

## Fetal toxicity associated with statins: A systematic review and meta-analysis

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### ABSTRACT

**Background and aims:** Statins are the drugs of choice for decreasing elevated low-density lipoprotein cholesterol. Based mostly on animal studies and case reports, they are forbidden to pregnant women and in the preconception period because of their possible teratogenic effects, for which causality has never been proven. The aim of this study was to systematically review the existing studies and to perform a meta-analysis on this topic.

**Methods:** The databases PubMed/MEDLINE, Scopus, and Web of Science were searched since the inception until May 16, 2020. The risk of bias for each clinical trial was evaluated using the Cochrane handbook criteria for systematic reviews. The National Institutes of Health (NIH) quality assessment tool was used for the evaluation of cohort and cross-sectional studies. Meta-analysis was performed on the extracted data. Heterogeneity was assessed using  $I^2$  measure and Cochrane's Q statistic. We calculated a pooled estimate of odds ratio (OR) and 95% confidence intervals (CI) using a random-effects model.

**Results:** 23 studies (nine cohort studies, six case reports, six case series, one population-based case-referent study and one clinical trial) with 1,276,973 participants were included in the systematic review and 6 of them ( $n = 1,267,240$  participants) were included in meta-analysis. The results of the critical review did not suggest a clear-cut answer to the question whether statin treatment during pregnancy is associated with an increased rate of birth defects or not, while the results of the meta-analysis indicated that statin use does not increase birth defects [OR (95%CI): 1.48 (0.90, 2.42),  $p = 0.509$ ], including cardiac anomalies [2.53 (0.81, 7.93),  $p = 0.112$ ] and other congenital anomalies [1.19 (0.70, 2.03),  $p = 0.509$ ].

**Conclusions:** We observed no significant increase of birth defects after statin therapy. Thus, there is still no undoubtful evidence that statin treatment during pregnancy is teratogenic, and this issue still needs to be investigated, especially there are more and more pregnant women at high CVD risk that could have benefited from the statin therapy.

### 1. Introduction

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors – statins have been widely used for almost four decades as the

drugs of first choice to decrease elevated low-density lipoprotein cholesterol (LDL-C) and thus reduce atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality [1–3]. Besides, this class of drugs possesses a plethora of pleiotropic effects [4–11], which are mostly

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independent of the impact on LDL-C. Since the data about their effects on pregnancy and fetal development were non existing or scarce, from the very beginning of their use women were advised to stop treatment with these drugs during the preconception period and pregnancy [12]. A number of studies on animals were published in the last 25 years suggesting that statins might cause fetal anomalies [13,14]. However, in these reports, in which more fetal anomalies were reported in animals treated with statins, excessive doses were used compared with the doses commonly prescribed to humans. Based mostly upon these studies, but also on some case reports, the U.S. Food and Drug Administration (FDA) claims that statins are not recommended for pregnant women and they are rated as “Pregnancy Category X” drugs, which means that studies have shown that they might cause birth defects and that the risks outweigh the benefit. The same recommendations were repeated in the recent guidelines of the European Society of Cardiology (2018) [15]. However, some more recent observational studies could not find an increased risk of congenital anomalies caused by statins in pregnancy when compared to control groups or the prevalence of congenital anomalies in the general population [16,17], especially in the group of patients with the extremely high levels of LDL-C such as those with heterozygous and homozygous familial hypercholesterolemia (FH), where no such complications were observed [2,3,12,15].

The main question of this systematic review and meta-analysis was: “Is there any scientific evidence that proves that statin therapy is associated with an increased rate of birth defects in women exposed to statins during pregnancy?”. Therefore, the aim of this study was to identify and analyze all the existing studies concerning this question, and to perform a meta-analysis if it could be meaningfully or reliably performed. To the best of our knowledge, this is the largest and the most comprehensive systematic review and meta-analysis aimed to investigate this issue.

## 2. Materials and methods

### 2.1. Literature search strategy

The databases PubMed/MEDLINE, Scopus, and Web of Science have been searched since the inception until May 16, 2020. In the search strategy, the following MeSH and text keywords were used: (*pregnancy OR pregnant\* OR gestation\* OR conception*) AND (*statins OR „statin therapy” OR „statins therapy” OR statin OR „HMG CoA reductase inhibitor” OR lovastatin OR fluvastatin OR pravastatin OR pitavastatin OR rosuvastatin OR atorvastatin OR simvastatin OR cerivastatin OR lipitor OR lescol OR „Lescol XL” OR mevacor OR altoprev OR pravachol OR crestor OR zocor OR livalo*). To further identify potentially related studies, the references of primary articles were also reviewed. All relevant articles were evaluated using predefined selection criteria.

