



Statins and congenital malformations: cohort study

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Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bmj.h1035>)

Cite this as: *BMJ* 2015;350:h1035
doi: 10.1136/bmj.h1035

Accepted: 15 January 2015

ABSTRACT

OBJECTIVE

To examine the teratogenic potential of statins.

DESIGN

Cohort study.

SETTING

United States.

PARTICIPANTS

A cohort of 886 996 completed pregnancies linked to liveborn infants of women enrolled in Medicaid from 2000 to 2007.

METHODS

We examined the risk of major congenital malformations and organ specific malformations in offspring associated with maternal use of a statin in the first trimester. Propensity score based methods were used to control for potential confounders, including maternal demographic characteristics, obstetric and medical conditions, and use of other drugs.

RESULTS

1152 (0.13%) women used a statin during the first trimester. In unadjusted analyses, the prevalence of malformations in the offspring of these women was 6.34% compared with 3.55% in those of women who did not use a statin in the first trimester (relative risk 1.79, 95% confidence interval 1.43 to 2.23). Controlling for confounders, particularly pre-existing diabetes, accounted for this increase in risk (1.07, 0.85 to 1.37). There were also no statistically significant increases in any of the organ specific malformations assessed after accounting for confounders. Results were similar across a range of sensitivity analyses.

CONCLUSIONS

Our analysis did not find a significant teratogenic effect from maternal use of statins in the first trimester. However, these findings need to be replicated in other large studies, and the long term effects of in utero

exposure to statins needs to be assessed, before use of statins in pregnancy can be considered safe.

Introduction

Statins are the most commonly used class of drug to treat hyperlipidemia. Since they were first brought to market, statins have been considered contraindicated in pregnancy based on animal data showing teratogenic potential at high doses and concern that they might disrupt cholesterol biosynthesis in the developing fetus.¹⁻³ Because of this, use during pregnancy is rare,⁴ and data about the effects of in utero exposure on fetal development are scarce in humans.¹⁻⁵ Those data that do exist derive primarily from registries, small cohort studies, and case reports.¹⁻⁵⁻¹² These studies have been inconsistent in their findings on the teratogenic potential of statins. For example, a review of spontaneous reports of exposure to statins during the first trimester to the US Food and Drug Administration suggested that lipophilic statins may increase the risk of central nervous system and limb anomalies,⁵⁻⁷ whereas a case series analysis from the National Birth Defects Prevention Study failed to observe the same distribution of defects.¹⁰ A meta-analysis of the small number of controlled studies (n=6, including a total of 618 women who used statins) failed to find an increase in the risk of birth defects, although the confidence interval was wide (pooled estimate of relative risk 1.15, 95% confidence interval 0.75 to 1.76).³

As the prevalence of risk factors for cardiovascular disease, including hypercholesterolemia, diabetes, hypertension, and obesity in women of reproductive age increases¹³ and as the indications for statin treatment expand,¹⁴ it is important to understand whether it is safe to use these drugs in patients who may inadvertently become pregnant; about half of all pregnancies in the United States are unintended.¹⁵ This need is also pressing since preclinical studies suggest a possible role for statins in the prevention of pre-eclampsia as a result of their pleiotropic effects on endothelial function and inflammation; human studies (using pravastatin) have begun examining this potential indication.¹⁶

We undertook an epidemiologic study to assess the association between statin use in the first trimester and the risk of congenital malformations, using data derived from a large cohort of Medicaid beneficiaries.

Methods

Cohort

The cohort was drawn from the Medicaid Analytic eXtract, which contains information on Medicaid beneficiaries. Medicaid is the joint state and federal health insurance program for people who are on a low income;

WHAT IS ALREADY KNOWN ON THIS TOPIC

Statins are the most commonly used class of medication used to treat hyperlipidemia

Statins are considered contraindicated for use in pregnancy

Data on the effects of in utero exposure to statins are few

WHAT THIS STUDY ADDS

Women taking statins during the first trimester of pregnancy were at an increased risk of delivering an infant with malformations

The association was explained by underlying characteristics of users, mainly pre-existing diabetes

Statins themselves did not seem to have any meaningful teratogenic effect

it covers approximately 40% of all births in the United States.¹⁷ The Medicaid Analytic eXtract is a healthcare utilization database that records demographic and Medicaid enrollment information on beneficiaries, as well as healthcare utilization claims, including all recorded diagnoses and procedures associated with inpatient admissions and outpatient visits. It also contains claims for all filled outpatient drug prescriptions.

