to the disproportionate number of prospective reports involving simvastatin for which pregnancy outcome was available (191 for simvastatin vs. 34 for lovastatin). The numbers of retrospective reports involving simvastatin and lovastatin were more closely comparable (52 for simvastatin vs. 38 for lovastatin). Of the 13 retrospectively reported anomalies, 7 involved exposure to lovastatin.

The rates for other adverse pregnancy outcomes, specifically elective and spontaneous abortions, were also similar to rates that have been reported for the general population (Alberman, 1992; Ventura et al., 2000). Although the rate of fetal death was higher than that reported for the general population (CDC, 2001), neither the timing of fetal death nor a review of the specific features of the individual cases indicates a common etiology suggestive of statin exposure. It is also possible that women who are treated with statins during their childbearing years may have other comorbidities (e.g., hypertension and maternal diabetes) that would increase their risk for adverse pregnancy outcomes, such as fetal death.

A range of miscellaneous adverse events involving both mother and baby, representing common complications of pregnancy with no apparent pattern, were reported. One report of a newborn with stiffness, probable epileptic seizures, and subsequent poor development was received, but no conclusions can be drawn from a single case report with limited information and an uncertain diagnosis.

There were 13 retrospective reports of congenital anomalies. By itself the number of retrospective reports is no basis for concern, considering the preferential reporting of drug exposures after congenital anomalies are diagnosed (Mitchell, 1994). Retrospective reports are still useful, however, because they may identify clusters of rare abnormalities and suggest associations that might otherwise go undetected.

The retrospective reports describe a range of congenital anomalies, and no specific pattern was identified. One case described "skull defects" reported as holoprosencephaly, but the presented information does not support that diagnosis. No abnormalities of facial development were reported, and the MRI findings were hydrocephalus and aqueductal stenosis with no mention of the specific features of holoprosencephaly. There was 1 literature report of a VATER phenotype (Ghidini et al., 1992). VATER is not a specific diagnosis; rather, it is a description of malformations that are commonly associated with each other (vertebral defects, anal atresia, tracheoesophageal fistula, esophageal atresia, radial limb reduction, and renal defect). The VATER phenotype has not been reported to be associated with abnormalities of cholesterol biosynthesis. There were 2 cases of lower-extremity dysplasia: 1 isolated, and 1 in combination with a right-sided aortic arch, skeletal and vertebral malformations, and urogenital abnormalities, including clitoromegaly. (Although there are features in this latter case that are consistent with VATER, the presentation is not classic for that diagnosis.) These reports are difficult to interpret; however, the data from this retrospective group are insufficient to suggest a causal relationship. Likewise, no conclusions can be drawn from a single report of an infant with a deformed right ear and canal atresia (microtia has an incidence of 1:6000–7000 live births [Mastroiacovo et al., 1995]). One report involved a complex neural tube defect and a cleft palate (Hayes et al., 2005), but neural tube defects (incidence: 1–2 per 1000 live births [Wynbrandt and Ludman, 2000]) are not a described manifestation of SLO. Findings such as a unilateral cleft lip, club foot, and complex congenital heart disease are either due to a single occurrence without a known biologic link to cholesterol metabolism or can be predicted to occur based on the frequency of such malformations in the general population.

In addition to a retrospective report of isolated cleft lip, a case of isolated cleft lip was also prospectively reported (see above). Given the frequency of orofacial clefting in the general population, the finding of 1 prospective and 1 retrospective report does not raise a specific concern.

The most prevalent malformations seen in our cases were limb malformations. Variably involving the upper and lower limbs and affecting preaxial and postaxial structures in 6 reported cases (1 prospective case of postaxial polydactyly, 2 retrospective cases of isolated limb defects, and 3 retrospective cases involving multiple anomalies), these malformations did not appear to fall into a specific pattern. Whether the retrospective and prospective data are examined independently or collectively, they fail to define a group of malformations suggestive of a like cause. Continued prospective case reporting will help us discern

[1]Additional data received during 2003 and 2004, following the cutoff period of this analysis, do not change the conclusions of the current review. The new data included a prospective report from the literature (Lemoine et al., 2001) of a newborn with stricture of the right ureteropelvic junction "needing just surveillance," a prospective report of an elective termination due a diagnosis of Down syndrome (41-year-old mother), and a retrospective report of a live-born child with thyroid hypoplasia. There were no reports of fetal or neonatal death.

whether there is any relationship between statin exposure and specific malformation phenotypes.

Our analysis updates the review of the WAES database by Manson et al. (1996) and is in agreement with their findings. The analyses presented here include an additional 7 years of data and continue to show no evidence of a notable increase in the overall rate of congenital anomalies in women exposed to statins versus the general population. However, these comparisons are not without limitations. A tendency toward a lower risk ratio may occur when rates from postmarketing surveillance are compared with those from actively ascertained birth outcomes (such as those in the MACDP) because active surveillance will likely identify more cases compared to spontaneous reports. Our calculations use the MACDP background rate of 3.15%, whereas the March of Dimes (2005) reports a background birth defect prevalence of ~4%. Background rates may vary depending on the population studied. Women in the background population (the control group) may differ in important respects from those in the exposed group, which is an additional limitation when the rate of congenital anomalies reported here is compared with historical data.

We also examined other adverse outcomes. These outcomes are inconsistently reported, and the adverse-experience reports collected in the safety database did not identify any unusual type of event or large number of reports over what would be expected in the population as a whole. Isolated reports of effects on fetal growth and neurological and developmental outcomes are not interpretable due to potential confounders, comorbid conditions, and the high expected background rates for these conditions in the general population. For example, multiple risk factors (including but not limited to maternal smoking, alcohol use, substance abuse, vascular disease, and renal disease) predispose an individual to IUGR, which involves 3–10% of all live births (Cunningham et al., 1997).