### 2.2. Selection criteria

All studies with original data, including any methodology performed on statin-exposed pregnant women in each trimester of pregnancy with adequate data about congenital anomalies or any birth defects that occurred during and after statin use by the pregnant women were included. Animal studies and articles in non-English languages were excluded.

### 2.3. Data extraction

Data extraction was done in three steps. First, the output of all three scientific databases was analyzed and the duplicate articles were removed. Studies were then screened separately by title and abstract by two researchers (AVA and SM) to identify seemingly related articles for the second screening. In the next step, two separate researchers (ZR and AS) carefully evaluated full texts of the remaining articles and identified studies that met the inclusion criteria for review. Data were extracted

from the studies by a pre-designed form that included the following information: the author’s name, year, country, the type of the study, population, statin exposure, and control group, trimester(s) of exposure to statins and outcomes. At all these stages, any ambiguities or disagreements between the evaluators were resolved through discussion and consensus.

### 2.4. Critical appraisal

Two authors (AVA and SM) independently assessed the quality of included studies. The risk of bias for each clinical trial was evaluated using the Cochrane handbook criteria for systematic reviews [18]. The National Institutes of Health (NIH) quality assessment tool was used for the evaluation of cohort and cross-sectional studies [19]. This tool has 14 questions and shows the quality as good, fair, and poor. No formal quality assessment was used for case reports and case series studies. Any disagreement between the researchers was resolved by discussion.

### 2.5. Statistical analysis

Meta-analysis was performed on the extracted data for dichotomous outcome of rate of birth defects. We calculated a pooled estimate of odds ratio (OR) and 95% confidence intervals (CI) by random effect with inverse variance (IV) weighting. We showed the result in the Forest plot by the subgroup analysis. Heterogeneity was assessed using  $I^2$  measure and Cochrane’s Q statistic [20] and illustrated by Radial plot. We performed subgroup analysis to find the potential source of the heterogeneity. Publication bias was evaluated by Egger’s test [21] and Funnel plot. All statistical analysis was performed using by STATA, version 14.0 (Stata Corp, College Station, TX) and R version 3.6.3.

## 3. Results

A total of 2128 studies were identified by searching three electronic databases and other sources (see methodology). After the removal of duplicates and apparently irrelevant studies, 98 articles remained to be screened by the full-text evaluation. After applying the selection criteria, 23 studies with 1,276,973 participants were included in the systematic review, and 6 studies with 1,267,240 participants were finally included in the meta-analysis (Fig. 1). The characteristics of these studies are shown in Table 1.

### 3.1. Quality assessment

Nine cohort and one case-referent studies were evaluated using NIH quality assessment tool for observational cohort and cross-sectional studies. In total, 70% of the studies had good quality, 20% had fair, and 10% had poor quality. The highest-quality studies were prospective cohort studies [22,23]. The quality of the clinical trial study [24] was assessed using the Cochrane risk of bias tool. This study concerning random sequence generation, blinding of participants, personnel, and outcomes assessors, incomplete outcome data, and selective reporting had a low risk of bias and in the domain of allocation concealment had an unclear risk of bias.

### 3.2. Characteristics of studies

The number of participants exposed to statins varied from one to 1152 subjects [16]. Five studies were performed on pregnant women with hypercholesterolemia [22,25–28] and three studies were performed on women who had preeclampsia or were at high risk for it [24, 29,30]. According to the methodology, the studies included nine cohort articles [16,22,23,25,28,31–34], six case reports [26,27,30,35–37], six case series [29,38–42], one clinical trial [24], and one population-based case-referent study [43]. The studies were published from 1992 to 2018.

