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Pregnancy outcome following maternal exposure to statins: a multicentre prospective study

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Objective This contribution addresses the risk associated with exposure to statins during pregnancy.

Design Multicentre observational prospective controlled study.

Setting European Network of Teratology Information Services.

Population Pregnant women who contacted one of 11 participating centres, seeking advice about exposure to statins during pregnancy, or to agents known to be nonteratogenic.

Methods Pregnancies exposed during first trimester to statins were followed up prospectively, and their outcomes were compared with a matched control group.

Main outcome measures Rates of major birth defects, live births, miscarriages, elective terminations, preterm deliveries and gestational age and birthweight at delivery.

Results We collected observations from 249 exposed pregnancies and 249 controls. The difference in the rate of major birth defects between the statin-exposed and the control groups was small and statistically nonsignificant (4.1% versus 2.7% odds ratio [OR] 1.5; 95% confidence interval [95% CI] 0.5–4.5, $P = 0.43$). In an adjusted Cox model, the difference between miscarriage rates was also small and not significant (hazard ratio 1.36, 95% CI 0.63–2.93, $P = 0.43$). Premature birth was more frequent in exposed pregnancies (16.1% versus 8.5%; OR 2.1, 95% CI 1.1–3.8, $P = 0.019$). Nonetheless, median gestational age at birth (39 weeks, interquartile range [IQR] 37–40 versus 39 weeks, IQR 38–40, $P = 0.27$) and birth weight (3280 g, IQR 2835–3590 versus 3250 g, IQR 2880–3630, $P = 0.95$) did not differ between exposed and non-exposed pregnancies.

Conclusions This study did not detect a teratogenic effect of statins. Its statistical power remains insufficient to challenge current recommendations of treatment discontinuation during pregnancy.

Keywords Birth defect, hydroxymethyl glutaryl coenzyme A reductase inhibitors, pregnancy, statins.

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Introduction

Hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly called statins, are primarily used to treat hyperlipidaemia. Genetic conditions such as familial hypercholesterolaemia may require statin treatment in young and otherwise healthy individuals. Furthermore, there is a trend for women to become pregnant later in life, leading to a growing number of women with childbearing potential likely to receive statin therapy. Efforts to make statins available as 'over-the-counter medication' to promote their use for primary cardiovascular prevention may also lead to increased exposure. Even though current recommendations are to discontinue statin treatment during pregnancy, the

incidence of inadvertent fetal exposure is likely to increase, as a significant number of pregnancies are unplanned.

Various experimental studies did not find statins to be teratogenic in animals: only lovastatin exposure at maternally toxic levels showed in one of these studies an increased incidence of skeletal defects and gastroschisis in the offspring.[1] Several studies on small numbers of human exposures indicate no increased risk of adverse pregnancy outcome after exposure during early pregnancy. A controlled prospective cohort study analysed the outcomes of 64 pregnancies after first-trimester exposure to statins (atorvastatin, simvastatin, pravastatin and rosuvastatin) and did not find an increased risk of major birth defects or pregnancy loss.[2] However, gestational age at birth and birthweight were lower in the statin-exposed group. Another study found no evidence of increased risk for fetal anomalies or any discernable pattern of birth defects among live births ($n = 64$) of women having received a prescription for statins in the first trimester of pregnancy.[3] Manufacturers collected pharmacovigilance data on lovastatin and simvastatin ($n = 225$) and found no increased risk of major birth defects in exposed pregnancies compared with general population rates. Furthermore, no specific pattern of anomalies was identified in 91 retrospectively collected cases.[4,5] Another case series did not observe any specific pattern of birth defects after statin exposure during pregnancy.[6]