Using Medicaid Analytic eXtract data from 46 US states and the District of Columbia from 2000 to 2007, our group created a cohort for the study of drug safety in pregnancy, as previously described in detail.^{18 19} We identified women age 12 to 55 years with completed pregnancies and linked them to liveborn infants. Using a validated algorithm based on delivery date and diagnostic codes in the maternal and infant records, we estimated the last menstrual period before the pregnancy.²⁰ We restricted the cohort to women who were continuously eligible for Medicaid from three months before the estimated last menstrual period month through one month post partum. To ensure complete ascertainment of claims throughout the entirety of pregnancy, we restricted our analysis to women without restricted benefits, private insurance, or certain capitated managed care programs that underreport claims to Medicaid Analytic eXtract. We also required that the linked infants met the same Medicaid eligibility criteria as their mothers for at least three months after birth, unless they died, in which case we allowed a shorter eligibility period. We excluded pregnancies in which the mother used known teratogenic drugs, including lithium, antineoplastic agents, retinoids, and thalidomide during the first trimester²¹ (n = 3528) and pregnancies in which the infant was diagnosed as having a chromosomal abnormality (n = 1175) (see supplementary figure S1).

Statin use

In the primary analysis we defined statin use based on one or more claims for a dispensed statin from the last menstrual period through day 90 of pregnancy (first trimester), the causal relevant window of exposure for congenital malformations. We considered the following statins: simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, and rosuvastatin. The reference group for the primary analysis consisted of women who were not dispensed a statin during the first trimester. Statins are only available as prescription drugs in the United States (that is, they are not available over the counter).

Outcomes

The primary study outcome was the presence of a congenital malformation in the infant. We defined congenital malformations based on the diagnosis of one or more organ specific malformations. Organ specific malformations assessed included central nervous system malformations; eye, ear, neck, and face malformations; cardiac malformations; respiratory malformations; cleft palate or lip malformations; gastrointestinal malformations; genitourinary malformations;

musculoskeletal malformations; or other malformations. These were identified based on the presence of international classification of diseases, ninth revision (ICD-9) diagnostic codes on two or more separate days in the infant inpatient or outpatient records during the first three months of life. We required diagnostic codes on separate days to increase the specificity of the definition, by excluding cases in which a single mention may be recorded to justify a diagnostic test to rule out that condition. Secondary outcomes included each of the nine organ specific categories of malformation.

Covariates

We considered four groups of potential confounders: maternal demographic characteristics, comorbid medical conditions, obstetric characteristics and conditions, and drugs dispensed to the mother. These covariates were selected because they are potential risk factors for malformations, or proxies for them. Demographic characteristics assessed included maternal age at delivery, race/ethnicity, geographic region, and year of delivery. Obstetric characteristics considered included multiparity and multiple gestations. Chronic comorbid medical conditions were defined during the baseline period (before the last menstrual period through to the end of the first trimester) and included pre-existing diabetes, dyslipidemia, pre-existing hypertension, chronic renal disease, obesity, and alcohol, tobacco, or illicit drug use/misuse. We included the number of distinct prescription drugs (other than statins) and physician visits in the three months before the last menstrual period as markers of general comorbidity. We also assessed the use of drugs during the baseline period, which may be markers for the presence or the severity of comorbid illness, including antihypertensives, insulin, and oral antidiabetes drugs, as well as the use of suspected teratogenic drugs during the first trimester (we excluded those pregnancies exposed to known teratogens).²¹