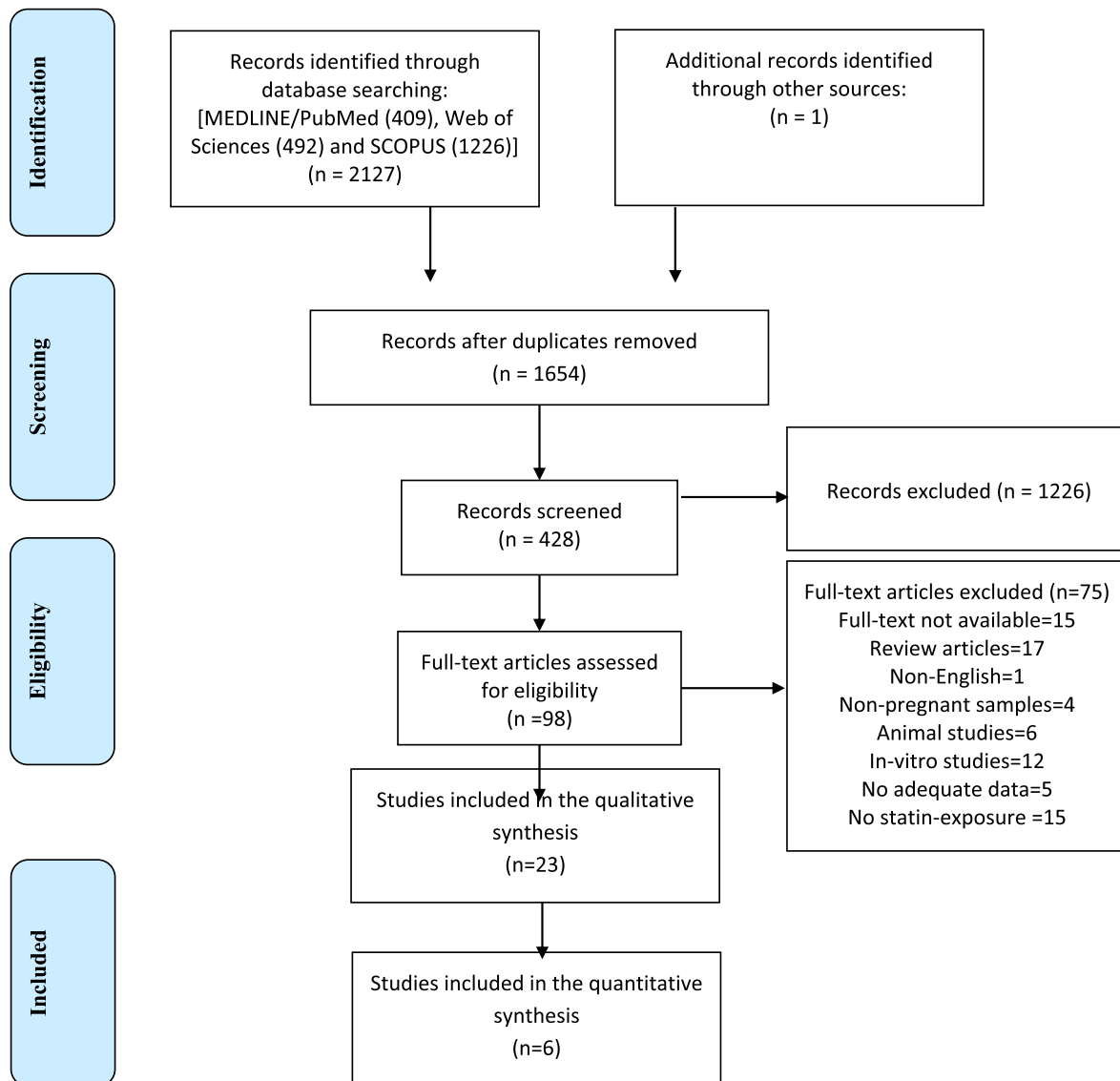


Fig. 1. PRISMA flow chart (preferred reporting items for systematic reviews and meta-analyses).

### 3.3. Types of statins and time of exposure

Concerning the type of statin used, in most studies it was atorvastatin [16,22,23,25,31–34,37,38,40,41,43] and simvastatin [16,22,23,31–34,38–43], each of them was used in thirteen studies. Pravastatin was used in 11 studies [22–24,26,29,30,32–34,36,40], lovastatin in 5 studies [16,26,32,39,42], cerivastatin in 4 studies [23,33,38,41], rosuvastatin in 2 studies [22,33], and fluvastatin in 2 studies [23,33]. In two studies, the type of statin used was not mentioned [27,28].

In most studies, women were exposed to statins during the first trimester of pregnancy [16,22,23,26,31–34,37–41,43]. In some other studies, statins were used in the second and third trimesters. Exposure time to statin has not been reported in the study of Toleikyte et al. [28].

### 3.4. The qualitative reporting of the results

#### 3.4.1. Case reports

In five case reports, in which women were exposed to statins during pregnancy, no congenital malformations were found at birth. However, in the case report by Ghidin et al. [26] a pregnant woman with hypercholesterolemia was exposed to lovastatin and dextroamphetamine sulphate for the first 5 weeks of pregnancy before a taking pregnancy

test. No fetal abnormality was detected by prenatal ultrasound examinations. Nevertheless, at birth multiple congenital musculoskeletal abnormalities were detected in the newborn. Dextroamphetamine is rated as category C and lovastatin as category X. Although the drug was taken in a critical period (first trimester), the causal relationship was not proven. However, as previously described, lovastatin might produce skeletal malformations in rats (at amounts 500 times greater than the maximum recommended dose) [26].