These reassuring data contrast with a fear of teratogenic potential raised from isolated retrospective case reports of malformations, data from spontaneous reporting and biological considerations. Cholesterol and its precursors are essential at different levels of cellular functioning, including cell growth control and proliferation, cytoplasmic membrane construction and steroid synthesis. Several published case reports and series describing major birth defects after statin exposure during the first trimester of pregnancy were considered to be indicative of a pharmacological basis for developmental toxicity. One case report described a newborn with multiple major birth defects (vertebral anomalies, anal atresia, tracheo-oesophageal fistula, and renal and radial dysplasia) following maternal treatment with lovastatin and dextroamphetamine during the first trimester of pregnancy.[7] Another case report described a fetus with a neural tube defect after lovastatin exposure during the first trimester of pregnancy.[8] A study based on data from spontaneous reporting to the US Food and Drug Administration, without a control group, presented 22 incidences of major birth defects after first-trimester exposure to cerivastatin, simvastatin, lovastatin or atorvastatin, including severe central nervous system and limb defects.[9,10] The authors suggested a causal link to dysregulation of cholesterol biosynthesis and Sonic-Hedgehog gene expression. Their physiological considerations pointed to the fact that the Hedgehog family of morphogens require covalently bound cholesterol for their activity, and that Hedgehog pathways are critical for the morphogenesis of the central nervous system, face, skeleton, musculature and viscera.[11,12] Furthermore, they stated that lipophilic statins such as simvastatin, lovastatin, atorvastatin, cerivastatin or fluvastatin have a better transplacental transfer than hydrophilic statins (pravastatin), implying that the former agents may carry a greater risk of interfering with embryonic development. However, comments on this study raised the question of whether the birth defects observed constituted a distinctive pattern. Possible confounding factors such as maternal diabetes were also discussed.[13]

Given these data and theoretical considerations, current advice is against statin use in pregnancy. The aim of this study was to address the risks associated with inadvertent exposure to statins during pregnancy.

Methods

Our prospective, controlled, multicentre study enrolled pregnant women who contacted, or whose physician contacted, one of 11 Teratology Information Services (TIS), seeking advice about statin exposure during the first trimester of pregnancy. Data were collected for exposures having occurred between 1990 and 2009. The participating centres are members of the European Network of Teratology Information Services (ENTIS), an organisation of counselling services providing information on safety and risks of exposure to medications and other agents during pregnancy and breastfeeding. Only one TIS was located in a country (UK) with a statin available as 'over-the-counter medication'. Standardised procedures for data collection were used by each centre.[14] Maternal characteristics (age, tobacco use, alcohol consumption, medical and obstetric history) and details of medication exposure (timing in pregnancy, duration, dose and concomitant medication) were collected at initial contact with the TIS during pregnancy, and so before the outcome was known. After the expected date of delivery, follow up was achieved through a structured telephone interview or mailed questionnaire to the woman or her physician. Details on the pregnancy outcome, gestational age at delivery, birthweight, birth defects and neonatal complications were obtained. In most cases, gathering of follow-up data was performed during the neonatal period. Pregnant women considered lost to follow up were not included in the analysis (overall rate of loss to follow up in the ENTIS group is known to range from 10 to 40% and is expected to be similar in both groups).

Pregnancy outcomes of women from the statin-exposed group were compared with the outcomes of a control group, for which advice during pregnancy was requested from the same TIS on exposure to agents known to be nonteratogenic.

Most common drug exposures in the control group were antibiotics (penicillins, cephalosporins), low-dose fluconazole, hepatitis B vaccine, oral contraceptives taken no later than up to the 5th week of pregnancy, analgesics (paracetamol, ibuprofen), antihistamines, beta-blocking agents, proton pump inhibitors, H_2 receptor antagonists, low-dose diagnostic radiation and topical preparations with negligible systemic absorption. No matching criteria other than the TIS centres were applied. Data collection at first contact and follow up were performed in the same way for both groups.

The primary outcome of interest was the rate of major birth defects. A birth defect was considered major if it caused a severe structural impairment or needed surgical correction. Major birth defects were diagnosed prenatally by targeted ultrasound or amniocentesis or at birth by physical examination of the newborn infant and appropriate imaging methods. As a consequence of the risk of missed diagnosis and under-reporting, minor birth defects were simply described without calculating rates of minor or total birth defects. Secondary endpoints were the rates of live births, miscarriages, pregnancy terminations, preterm deliveries (<37 weeks of gestation), and gestational age and birthweight at delivery. In case of multiple pregnancies, each liveborn infant was included individually in the analysis. Gestational age was defined as number of weeks since last menstrual period.