Limited data on pregnancy outcomes are available from other sources. Rosa (1994) reported the findings of a prospective Michigan Medicaid survey that identified 1 congenital anomaly (an unspecified cardiovascular defect) in 11 exposures to lovastatin (3 were first-trimester exposures [including the anomaly report], and the others were either not first-trimester exposures or of unknown timing). As of 2003, Merck & Co., Inc. began to receive aggregate data from the Swedish Medical Birth Registry (2004) regarding certain product exposures during pregnancy. Twenty-seven of 732,509 live births entered into the Swedish pregnancy registry between 1 July 1995 and 29 February 2004 resulted from pregnancies in which the mother reported exposure to simvastatin at the first antenatal visit. The Swedish Medical Birth Registry assessor commented that there was an increased incidence of preterm infants and infants with low birth weight, possibly attributable to maternal diabetes and the use of antihypertensive drugs by these women. There was 1 report of an unspecified cardiac defect; however, the report states that the condition was "mild" and "a diagnosis of an unspecified cardiac defect often means a murmur that spontaneously resolves." There was also a report of a full-term infant with a unilateral undescended testicle at birth, a condition that may resolve spontaneously. Although these observations are based on extremely limited numbers, they are consistent with the results of our review of the WAES database.

Recently, Edison and Muenke (2004a, b) reported on all cases submitted to the Food and Drug Administration involving a first-trimester exposure to any statin. Since reports of normal pregnancy outcome (i.e., without maternal or fetal adverse events) are not as a rule submitted to regulatory agencies, reports of pregnancies with a normal outcome would generally not have been available to these investigators. Thus, we caution against overinterpretation of individual case reports. The cases suggestive of major skeletal and central nervous system abnormalities involving simvastatin and lovastatin listed in the authors' tables were retrospectively reported. The diagnoses are as stated by the reporter, and there are no uniform case definitions. The case initially characterized as holoprosencephaly following exposure to lovastatin involved a cardiac ventricular septal defect, but no cerebral ventricular defect (Edison and Muenke, 2005) (Table 3). The exposure estimates involve multiple assumptions regarding the number of prescriptions dispensed to women of childbearing age worldwide, adherence to therapy, exposed pregnancies, fraction of pregnancies not terminated, and unplanned births. Isolated unrelated cases can be explained by chance events, and there is no clustering of developmentally related malformations. Although a pharmacological basis for developmental toxicity is postulated, teratogenic effects were not seen in animal studies involving several different statins (Tanase et al., 1987a, b; Wise et al, 1990; Dostal et al., 1994; von Keutz and Schluter, 1998; Dostal et al., 1994; Henck et al., 1998; Lankas et al., 2004). Experimental treatment with lovastatin has not been shown to adversely affect Sonic hedgehog signaling (Incardona et al., 1998; Muenke and Beachy, 2001).

Although the findings of our review suggest that maternal exposure to simvastatin and/or lovastatin does not have a negative impact on pregnancy outcomes, the inherent limitations of postmarketing data affect the strength of the conclusions that can be reached. The vast majority of the reports discussed in this review were received as part of routine postmarketing surveillance. The quality of the information provided is variable. Although systematic attempts are made to obtain further information, spontaneous reports are often incomplete and may contain unsubstantiated exposure and outcome information from varied sources. The diagnoses reflect the terminology of the reporters rather than uniform case definitions. Information on maternal disease, additional drug exposures, and other potential confounding variables may be missing or incomplete and may differ from the population-based comparison group. Limited information on preterm delivery, low birth weight, and head circumference make it difficult to assess these outcomes, and patterns of minor anomalies and developmental abnormalities (possible consequences of teratogenic exposure) would not be detected using this data set. Finally, spontaneous reporting is a passive surveillance system wherein neither the true number of reports (numerator) nor the population from which they are drawn (denominator) is known.

There are other limitations to these analyses. The number of cases with a known outcome was small ($n = 158$ [154 live births and 4 fetal deaths]). Despite attempts to obtain follow-up information in all cases, outcomes were obtained for only 58% of the prospective reports and are not known for the remainder. It should be noted that these analyses lack sufficient power to detect small increases in overall

risk, and we are also unable to conclude whether or not there is an increase in the incidence rate of any individual congenital anomaly.

In conclusion, our review provides no indication of an association between maternal exposure to simvastatin and/or lovastatin and the occurrence of any adverse pregnancy outcomes. The overall rate of congenital anomalies and other adverse outcomes appears to be similar to reported background rates for the general population, and no pattern of congenital anomalies was identified for either the prospectively or retrospectively reported pregnancies.

We fully acknowledge that the strength of our conclusions is limited by the small number of reports available and the limitations inherent in any analysis of voluntary postmarketing data. Nevertheless, the information presented here may be useful to women and their health care providers. Drugs should be used during pregnancy only if the potential benefits of therapy outweigh the potential risks. Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with hypercholesterolemia. Therefore, simvastatin and lovastatin should be administered to women of childbearing age only when they are highly unlikely to conceive. The use of simvastatin and lovastatin during pregnancy remains contraindicated.

ACKNOWLEDGMENTS

The authors wish to dedicate this manuscript to the memory of our friend and colleague Bengt-Erik Wiholm.

The authors thank Dr. Wendy Battisti for assistance in preparing the manuscript.

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