#### 3.4.2. Case series studies

In a case series study on 178 pregnant women who had been exposed to statins during the first trimester of pregnancy, five severe defects of the central nervous system and five limb deficiencies were observed [38]. Peterson et al. found based upon 22 cases of birth defects, in which exposure to statins occurred during pregnancy, that the most common anomalies were congenital heart defects and cleft lip with or without cleft palate. In 54.5% of cases, the statin used was atorvastatin [41]. In 99 prospective and 35 retrospective cases of exposure to lovastatin and simvastatin during pregnancy, Manson et al. found nine cases of congenital abnormalities. There were two cases of central nervous system defects, two reports of limb anomalies, and one hypospadias, one VATER (vertebral anomalies, anal atresia, tracheoesophageal fistula

**Table 1**  
Summary of characteristics of studies included in the systematic review.

First author, (year)	Country	Type of study	Population (number of subjects)	Statin exposure	Control	Trimester	Outcomes
Bateman, (2015) [16]	United States	Cohort	886,996 completed pregnancies linked to live born infants	1152 women used a statin. Most commonly used statins: atorvastatin (n = 538), simvastatin (n = 319), and lovastatin (n = 132)	885,844 women were unexposed to statins	First	No significant teratogenic effect from maternal use of statins was found.
Botha, (2018) [25]	South Africa	Cohort	39 pregnancies with homozygous familial hypercholesterolaemia	18 women exposed to statin. Most common statins used was atorvastatin	21 women used no statin	Before conception, first and second trimesters	There was no statistical difference in the rate of congenital malformations between the statin exposed and unexposed groups.
Brownfoot, (2015) [29]	Japan	Case series	4 pregnant women with preeclampsia presenting at 23–30 weeks of gestation	Pravastatin (n = 4)	None	Second and third	There were no fetal or neonatal abnormalities and no neonatal deaths.
Colvin, (2010) [31]	Australia	Registry-based cohort	51 pregnant women exposed to statins during pregnancy and non-exposed pregnant women	Atorvastatin (n = 33) and simvastatin (n = 18)	106,074 women with a pregnancy event	First	The risk for any congenital anomaly for simvastatin was OR 1.2, 95% CI 0.2–8.9 and for atorvastatin was OR 0.6, 95% CI 5 0.1–4.6
Costantin, (2016) [24]	United States	Pilot randomized controlled trial	21 women at high risk for preeclampsia	10 women used daily pravastatin	Placebo (n = 10)	Second and third	There were no significant differences between two groups regarding congenital anomalies.
Daud, (2017) [43]	Netherlands	Population-based case-referent study	4805 live born cases with congenital anomaly	Atorvastatin, and Simvastatin	Referent population (n = 31055)	First	There was no difference between those exposed to statins and the referent population.
Edison, (2004) [38]	United States	Case series	178 pregnant women with statin exposure during pregnancy	There were 20 reports of malformations in 9 neonates of women who used cerivastatin, simvastatin, lovastatin, atorvastatin	No control	First	There were five neonates with severe defects of the central nervous system and five unilateral limb deficiencies (one newborn had both of these malformations).
Ghidin, (1992) [26]	United States	Case report	A pregnant woman with hypercholesterolaemia	Lovastatin and dextroamphetamine for 5 weeks	–	First	Multiple congenital anomalies were detected: asymmetric chest, thoracic scoliosis, absent left thumb, foreshortened left forearm, and left elbow contracture, fusion of the ribs, butterfly vertebrae, left radial aplasia.
Kozlowski, (2017) [30]	Poland	Case report	A preeclamptic woman with previous four pregnancy losses and with a history of chronic hypertension, hypothyroidism, polycystic ovarian syndrome with insulin resistance	Pravastatin from 17 weeks of gestation to delivery	–	Second and third	Fetal growth restriction and decreasing volume of amniotic fluid at 33 weeks of gestation were found.
Lee, (2018) [32]	United States	Cohort	379,238 singleton pregnancies	280 pregnancies exposed to atorvastatin (n = 28, 10.0%), lovastatin (n = 104, 37.1%), pravastatin (n = 8, 2.9%), and simvastatin (n = 140, 50%)	378,950 pregnancies unexposed to statin	First	There were no congenital anomalies. In general, the percentage of congenital cardiac anomalies in neonates of the pregnant women who were exposed to statins was higher than in those who were not ( $p = 0.009$ ). First-trimester statin exposure was associated with an increased risk of

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Table 1 (continued)