Statistical analysis

The birth defect rates were calculated taking into account anomalies in live births, in elective terminations of pregnancies (ETOPs) and in miscarriages. Conversely, crude miscarriage rates among exposed pregnancies or controls were calculated after exclusion of ETOPs. Furthermore, miscarriage rates were analysed using an event-history-based approach (cumulative incidence function), to take into account the facts that women did not enter the cohort at time of conception—thus inducing left-truncation—and that miscarriage, ETOP and live birth represent competing risks.[15] Cox proportional cause-specific hazards models were also performed to assess the association of the exposure with miscarriage, ETOPs and live birth.

Adjustment for possible confounders was made with a propensity score.[16] Using boosted regression trees and including as covariates TIS centre, maternal age, alcohol consumption (no/yes), smoking habits (no/yes), number of previous ETOPs and miscarriages, and gestational age at entry time into the cohort.[17] The association of statin exposure with miscarriage, induced abortion and live birth was then assessed using Cox proportional cause-specific hazards models, weighted by the inverse of the propensity score.[18] As some imbalance in the distribution of maternal age was still observed after weighting by the propensity score, age was also included in the Cox models (except for ETOPs, where the low number of events allowed no other covariate addition). The Cox models were further stratified according to TIS centre, i.e. allowing the baseline hazards to vary across centres.

Multiple imputation was used to deal with missing values. Following White et al.,[19] the cumulative cause-specific hazards and event indicators, along with the covariates, were included in the imputation model. For each imputed data set, we estimated the propensity score and fitted the weighted Cox models. Results were combined using Rubin's rule.[20]

Categorical data were compared by chi-square test or Fisher's exact test. Continuous data did not follow normal distribution and were compared using Mann–Whitney test. Statistical analyses were performed with SPSS STATISTICS 18 (SPSS Inc., Chicago, IL, USA) and R version 2.13.2.

Results

Observations from a total of 249 women exposed to statins during the first trimester of pregnancy were collected and compared with a matched control group of 249 women exposed to agents known to be nonteratogenic.

Maternal characteristics

The comparison of maternal characteristics and obstetric history between the statin-exposed group and the control group is shown in Table 1. The median maternal age was 1 year older in the exposed group (33 versus 32 years). A higher proportion of women in the statin-exposed group reported tobacco use (17.6% versus 8.7%). The median gestational age at initial contact was 1 week earlier in the statin-exposed group (8 versus 9 weeks). There were no significant differences between the groups with respect to alcohol consumption, history of miscarriages and ETOPs. However, for all of these parameters data collection appeared less complete in the control group.

Underlying medical conditions were reported in 78% of the women in the statin-exposed group. These included: hypercholesterolaemia ($n = 168$), diabetes ($n = 13$), myocardial infarction/ischaemic heart disease ($n = 10$), hypertension ($n = 9$), psychiatric disorder ($n = 8$), cerebrovascular accident ($n = 7$), overweight/obesity ($n = 7$), chronic kidney disease ($n = 5$), pulmonary embolism ($n = 4$), thyroid dysfunction ($n = 4$), asthma ($n = 3$), epilepsy ($n = 3$), chronic liver disease ($n = 2$), arrhythmia ($n = 1$), mitral insufficiency ($n = 1$), pancreatitis ($n = 1$), cervical dysplasia ($n = 1$) and sickle cell anaemia ($n = 1$). Nine per cent of these women had more than one medical condition. Conditions reported in women from the control group included: infection ($n = 22$), pain ($n = 18$), gastric/duodenal disease including constipation, reflux disease and nausea ($n = 18$), asthma ($n = 13$), allergy ($n = 10$), hypertension ($n = 5$), skin diseases ($n = 5$), pharyngitis ($n = 5$) and other ($n = 10$).