Statistical analyses

We first determined the baseline characteristics of women in the cohort, stratified by statin use during the first trimester of pregnancy, and the frequency of malformations in the infants of women who did or did not use statins. This made it possible to calculate an unadjusted risk ratio and 95% confidence intervals for congenital malformations associated with statin use. Because pre-existing diabetes was expected to be an important confounder, we estimated the association between statin use and the primary outcome stratified on pre-existing diabetes using the Mantel-Haenszel method.²²

To account for all measured differences in baseline characteristics between women who did and did not use statins, we used propensity score based methods. The propensity score was determined using a logistic regression model that estimated the probability of being dispensed a statin in the first trimester based on all potential confounding variables mentioned, without further selection. Based on propensity score, we matched women who did and did not use statins in the

first trimester in a fixed 1:3 ratio, using a nearest neighbor greedy matching algorithm with a maximum matching distance of 0.05; covariate distribution and the risk ratio and 95% confidence interval for malformations were described in the matched cohort. In an alternative approach (which should be interpreted as the primary result), intended to preserve the information content of the large group of women who did not use statins, we conducted propensity score stratified analyses using the Mantel-Haenszel method after the creation of 100 strata of equal propensity score width.²² We additionally used high dimensional propensity scores to adjust for empirical covariates in addition to the investigator specified covariates, as confirmatory analyses; high dimensional propensity scoring has been shown to further improve control of confounding in some circumstances.²³ In this approach, the algorithm for high dimensional propensity scores evaluates thousands of inpatient and outpatient diagnoses and procedures as well as pharmacy claims, and prioritizes 100 covariates that may act as proxies for unmeasured confounders. These are then combined with investigator specified covariates for inclusion in the propensity scores model. The high dimensional propensity scores based analyses were conducted using stratification, as described.

Subgroup and sensitivity analyses

We performed several subgroup and sensitivity analyses to assess the robustness of our primary findings (any congenital malformation), again using stratification by propensity score. Because they more readily cross the placenta, lipophilic statins (simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin) have been postulated to have greater teratogenic potential than hydrophilic statins.²⁻²⁴ We therefore separately assessed the association between use of lipophilic statins during the first trimester and malformations, with exposure defined based on the specific statin prescribed.²⁵ To estimate the potential impact of exposure misclassification, we explored two alternative definitions of first trimester statin use: firstly, days supply of statin overlapping the first trimester, based on dispensings in the 90 days before the last menstrual period through to the end of the first trimester (for example, a woman would be considered to have used a statin if she was dispensed a statin before pregnancy, but with a supply that would be expected to extend into pregnancy); and secondly, two or more statin dispensings during the first trimester. To assess the potential impact of outcome misclassification we defined malformations based on a single diagnostic code in the infant inpatient or outpatient record, extended the follow-up of infants to one year, and defined malformations based on codes in either the mother or the infant claims, since in some circumstances in Medicaid Analytic eXtract, infants' conditions are applied to the mother's claims history for the first several months after birth. We also performed a probabilistic assessment to explore the effect of potential outcome misclassification across a range of potential sensitivities and specificities for the malformations, and an assessment of the potential impact of analysis

based only on live births (see supplementary appendix 1 and 2).^{19 26 27} Because some women had more than one pregnancy included in the cohort, we also repeated the analysis restricting it to the first pregnancy recorded. We also considered the possible effect of the complex relation between preterm delivery and malformations, since infants with malformations are more likely to be born preterm and infants born preterm will sometimes have conditions that might be coded as malformations that would have spontaneously resolved had the infant been carried to term. We therefore performed a secondary analysis restricting the cohort to term deliveries.

Results

Our primary cohort consisted of 886 996 pregnancies. Of these, 1152 (0.13%) women filled a prescription for statin drugs during the first trimester. The most commonly used statins were atorvastatin (n=538), simvastatin (n=319), and lovastatin (n=132) (see supplementary table S1).

There were important baseline differences between women who did and did not use statins (table 1). Statin users tended to be older, were less often African-American, and had a higher prevalence of all of the comorbid conditions considered. Pre-existing diabetes was common in women who filled prescriptions for statins (45.1%). These women were also more likely to use anti-hypertensives, insulin, and oral antidiabetes drugs, and had greater healthcare utilization, including physician visits and non-statin prescription drugs. After matching on the propensity score, 96.3% of the exposed pregnancies were retained in the analysis and covariates were balanced, with a standardized difference of less than 0.15 in the frequency of all covariates.