First author, (year)	Country	Type of study	Population (number of subjects)	Statin exposure	Control	Trimester	Outcomes
Manson, J.M (1996) [39]	Multinational study (12 countries) <sup>a</sup>	Case series	134 reports of exposure to statins during pregnancy	99 prospective and 35 retrospective reports of using lovastatin and simvastatin during pregnancy	–	First trimester in 89% of cases	ventricular septal defect ( $p < 0.001$ ). No association was found with atrial septal defect, conotruncal defect, single ventricle physiology, and patent ductus arteriosus after adjustment for maternal characteristics. There was no relationship between exposure to statins during pregnancy and the occurrence of adverse pregnancy outcomes. There were nine reports of congenital anomalies (two cases with central nervous system defects, two reports of limb anomalies, and one hypospadias, VATER association, cleft lip, and trisomy 18).
McElhatton, (2008) [40]	United Kingdom	Case series	Pregnant women exposed to statins during pregnancy	25 pregnancies exposed to atorvastatin, simvastatin, and pravastatin (no details)	–	First trimester in 88% of cases	There was an increased rate of congenital malformations after exposure to statins (4 out of 18 live born).
McGrogan, (2017) [33]	United Kingdom	Cohort	2924 pregnant women	281 women exposed to simvastatin (n = 152), atorvastatin (n = 103), cerivastatin (n = 2), rosuvastatin (n = 6), pravastatin (n = 8), fluvastatin (n = 4), and combination (n = 6)	2643 pregnancies unexposed to statin	Three months before and/or during the first trimester	Important differences in the proportions of pregnancy loss – it was significantly higher in those exposed to statins compared with the control group. There were nine anomalies in seven newborns in those exposed to statin compared to 49 anomalies in 48 newborns in the control group.
Ofori, (2007) [34]	Canada	Registry-based cohort	259 women were prescribed statins during or before pregnancy	153 women exposed to atorvastatin, pravastatin and simvastatin during pregnancy	106 women exposed to statins between 1 year before and 1 month before pregnancy	First trimester	There was no detectable pattern in fetal congenital anomalies or evidence of an increased risk in the live-born infants of women who used statins during pregnancy compared to the control group.
Otten, (2017) [35]	Germany	Case report	A 40 years old was pregnant with history of severe, recurrent early-onset HELLP syndrome	Pravastatin was commenced at 13 weeks of gestation until delivery	–	The final week of the first trimester to the third trimester	A neonate without major malformations was born at term.
Petersen, (2008) [41]	United states	Case series	22 cases of birth defect with maternal exposure to statins	In 22 cases, mothers took statins, including atorvastatin, simvastatin, cerivastatin, and pravastatin	–	All but one were exposed in the first trimester	The most common anomalies were congenital heart defects (n = 12) and cleft lip with or without cleft palate (n = 4) 12 cases were exposed to atorvastatin.
Pollack, (2005) [42]	United states	Case series	477 reports of exposure to statins during pregnancy	386 prospective and 91 retrospective reports of exposure to simvastatin and/or lovastatin	–	First trimester exposure was reported in 162 subjects	The rate of congenital anomalies in the statin group and general population were not different

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Table 1 (continued)

First author, (year)	Country	Type of study	Population (number of subjects)	Statin exposure	Control	Trimester	Outcomes
Singh, (2013) [27]	India	Case report	A pregnant woman with familial hypercholesterolemia and cardiomyopathy	Statin was used until week 24. The type of statin was not mentioned	–	Before pregnancy, the first trimester and up to 24 weeks from the second trimester	A healthy neonate was born at 36 weeks of gestation.
Taguchi, (2008) [22]	Canada	Cohort	128 pregnant women with hypercholesterolemia	64 women used atorvastatin (n = 46), simvastatin (n = 9), pravastatin (n = 6), rosuvastatin (n = 3)	64 women used non-teratogen lipid = lowering agents	First	There was no difference in the rate of major malformations between the statin group and the control group.
Teelucksing, (2004) [36]	India	Case report	A woman with the metabolic syndrome who was unaware of her pregnancy	Pravastatin was used until week 24 of gestation	–	Before pregnancy, the first trimester and up to 24 weeks from the second trimester	No gross anatomic abnormalities were found at birth. Neonatal period was uncomplicated, and no early developmental abnormalities were found.
Toleikyte, (2015) [28]	Norway	Registry-based cohort	1093 familial hypercholesterolemic women with 2319 births.	16 cases used a statin during pregnancy. The type of statins was not mentioned	General population (n = 2,304,067)	Not mentioned	The frequency of all congenital malformations did not change significantly from the period before (years 1979–1991) and the period after (years 1992–2006) statin introduction in study population.
Winterfeld, (2013) [23]	Multinational study <sup>b</sup>	Cohort	598 pregnant women	249 pregnant women who were seeking medical advice about statin exposure during pregnancy. They had used simvastatin (n = 124), atorvastatin (n = 67), pravastatin (n = 32), rosuvastatin, (n = 18), fluvastatin (n = 7), and cerivastatin (n = 1)	249 women used no statins	First trimester in 86% of cases	There was no difference in the rate of major birth defects between those exposed to statin and the control group.
Yaris, (2004) [37]	Turkey	Case report	A diabetic and hypertensive woman with an unplanned pregnancy	She used rosiglitazone, gliclazide, and atorvastatin during the first 7 weeks of gestation	–	First	No congenital abnormality was detected at birth. No developmental abnormalities were found in the first four months after birth.

<sup>a</sup> Australia, Belgium, Canada, France, Germany, Luxemburg, Mexico, Netherlands, Norway, South Africa, United Kingdom, and the USA.