Table 1. Maternal characteristics and obstetric history

Characteristics	Statins (n = 249)	Controls (n = 249)	P value
Maternal age, years; median (IQR) (n = 242; 240)	33 (29–37)	32 (28–36)	0.032
Tobacco use, n (%) (n = 193; 173)	34 (17.6)	15 (8.7)	0.014
Alcohol consumption, n (%) (n = 148; 161)	10 (6.8)	11 (6.8)	0.98
GA at initial contact, weeks; median (IQR) (n = 246; 195)	8 (6–10)	9 (6–13)	0.002
Gravida, n (%) (n = 226; 198)			
1	77 (34.1)	64 (32.3)	0.17
2	53 (23.5)	62 (31.3)	
≥3	96 (42.5)	72 (36.4)	
Para, n (%) (n = 223; 198)			
0	90 (40.4)	78 (39.4)	0.018
1	52 (23.3)	70 (35.4)	
2	53 (23.8)	29 (14.6)	
≥3	28 (12.6)	21 (10.6)	
Previous miscarriages, n (%) (n = 211; 183)			
0	187 (88.6)	166 (90.7)	0.50
1	18 (8.5)	14 (7.7)	
>1	6 (2.8)	3 (1.6)	
Previous ETOP, n (%) (n = 211; 186)			
0	201 (95.3)	176 (94.6)	0.77
≥1	10 (4.7)	10 (5.4)	

IQR, interquartile range; GA, gestational age; ETOP, elective termination of pregnancy.

Statin exposure

Simvastatin (n = 124) was the most commonly used agent, followed by atorvastatin (n = 67), pravastatin (n = 32), rosuvastatin (n = 18), fluvastatin (n = 7), and cerivastatin (n = 1). Therapy was started before conception in 89% of exposed women. Approximately half of the women (48%) continued statin treatment beyond week 5 of gestation and 21% beyond week 7. Eighty-six per cent of the women took statin treatment only during the first trimester and 6% continued into the second trimester (Table 2). The median duration of statin treatment during pregnancy was 6 weeks (interquartile range [IQR] 4–7 weeks).

Pregnancy outcome

The rate of major birth defects did not differ largely between the statin-exposed group and the control group, and the difference was not statistically significant (4.1% versus 2.7% odds ratio 1.5; 95% confidence interval [95% CI] 0.5–4.5, P = 0.43, Table 3). In the statin-exposed group, one pregnancy was electively terminated because of a chromosomal anomaly (trisomy 21). One pregnancy ended in a fetal death at week 27, with the fetus having severe cardiomegaly. Another pregnancy ended in fetal death at an unknown gestational age, with the fetus showing urethral obstruction. In the absence of information concerning ultrasound diagnosis and treatment modality, an infant presenting with hip luxation was classified as having a minor birth defect. Concurrent medication and details of observed major and minor birth defects in the statin-exposed and the control groups are shown in Tables 4 and 5.

A total of 22 (8.8%) elective pregnancy terminations were observed in the statin-exposed group and 11 (4.4%) in the control group. The ETOP rate, as estimated by the cumulative incidence function, was therefore higher in the statin-exposed group (9.3%, 95% CI 5.3–16.2) than in the control group (4.8%, 95% CI 1.7–13.5). However, in the adjusted Cox model, statin exposure was not associated with a statistically significant risk for elective pregnancy termination (hazard ratio [HR] 1.96, 95% CI 0.60–6.44, P = 0.266; Table 6). The crude live birth rates were lower in the statin-exposed group (77.9%) than in the control group (88.4%), with live birth rates estimated by cumulative incidence function as 69.9% (95% CI 61.7–77.8) for the exposed and 85.2% (95% CI 76.9–91.8) for the controls. In the adjusted Cox model, neither statin exposure nor maternal age was associated with a statistically significant risk for earlier delivery times.

Higher crude miscarriage rates were observed in the statin-exposed group (14.5%) than in the controls (7.6%). The miscarriage rate estimated by the cumulative incidence function was higher in the statin-exposed group (20.7%, 95% CI 14.4–29.4) than in the control group (9.9%, 95% CI 5.4–18.1; Figure 1). However, the difference was not significant according to the adjusted Cox model (HR 1.36, 95% CI 0.63–2.93, P = 0.432). Older maternal age was associated with a significantly higher risk for miscarriage (HR = 1.14, 95% CI 1.08–1.21, $P < 10^{-3}$). Table 6 presents the results of the weighted Cox models for miscarriage, ETOP and live birth.