Overall, congenital malformations were present in 73 (6.34%) of the pregnancies in which statins were used and 31 416 (3.55%) in which they were not; the unadjusted relative risk for malformations was 1.79 (95% confidence interval 1.43 to 2.23, table 2). After stratification on pre-existing diabetes, this increase in risk associated with statin use was substantially attenuated (1.34, 1.07 to 1.68). With further adjustment for all potential confounders, this apparent increase in risk associated with statins was no longer present for propensity score matched analyses (1.04, 0.79 to 1.37) and for propensity score stratified analyses (1.07, 0.85 to 1.37).

In the unadjusted analyses of organ specific malformations, both central nervous system and cardiac malformations were significantly more common in the statin exposed pregnancies (3.04 (1.27 to 7.30) and 3.05 (2.30 to 4.03), respectively), but after adjustment for confounders through propensity score stratification these apparent associations were no longer present (figure 1). None of the other organ specific malformations was significantly associated with statin use, though confidence intervals were wide. There were no cases of limb reduction anomalies or holoprosencephaly in the infants of women who used statins in the first trimester; malformations previously hypothesized to be associated with exposure to statins.^{5 7}

Table 1 | Baseline characteristics of cohort stratified by statin use. Medicaid Analytic eXtract, 2000–07

Characteristics	No (%) in full cohort		No (%) in propensity score matched cohort	
	Statins (n=1152)	No statins (n=885 844)	Statins (n=1109)	No statins (n=3327)
Age group (years):				
≤19	64 (5.6)	260 664 (29.4)	64 (5.8)	164 (4.9)
20–24	162 (14.1)	315 354 (35.6)	162 (14.6)	482 (14.5)
25–29	243 (21.1)	180 794 (20.4)	243 (21.9)	767 (23.1)
30–34	324 (28.1)	84 014 (9.5)	316 (28.5)	940 (28.3)
35–39	256 (22.2)	36 964 (4.2)	234 (21.1)	700 (21)
≥40	103 (8.9)	8054 (0.9)	90 (8.1)	274 (8.2)
Race/ethnicity:				
White, non-Hispanic	484 (42)	360 241 (40.7)	469 (42.3)	1376 (41.4)
Black, non-Hispanic	296 (25.7)	301 951 (34.1)	293 (26.4)	805 (24.2)
Hispanic	197 (17.1)	133 614 (15.1)	185 (16.7)	659 (19.8)
Asian	75 (6.5)	30 259 (3.4)	68 (6.1)	222 (6.7)
Other	66 (5.7)	41 952 (4.7)	61 (5.5)	176 (5.3)
Unknown	34 (3.0)	17 827 (2.0)	33 (3.0)	89 (2.7)
Patient characteristics:				
Pre-existing diabetes	520 (45.1)	27 090 (3.1)	477 (43)	1313 (39.5)
Dyslipidemia	773 (67.1)	27 809 (3.1)	730 (65.8)	2340 (70.3)
Pre-existing hypertension	468 (40.6)	44 248 (5)	436 (39.3)	1268 (38.1)
Chronic renal disease	48 (4.2)	4110 (0.5)	44 (4)	102 (3.1)
Obesity	269 (23.4)	47 003 (5.3)	262 (23.6)	766 (23)
Multiple births	76 (6.6)	31450 (3.6)	76 (6.9)	238 (7.2)
Multiparous	1023 (88.8)	670 477 (75.7)	984 (88.7)	2970 (89.3)
Alcohol misuse	46 (4.0)	23 153 (2.6)	44 (4)	147 (4.4)
Tobacco use	127 (11.0)	68 824 (7.8)	125 (11.3)	368 (11.1)
Illicit drug use	74 (6.4)	47 230 (5.3)	72 (6.5)	244 (7.3)
Drugs:				
Antihypertensives	619 (53.7)	58 882 (6.7)	576 (51.9)	1684 (50.6)
Insulin	351 (30.5)	11 015 (1.2)	314 (28.3)	808 (24.3)
Oral antidiabetes drugs	447 (38.8)	11 251 (1.3)	404 (36.4)	1017 (30.6)