<sup>b</sup> 11 centers in Europe.

with esophageal atresia, renal and radial dysplasia), one cleft lip, and one trisomy 18<sup>39</sup>. The authors have stated that while the number of prospective reports available for evaluation was only sufficient to rule out a three-to fourfold increase in the overall frequency of congenital anomalies, these proportions did not exceed what would be expected in the general population. The findings of another case series showed that the rate of congenital anomalies in the statin group and the general population was not different [42]. McElhatton et al. reported an increased rate of congenital malformations after exposure to statins in the first trimester of pregnancy (4 from 18 live born) [40]. Brownfoot et al. found no fetal or neonatal abnormalities in four women who were exposed to pravastatin during the second and third trimesters of pregnancy [29].

### 3.4.3. Cohort studies

In six cohort studies (n = 889,113), most of which involved statin exposure in the first trimester, there was no difference in birth defects between the group exposed to statin and the control group [16,22,23,25,28,34]. The results of a registry-based cohort by Colvin et al. showed

that when pregnant women were exposed to atorvastatin and simvastatin in the first trimester, the risk for any congenital anomaly for simvastatin was OR 1.2, 95%CI 0.2–8.9 and for atorvastatin was OR 0.6, 95%CI 0.1–4.6<sup>31</sup>. Another cohort study on 379,238 singleton pregnancies found that the percentage of congenital cardiac anomalies in pregnant women who were exposed to statins was higher than those who were not ( $p = 0.009$ ) [32]. McGrogan et al. reported nine anomalies in seven newborns in the statin exposed cohort compared to 49 anomalies in 48 newborns in the control cohort. No details were given on the type of anomalies [33].

### 3.4.4. Case-control study

A population-based case-referent study was performed by Daud et al. in 2017 on 4805 live-born cases with congenital anomalies compared to the referent population [43]. The results showed that there were no differences between those who were taking statins and the referent population.

3.4.5. *Interventional study*

In a pilot, multicenter, double-blind, placebo-controlled, randomized trial, 21 women at high risk for preeclampsia were assigned to pravastatin (n = 10) and placebo (n = 10) in the second and third trimesters [24]. The results showed that there were no differences between the two groups in rates of congenital anomalies (one hypospadias and one coarctation of the aorta in the intervention group and one polydactyly and one ventriculomegaly in the control group).

3.5. *Results of the meta-analysis*

We analyzed six studies (n = 1,267,240) for the rate of birth defects following maternal exposure to statins. The results indicate that exposure to statins has caused a numerically increased (although not significant) rate of birth defects in sub-group analysis of cardiac anomalies (OR (95%CI) 2.53 (0.81, 7.93), p = 0.112), and other congenital anomalies (OR (95%CI) 1.19 (0.70, 2.03), p = 0.509) (Fig. 2). In the overall analysis, statin use does not increase birth defects (OR (95%CI) 1.48 (0.90, 2.42), p = 0.509) (Fig. 2). Heterogeneity was obtained in the radial plot (I<sup>2</sup> = 56.4%, p = 0.025) (Fig. 3). There was no publication bias according to Egger’s test (p = 0.263) (Fig. 4).

4. *Discussion*

The results of our critical review of case reports, case series studies, cohort studies, a case control study and an interventional study did not suggest a clear-cut answer to the question whether statin treatment during pregnancy is associated with an increased rate of birth defects or not. It has to be stressed that no causality between treatment with statins in pregnancy and birth defects could be clearly proven in any study. The results of our meta-analysis indicate that exposure to statins during

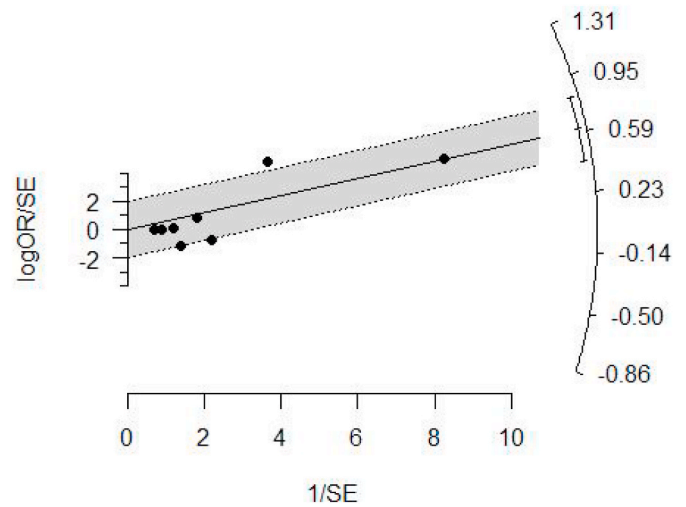


Fig. 3. Radial plot for heterogeneity of rate of birth defects following maternal exposure to statins.

pregnancy was not related to an increased rate of birth defects.