Prematurity was more frequent in statin-exposed pregnancies (16.1% versus 8.5%; OR 2.1, 95% CI 1.1–3.8, P = 0.019). Nonetheless, median gestational age at birth (39 weeks, IQR 37–40 versus 39 weeks, IQR 38–40, P = 0.27) and birthweight (3280 g, IQR 2835–3590 versus 3250 g, IQR 2880–3630, P = 0.95) did not differ significantly between exposed and non-exposed pregnancies. Of 31 preterm deliveries in the statin-exposed group, 16 (52%) were late preterm deliveries that occurred in the 36th week of gestation. Premature delivery was associated with pregnancy complications in eight (26%) women in the exposed group. These included: pre-eclampsia (n = 2), placenta praevia

Table 2. Maternal exposure to statins

Medication	*n** (%)	Discontinuation of medication (weeks of gestation)			Daily dose (mg)		
		Median	IQR	Range	Median	IQR	Range
Simvastatin	124 (50)	6	5–7	3–30	20	10–20	5–80
Atorvastatin	67 (27)	6	5–8	0–16	20	10–20	10–80
Pravastatin	32 (13)	5	4–6	1–40	20	20–20	10–40
Rosuvastatin	18 (7)	6	5–7	4–27	10	10–15	40–80
Fluvastatin	7 (3)	5	4–5	2–6	40	40–40	5–20
Cerivastatin	1 (<1)	6	–	–	–	–	–

IQR, interquartile range (25th to 75th centiles).
*Total *n* = 249.

Table 3. Pregnancy outcome

	Statins	Controls	Crude OR (CI)	*P* value
Live-born infants (*n*)	194	224		
Multiple gestations (*n*)	–	Four sets of twins		
Pregnancies resulting in live-born infants (%)	194/249 (77.9)	220/249 (88.4)		0.002
ETOP (%)	22/249 (8.8)	11/249 (4.4)		0.048
Miscarriage or fetal death (ETOPs excluded) (%)	33/227 (14.5)	18/238 (7.6)	2.1 (1.1–3.8)	0.016
Major birth defects* (%)	8/197 (4.1)	6/224 (2.7)	1.5 (0.5 –4.5)	0.43
Major birth defects not chromosomal or genetic (%)	7/197 (3.6)	6/224 (2.7)	1.3 (0.4 –4.0)	0.60
Preterm delivery (%)	31/193 (16.1)	18/213 (8.5)	2.1 (1.1–3.8)	0.019
Gestational age at birth in weeks; median (IQR) (*n* = 193; 213)	39 (37–40)	39 (38–40)		0.27
Birthweight (g); median (IQR) (*n* = 185; 205)	3280 (2835–3590)	3250 (2880–3630)		0.95

OR, odds ratio; CI, confidence interval; ETOP, elective termination of pregnancy; IQR, interquartile range.
*Including live births and anomalies in elective terminations of pregnancies and miscarriages: one ETOP plus two miscarriages or fetal deaths in the statin group, none in the control group.

(*n* = 2), pre-existing diabetes (*n* = 2), gestational diabetes (*n* = 1), and pyelonephritis and polyhydramnios (*n* = 1). The most serious complications in preterm infants in the exposed group were: neonatal death (at 22 weeks of gestation) and psychomotor retardation (premature birth at 29 weeks of gestation, convulsions). In the control group, preterm delivery was associated with pregnancy complications in 3 (17%) women. Two suffered from pre-eclampsia and one from placenta praevia. In the control group, the most serious complications in preterm infants included: respiratory distress syndrome requiring transfer to an intensive-care unit (premature birth at 30 weeks; normal outcome) and necrotising enterocolitis treated by ileostomy (premature birth at unknown gestational age).

In full-term infants born to the statin-exposed mothers, neonatal health problems included respiratory distress (*n* = 9), jaundice (*n* = 5), newborn presenting small stature and weight for gestational age (*n* = 3), meconium-stained amniotic fluid (*n* = 2), transient tachypnoea (*n* = 1), cyanosis (*n* = 1), gastrointestinal stasis and rectorrhagia (*n* = 1), and neonatal hypoglycaemia (*n* = 1). One full-term neonate suffering from respiratory distress died on the second day of life. In the full-term infants born to the control group, neonatal morbidity included macrosomia (*n* = 3), jaundice (*n* = 1), respiratory distress (*n* = 1), transient tachypnoea (*n* = 1), and newborn presenting small stature and weight for gestational age (*n* = 1).