Also included in propensity score model were delivery year, region, exposure to potentially teratogenic drugs during first trimester (including angiotensin converting enzyme inhibitors, fluconazole, aminoglycosides, folic acid antagonists, methimazole, potassium iodide, tetracycline, danazol, misoprostol, coumadin, and propylthiouracil), number of physician visits for any reason from 90 days before to last menstrual period, and number of distinct non-statin prescriptions drugs from 90 days before to last menstrual period.

Table 2 | Risk for major congenital malformations in infants of women who did or did not use statins during first trimester. Medicaid Analytic eXtract 2000–07

Statin use	Full cohort			Relative risk (95% CI)		
	Total No	No of congenital malformations	Risk (%)	Unadjusted	Stratified on diabetes	Propensity score stratified
No statins	885 844	31 416	3.55	Referent	Referent	Referent
Statins	1152	73	6.34	1.79 (1.43 to 2.23)	1.34 (1.07 to 1.68)	1.07 (0.85 to 1.37)

Estimates across the subgroup and sensitivity analyses were generally similar to those of the primary analysis. The largest increase in the observed risk estimate occurred in women in whom statin use was defined based on two dispensings in the first trimester (1.44, 0.99 to 2.09, table 3). However, after stratification based on high dimensional propensity scores, the relative risk estimate associated with two dispensings was further attenuated (1.20, 0.81 to 1.80) (see supplementary table S2). In the analysis that required a full year of eligibility and follow-up of the infants, the risk estimate for the association between statin use and congenital malformations was significant (1.24, 1.01 to 1.53); this risk estimate also attenuated with stratification on the high dimensional propensity scores and was no longer significant (1.10, 0.89 to 1.36). Stratification by high dimensional propensity scores across the other analyses resulted in estimates that were qualitatively similar to

those of the main analysis. Correcting for potential outcome misclassification resulted in an increase in the point estimate of 9.8% (see supplementary table S3).

Discussion

In this cohort of 886 996 pregnancies among Medicaid beneficiaries, we found no significant association between maternal use of statins in the first trimester and risk for congenital malformations either overall or for any of the organ specific malformations examined after accounting for confounding variables. The upper bound of the confidence interval from our primary analysis implies our findings would be consistent with no more than a 37% increase in the overall risk of congenital malformations. Our findings therefore suggest that statins are not likely to be major teratogens.

These results have several important implications. Firstly, there are increasing numbers of women of

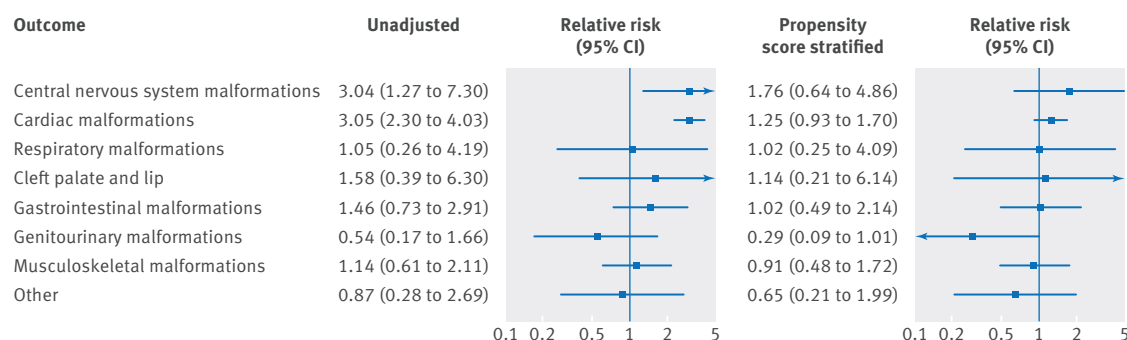


Fig 1 | Relative risks (95% confidence intervals) comparing risk for organ specific malformations in infants of women who did or did not use statins during the first trimester. Medicaid Analytic eXtract 2000–07. *Risk estimate for eye, ear, neck, and face malformations not shown as there were no occurrences in infants exposed to statins (see supplementary table S5 for number and risk of each malformation type)