There are only two critical reviews and meta-analyses published so far on the fetal safety of statins, one in 2012 and one in 2014 [44,45]. The results of the first one indicated that statins were unlikely to be teratogenic, that congenital anomalies in newborns whose mothers were treated with statins during pregnancy were isolated, and that there was no consistent pattern to suggest that a common mechanism could underlie these defects [44]. Neither the second report suggested that use of statins in pregnancy might carry teratogenic risk [45]. The results of our

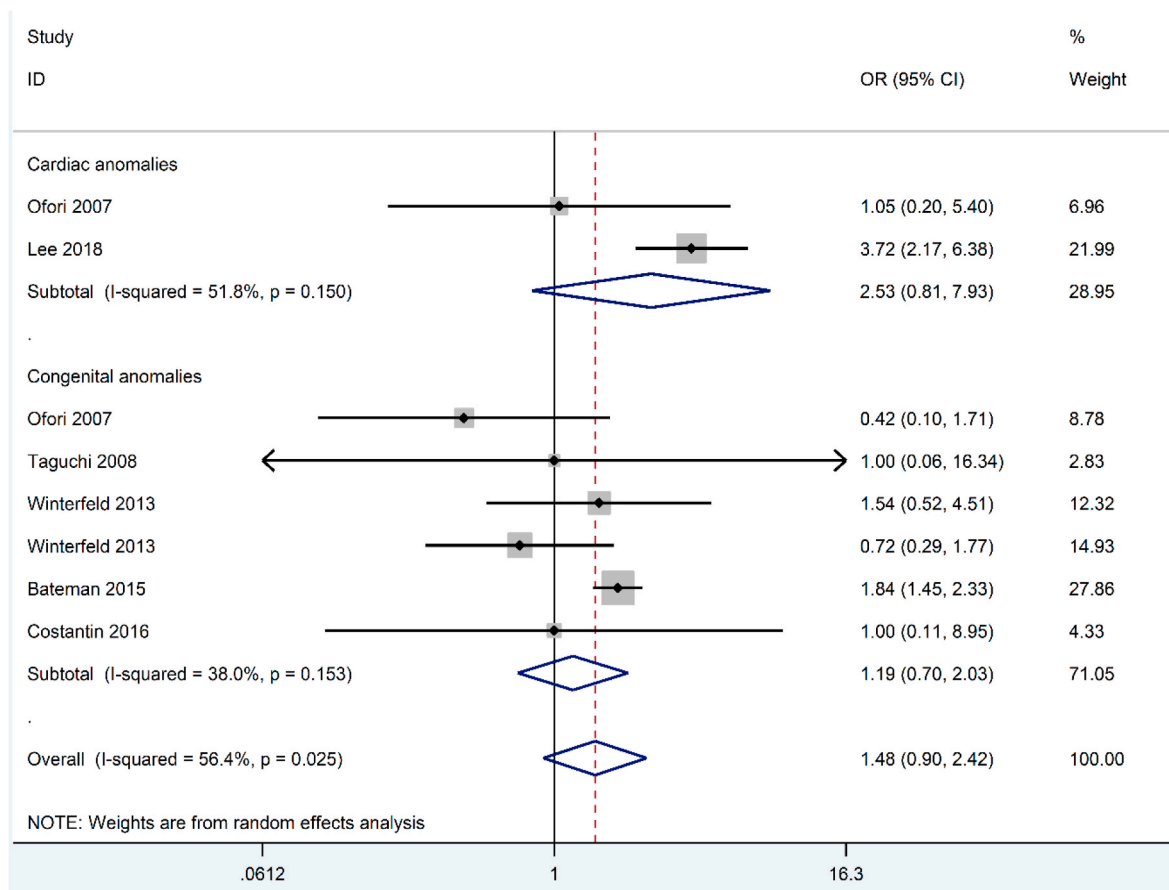


Fig. 2. Forrest plot for odds ratio of rate of birth defects following maternal exposure to statins.

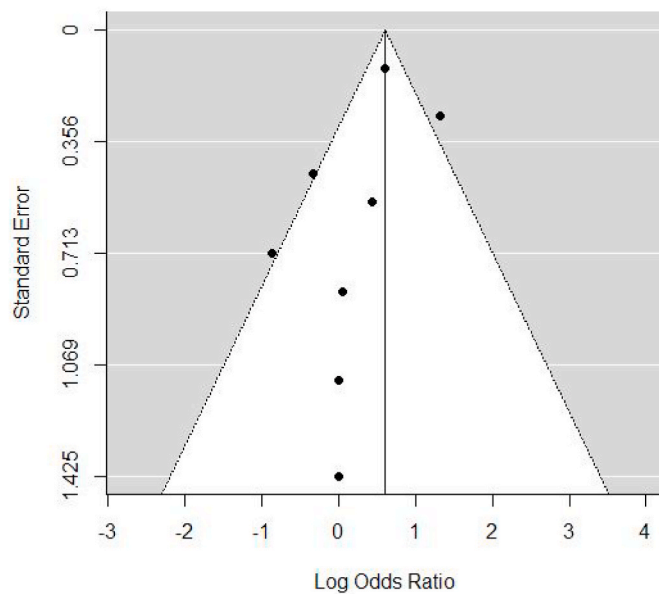


Fig. 4. Funnel plot for publication bias of rate of birth defects following maternal exposure to statins.