Discussion

Our multicentre observational prospective controlled study found no statistically significant difference in the rate of major birth defects between statin-exposed pregnancies and a control group. Both groups had observed birth defect rates within the expected baseline risk in the general population. This negative finding supports several published reports

Table 4. Birth defects in statin-exposed pregnancies, concomitant drug exposure and maternal condition

Major birth defects	Exposure (weeks of gestation)	Concurrent medication and exposure time (weeks of gestation)	Maternal condition
Atorvastatin			
Missing middle phalanx, right ring finger	0–8	Metformin (0–8), Novorapid insulin,* Insulin detemir,* Tobacco	Pre-existing diabetes
Dilated left renal pelvis	0–6	Enalapril*	Essential hypertension
Cutaneous angioma	0–5	–	Hypercholesterolaemia
Pravastatin			
Sacrococcygeal teratoma, hip joint deformity	0–5	Alprazolam (0–6)	Hypercholesterolaemia, pyelonephritis (32)
Urethral obstruction, fetal death	0–7	Enalapril (0–7), Amlodipine (0–7), Methyldopa (8–?)	Essential hypertension
Rosuvastatin			
Trisomy 21, ETOP	0–5	Metformine (0–6), Allopurinol (0–6)	Pre-existing diabetes, hyperuricaemia
Fetal cardiomegaly, severe fetal arrhythmia, fetal death at 27 weeks of gestation	0–27	Valsartan (0–27)	Sickle cell anaemia, renal insufficiency
Haemangioma on neck and left temple	0–?	Ezetimib (0–?)	Hypercholesterolaemia
Minor birth defects and development disorders			
Pravastatin			
Inguinal hernia	0–4	Metoprolol (0–4), low-dose aspirin (0–39)	Angina pectoris
Choroid plexus cyst	0–1	–	Hypercholesterolaemia
Simvastatin			
Hip luxation**	0–6	–	Hypercholesterolaemia
Inguinal hernia	0–5	Paroxetine (0–7), Fluoxetine (7–9), Varenicicline (0–9), Meclozine,* Pyridoxine, * Amoxicillin, * Erythromycin,* Salbutamol, * Ipratropium, * two chest X-rays*	Depressive episode, overweight (BMI 29)
Sacral pit	0–26	Enalapril (0–26), Labetalol,* Nifedipine,* Ferrous sulphate*	Essential hypertension
Choroid plexus cyst	0–16	–	Hypercholesterolaemia
Umbilical hernia, surgery at age of 3 years	0–6	–	Hypercholesterolaemia
Congenital hydrocele	0–18	–	Hypercholesterolaemia

*Time of exposure unknown.
**No information concerning ultrasound diagnosis or treatment.

indicating no increased risk for major birth defects following maternal exposure to statins during pregnancy.[2–6] However, these results must still be interpreted with caution, considering the limited statistical power of the study, which would only have allowed ruling out with reasonable certainty a 4.5-fold increase in major birth defects following statin treatment. In contrast to the study based on data from spontaneous reporting to the US Food and Drug Administration,[10] we did not observe a particular pattern of fetal birth defects in the statin-exposed group, and none of the infants had central nervous system anomalies. However, data on long-term follow up and information on developmental milestones, that may contribute to detecting central nervous system anomalies, were not available. In our cohort, one child had a limb defect. The 34-year-old mother took atorvastatin up to gestational week 8. She presented with diabetes treated by metformin up to the week 8 of gestation, then received insulin treatment until delivery. She also reported tobacco use. In week 38, a male infant weighing 3628 g was delivered by caesarean section, reported to be healthy other than a missing middle phalanx on the right ring finger. The family history for previous birth defects was

Table 5. Birth defects in control pregnancies, drug exposure and maternal condition

	Medication	Exposure (weeks of gestation)	Maternal condition
Major birth defects			
Hypospadias	Fluconazole	3	Candidiasis
Bilateral hexadactyly, coloboma affecting optic nerves and macula	Amoxicillin, Paracetamol	21–22	Infection (not specified)
Hip luxation (requiring Pavlik harness for at least 1 year)	Diclofenac	25–26	Wrist pain
High jejunal atresia (had tapering duodenoplasty)	Ranitidine	?	Dyspepsia
Absent left middle finger	Omeprazole	?	Gastro-oesophageal reflux disease
Right ventricular hypotrophy	–	–	None
Minor birth defects, development disorders and other anomalies			
Skin stained red-rose with a border in the median line	Salbutamol	0–40	Asthma
Tongue attached	Metamizole	?	Unknown
Haemangioma	–	–	None