reproductive age with potential indications for statins for the primary and secondary prevention of cardiovascular disease. Some have argued for avoiding these drugs in young women who are not using effective contraception, because of concerns about the possibility of inadvertent use during pregnancy.^{14–28} Our findings suggest such concerns may not be warranted. Secondly, based on the potential for statins to interfere with some of the pathologic mechanisms underlying pre-eclampsia, there is growing interest in their potential use in preventing this pregnancy complication.¹⁶ If effective for this indication, statins may become more frequently used in pregnancy, and our findings bolster confidence that these drugs can be used in this clinical context without undue concern about teratogenesis. Finally, our results, combined with the results of earlier observational studies, suggest the need for a critical reappraisal of the US Food and Drug Administration and other regulator's classification of these drugs as absolutely contraindicated in pregnancy.

Strengths and limitations of this study

Our study has several important strengths. Firstly, Medicaid Analytic eXtract is one of the largest and most comprehensive databases of its kind. With 886 996 completed pregnancies included in the study cohort and

1152 women using statins during the first trimester, our study allows for more precise estimates of the risk of malformations associated with statin use than previous studies examining this association. Furthermore, the database contains detailed information on patient characteristics, including maternal demographic characteristics, medical and obstetrical conditions, and healthcare utilization, as well as information on drug use, which can serve as a marker for the presence of comorbid conditions and their severity. The capture of these covariates allows detailed assessment and adjustment of conditions that might confound the association between statin users and non-users. Additionally, information on statin use in the database derives from claims collected in a prospective manner for filled prescriptions, so that our findings are not susceptible to recall bias, a problem that has afflicted studies of drug induced teratogenesis in the past.

Our study is also subject to certain limitations inherent in its design. Because Medicaid Analytic eXtract is based on healthcare utilization data, we relied on physician coding to define the presence of a malformation. However, our group has previously validated certain specific malformations in Medicaid Analytic eXtract by chart review and found that when two or more codes are recorded in the claims, the diagnosis has a high positive predictive value.²⁹ Though requiring two

Table 3 | Sensitivity and subgroup analyses comparing risk for major congenital malformations in infants of women who did or did not use statins during first trimester. Medicaid Analytic eXtract 2000–07

Analyses	No of outcomes/No of patients		Relative risk (95% CI)	
	Statins	No statins	Unadjusted	Propensity score stratified
Exposure definition:				
Lipophilic statins	66/1033	31 416/885 844	1.80 (1.43 to 2.28)	1.07 (0.83 to 1.37)
Exposure based on days supply overlapping first trimester	97/1599	31 392/885 397	1.71 (1.41 to 2.08)	1.03 (0.84 to 1.27)
Exposure based on two dispensings in first trimester	28/335	31 461/886 661	2.36 (1.65 to 3.36)	1.44 (0.99 to 2.09)
Outcome definition:				
Malformation based on single diagnosis code in infant record	155/1152	77 253/885 844	1.54 (1.33 to 1.79)	1.10 (0.94 to 1.29)
Require full year of infant eligibility (ascertain outcomes for one year)	92/862	37 424/687 920	1.96 (1.62 to 2.38)	1.24 (1.01 to 1.53)
Definition of malformation based on codes in infant or maternal record	90/1152	36 787/885 844	1.88 (1.54 to 2.29)	1.09 (0.88 to 1.35)
Subgroups:				
Examine only first pregnancy for women with more than one pregnancy in cohort	67/1054	27 702/783 034	1.80 (1.42 to 2.27)	1.02 (0.79 to 1.32)
Restrict to term deliveries (exclude preterm deliveries)	41/916	21 964/785 884	1.60 (1.19 to 2.16)	1.19 (0.86 to 1.64)