critical review and meta-analysis, to the best of our knowledge, present the largest and the most comprehensive view on the role of statin in pregnancy, both from case reports and case series, with the validation within meta-analysis of available studies.

In contrast with the general perception and recommendations that treatment with statins in pregnancy and even in the preconception period should be avoided, most recent data indicate that statins could have beneficial effects in pregnancy. For example, it has been reported recently that statins might protect endothelial function in the mother and placenta thus rescuing fetal cardiovascular dysfunction in complicated pregnancies [46]. It seems also that statins might be useful (mainly pravastatin) for preventing or treating preeclampsia [47]. The results of animal studies suggest that statins might reduce preterm labor and inhibit myometrial contractions thus preventing preterm birth [48]. A case report has been published showing that a statin can reverse an angiogenic/anti-angiogenic imbalance and prevent fetal death in massive perivillous fibrin deposition of the placenta (MPFD) or maternal floor infarction (MFI), which is a serious condition associated with recurrent complications including fetal death and severe fetal growth restriction [30]. It seems, therefore, that potential beneficial pleiotropic effects (besides those LDL-C lowering) of treatment with statins in pregnancy, which still have to be proven on a larger number of cases, might even outweigh the potential risks of possible teratogenic effects of these drugs, which were not clearly proven in any analysis, including this meta-analysis. Based on this, it seems that statins might be reconsidered to be used, especially in very high-risk CVD pregnant women, and especially in those with HoFH and HeFH with severe hypercholesterolemia, where the disease itself might be dangerous both for the mother and fetus, and only when the benefit outweighs the risk. Based on available data, it also seems that statin might have some additional beneficial effects, especially in the late 3rd trimester [12].

In this study, it was shown that statin therapy has no effect on the development of fetal abnormalities. However, due to the fact that teratogenic factors have different effects depending upon the dose, route of exposure, duration of exposure, as well as individual conditions, statin treatment during pregnancy cannot be explicitly proven to be harmless. Since pregnancy and care during this period are very important for the health and development of the fetus and newborn, pregnant women should refrain from taking drugs arbitrarily and excessively during this period. Planning prevention, as well as education, to avoid

the arbitrary use of herbal and synthetic drugs and exposure to factors whose risk is not clearly identified during pregnancy seems to be necessary.

The present meta-analysis, while being the largest thus far, is limited by lack of sufficient evidence from large-scale prospective cohorts and interventional studies. Moreover, there is a lack of data on direct comparison of different statins as their impact on fetal health and birth defects. Another limitation of this study was that not enough data was available to take into account statin doses, which may have a major impact on this issue. Furthermore, recently some combined drugs, which contain statin and other lipid-lowering drugs, such as fenofibrate and ezetimibe are available. Effects of these drugs, as well as other novel lipid-lowering medications [49,50], during pregnancy should be carefully evaluated. There is also lacking evidence of any long-term effect of statin use during pregnancy on the growth and development of the neonate. Finally, the potential benefits of statin use in pregnant mothers with FH needs further investigations.

In conclusion, the results of this meta-analysis indicate that treatment with statins during pregnancy is not linked to a significant increase in the rate of birth defects.

#### CRediT authorship contribution statement

**Amir Vahedian-Azimi:** conceived the study, prepared the first draft of manuscript. **Somayeh Makvandi:** prepared the first draft of manuscript. **Željko Reiner:** conceived the study, prepared the first draft of manuscript, supervised this study, critically revised the draft manuscript and the revised version, supervised this study. responsible for the submission of this paper and the revised version. **Amirhossein Sahebkar:** critically revised the draft manuscript and the revised version. All authors approved the final version for submission.

#### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MB - speakers bureau: Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Polpharma, Sanofi-Aventis, Servier and Valeant; consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, Lilly, MSD, Polfarmex, Resverlogix, Sanofi-Aventis; Grants from Sanofi and Valeant. ZR has received honoraria from Sanofi-Aventis; MK has received honoraria (for lectures and consultancy) from Abbott and Menarini, and research funding from Amryt Pharma, Amgen, and Sanofi, and has participated in clinical trials with Amgen, Medicines Company, Regeneron, and Sanofi within the last 2 years. All other authors have nothing to disclose.

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