Table 6. Miscarriage, elective termination of pregnancy and live birth: results of the weighted Cox models

	HR	SE	95% CI	*P* value
Miscarriage				
Statin	1.360	0.391	0.632–2.927	0.432
Age	1.144	0.029	1.081–1.211	<0.001
Elective termination of pregnancy				
Statin	1.962	0.606	0.598–6.437	0.266
Live birth				
Statin	0.951	0.109	0.769–1.177	0.646
Age	1.006	0.011	0.984–1.028	0.587

HR, hazard ratio; SE, standard error; CI, confidence interval.

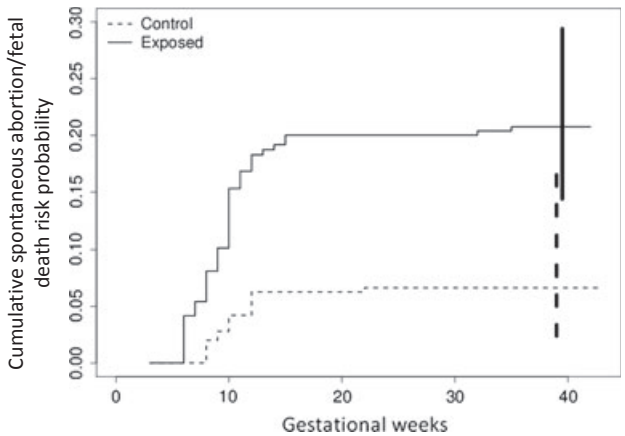

Figure 1. Cumulative incidences of miscarriage/fetal death in pregnancies exposed to statins (n = 235, solid line) versus controls (n = 187, dashed line) over gestational weeks.

unknown. The fetus presenting with cardiomegaly and severe arrhythmia resulting in fetal death at 27 weeks of gestation was exposed to rosuvastatin throughout the entire pregnancy. The 40-year-old mother was reported to have sickle cell anaemia and chronic kidney disease. She was also treated with valsartan until 27 weeks of gestation, which has been associated with an increased risk for adverse fetal outcome.

We analysed the various statins as one homogeneous group. However, heterogeneity based on pharmacodynamic and pharmacokinetic differences among the statins cannot be ruled out. In our study, major birth defects were observed in infants exposed to pravastatin and rosuvastatin, both hydrophilic statins that might be transferred transplacentally to a lesser extent than other statins. Conversely, no major birth defect was observed in infants exposed to simvastatin, a hydrophobic compound, even though 50% of the women had received this statin during pregnancy. These small numbers do not allow any firm conclusions to be drawn but they do not appear to support a higher risk of lipophilic statins (as hypothesised in the literature).[10] Furthermore, our cohort did not include any exposure to lovastatin, and only a few women were exposed to cerivastatin and fluvastatin. As one of the hypothesised teratogenic mechanisms for statins may involve an ongoing alteration of cellular metabolism and regulation, exposure limited to the early first trimester, such as observed in the majority of the women in our study, may not cover the most sensitive period for induction of teratogenic effects.

There was a higher rate of ETOPs in the statin-exposed group. However, in the adjusted Cox model, statin exposure was not associated with a statistically significant risk for

elective pregnancy termination. ETOPs may in part have been undergone as a result of the concerns of pregnant women or their physicians regarding the medication's effect on pregnancy outcome. Since approximately three-quarters of the women had another medical condition in addition to presumed hypercholesterolaemia, including diabetes and myocardial infarction/ischaemic heart disease, the underlying maternal condition may also have played a role in the decision to voluntarily terminate pregnancy. As current recommendations advise women to stop statin treatment before conception, pregnancies in the statin-exposed group could more likely have been unplanned, leading to a poorer acceptance.