diagnostic codes may result in high specificity for the outcome at the cost of some sensitivity, when an outcome is defined with high specificity and non-differential sensitivity, results from an observational study will yield unbiased estimates of relative risk.³⁰ The validity of our outcome definition is given additional credence by our ability to reproduce the known associations between pre-existing diabetes and both overall malformations and certain organ specific malformations (see supplementary table S4).³¹ Also, when we performed a probabilistic assessment of outcome misclassification across a range of conservative estimates for sensitivity and specificity of the outcome, the risk estimate for statin use increased only slightly, suggesting our null findings are robust to any realistic degree of outcome misclassification. Our database lacks robust capture of certain potential confounders, such as body mass index. However, given the direction of the associations, additional adjustment for body mass index or other similar risk factors would, if anything, tend to attenuate the relative risk further. In addition, based on the requirements of the data use agreement intended to protect patient privacy, we cannot disclose counts on fewer than 11 malformations. Finally, our definition of statin use is based on a dispensed statin during the first trimester. While it is likely a reasonable assumption that if a statin is dispensed, it is taken, this cannot be empirically verified. In an effort to further increase the specificity of our exposure definition, we performed a sensitivity analysis in which we defined statin use on the basis of two dispensings during the first trimester; after stratification based on the high dimensional propensity scores, the risk estimate from this analysis was also close to the null (relative risk 1.20).

An additional limitation is that the database only includes information on live births. However, a sensitivity analysis suggests that termination rates for the indication of fetal malformation would need to be unrealistically different between women who did or did not use statins to substantially shift the risk estimate (see supplementary appendix 1). Yet, while we can conclude that statins do not significantly increase the overall risk of malformations, we cannot exclude the possibility that they confer risk of rare, specific malformations that could not be identified in this analysis, or that individual statins are associated with specific risks. Nor can we comment on any long term effects on the fetus of in utero exposure to statins. In our sensitivity analysis in which we required a full year of eligibility and follow-up of the infants, the risk estimate for the association between statin use and congenital malformations was statistically significant. Whether this is a chance finding in the setting of multiple sensitivity analyses or a real association cannot be determined. Notably, the effect estimate attenuates and the statistically significant increase is no longer present when we stratify on the high dimensional propensity scores (see supplementary table 2S). Finally, our cohort was drawn from Medicaid beneficiaries. Though the results should be generalizable to other populations, even if they are not this group is of intrinsic interest as Medicaid

provides coverage for nearly half of all deliveries in the United States.

Conclusion

Our analysis did not find a significant teratogenic effect from use of statins in the first trimester. Our findings suggest that inadvertent use during the first trimester may not be as worrisome as the FDA's class X (contraindicated for use in pregnancy) designation suggests. However, more information about the long term effects of in utero exposure to statins and about the effect on other neonatal outcomes, as well as replication of our findings in other large datasets with well measured information on statin use, confounders, and outcomes, are needed before statin use during pregnancy can be considered safe.

Contributors: BTB, SH-D, and KFH were involved in all parts of the study. HM was involved in data analysis and revising the manuscript critically for important intellectual content. MAF, EWS, JLE, JMF, RJD, CA-C, and JA were involved in interpreting the data and revising the manuscript critically for important intellectual content. BTB and KFH are the guarantors.

Funding: This study was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the NIH (Bethesda, MD) under award No K08HD075831 (BTB), the National Heart Lung and Blood Institute of the NIH under award No K24HL096141 (EWS), and the National Institute of Mental Health of the NIH under award No K01MH099141 (KFH). Medicaid Analytic eXtract pregnancy cohort creation was supported by the Agency for Healthcare Research and Quality (AHRQ) (grant R01HS018533). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: SHD has consulted for GlaxoSmithKline-Biologics and AstraZeneca for unrelated projects. JMF has consulted for Aetion and received grant support from Merck for unrelated projects. PhRMA, Takeda, Pfizer, and Bayer provide training funds for pharmacopidemiology students at Harvard School of Public Health (SHD) for unrelated projects.

Ethical approval: The Partners institutional review board approved the use of the deidentified database for research.

Data sharing: No additional data available.

Transparency: The lead author (BTB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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**Figure showing selection of cohort
Tables, appendix, and additional figures**