The crude miscarriage rate was significantly higher in the statin-exposed group in comparison to the control group, although the higher incidence among exposed pregnancies (14.5%) was still within the normal background range, and the difference between the two groups was not significant in the adjusted Cox model. Statin-exposed women, or their healthcare providers, contacted the TIS earlier than those in the control group. Miscarriage is well known to be the most common complication of early pregnancy,[21] its occurrence decreasing with increasing gestational age. It is therefore estimated that 8–20% of clinically recognised pregnancies under 20 weeks of gestation will undergo miscarriage and 80% of those occur in the first 12 weeks of gestation.[22,23] Statin-exposed women were slightly older than women in the control group. More advanced maternal age is the most important risk factor for miscarriage in healthy women, and in the adjusted Cox model older age was associated with a significantly higher risk for miscarriage. A study evaluating the effect of maternal age on pregnancy outcome that reviewed over 1 million pregnancies found the following approximate frequencies of clinically recognised miscarriage according to maternal age: age 20–30 years (9–17%), age 35 (20%), age 40 (40%) and age 45 (80%).[24] Therefore, both the 1-week earlier gestational age at TIS contact and the 1-year maternal age difference between our exposed and control women may explain a significant part of the higher miscarriage rate observed in the statin-exposed group. Furthermore, some women in the statin group had comorbidities (diabetes, overweight) that may have increased their risk of adverse pregnancy outcome, including miscarriage. Pregnancy body mass index above 25 kg/m^2 and poor glycaemic control in diabetic women during the period of fetal organogenesis have also been associated with an increased risk of miscarriage.[25,26]

The rate of preterm deliveries was increased by two-fold in the statin-exposed group compared with the control group. However, half of these occurred during the 36th week of gestation, and median gestational age at birth and birthweight were comparable between both groups. An increased risk for preterm delivery and lower birthweight after statin exposure has previously been reported.[2,27] However, a higher percentage of women in the exposed group had pregnancy complications such as pre-eclampsia or placenta praevia, so contributing to an increased risk of premature delivery. Underlying maternal condition may therefore have played a confounding role here. Furthermore, a higher proportion of women in the statin-exposed group reported tobacco use, and smoking is known to represent another definite risk factor for preterm delivery.[27]

The general strengths and limitations of collaborative ENTIS studies have been discussed previously.[14] The prospective documentation of exposure data results in good reliability with respect to exposure time, thereby minimising recall bias. The limitations of this study include in particular the relatively small sample size. The nonsignificant difference between birth defect rates in both groups and the absence of a distinctive pattern of birth defects in the statin-exposed group are clearly reassuring; however, small effects may not have been detected by our study. Statins were analysed as a homogeneous group, to explore a potential class effect. When taken individually, only a very limited number of women were exposed to specific statins such as cerivastatin and fluvastatin, and differences in teratogenic properties between each substance cannot be excluded. It is important that research is continued to increase sample sizes and allow examination of more infrequent outcomes. Another limitation is that some factors considered potential confounders were not fully documented, such as maternal disease and treatment indication. Maternal comorbidities were probably under-reported, as metabolic syndrome often combines hyperlipidaemia with overweight or obesity, and these comorbidities were seldom reported. A disease-matched comparison group would have allowed a more detailed account of the differences in maternal characteristics and comorbidities between the groups. Further limitations include reliance on self-reported drug exposure and maternal interview as a source for outcome data variation in timing of follow up, and combination of data from multiple teratogen information services. Selection of women contacting a TIS or being lost to follow up may be suspected, but the same procedure was applied to exposed and control pregnancies, so limiting risk of potential bias.

Conclusion

This study did not detect a significant teratogenic effect of statins after exposure during the first trimester of pregnancy. However, its statistical power was not sufficient to challenge the current recommendation to discontinue treatment during pregnancy. At most, the results provide a base for reassurance in case of inadvertent exposure. Further research is still required to better assess the safety of statins during pregnancy.

Disclosure of interests
None.

Contribution to authorship
UW contributed to data collection, data analysis, manuscript writing and submission; AA contributed to data analysis; AP contributed to conception of the study, data collection and manuscript writing; LER contributed to data collection and manuscript writing; PM contributed to birth defect classification; BC, TV, SS, MC, MDS, AP, MB, JE and EM contributed to data collection, and TB contributed to data analysis, manuscript writing and project supervision.

Details of ethics approval
This observational cohort study did not require ethics committee approval.

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