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A systematic review and meta-analysis on the effects of statins on pregnancy outcomes

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ABSTRACT

Background and aims: Statins are contraindicated in pregnancy, due to their potential teratogenicity. However, data are still inconsistent and some even suggest a potential benefit of statin use against pregnancy complications. We aimed to investigate the effects of statins on pregnancy outcomes, including stillbirth, fetal abortion, and preterm delivery, through a systematic review of the literature and a meta-analysis of the available clinical studies.

Methods: A literature search was performed through PubMed, Scopus, and Web of Science up to 16 May 2020. Data were extracted from 18 clinical studies (7 cohort studies, 2 clinical trials, 3 case reports, and 6 case series). Random effect meta-analyses were conducted using the restricted maximum likelihood method. The common effect sizes were calculated as odds ratios (ORs) and their 95% confidence interval (CI) for each main outcome.

Results: Finally, nine studies were included in the meta-analysis. There was no significant association between statin therapy and stillbirth [OR (95% CI) = 1.30 (0.56, 3.02), p=0.54; I^2 = 0%]. While statin exposure was significantly associated with increased rates of spontaneous abortion [OR (95% CI) = 1.36 (1.10–1.68), p=0.004, I^2 = 0%], it was non-significantly associated with increased rates of induced abortion [OR (95% CI) = 2.08 (0.81, 5.36), p=0.129, I^2 = 17.33%] and elective abortion [OR (95% CI) = 1.37 (0.68, 2.76), p=0.378, I^2 = 62.46%]. A non-significant numerically reduced rate of preterm delivery was observed in statin users [OR (95% CI) = 0.47 (0.06, 3.70), p=0.47, I^2 = 76.35%].

Conclusions: Statin therapy seems to be safe as it was not associated with stillbirth or induced and elective abortion rates. Significant increase after statin therapy was, however, observed for spontaneous abortion. These results need to be confirmed and validated in future studies.

1. Introduction

Statins, HMG-CoA reductase inhibitors, are cholesterol-lowering drugs indicated in the treatment of hypercholesterolemia for the prevention of cardiovascular risk [1,2]. However, it is widely recognized that statins can also exert a variety of cholesterol-independent pharmacological effects (*e.g.*, pro-angiogenic, anti-inflammatory, immune-regulatory, and antioxidative effects), namely pleiotropic effects, which make them valuable candidate for additional therapeutic purposes beyond the cholesterol-lowering one [3–9].

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Due to their undisputed efficacy and their good safety profile, statins are widely prescribed drugs [1,2,10]. However, they are contraindicated when pregnancy is planned and during pregnancy [11–13], based on early reports from animal studies showing an increased risk of teratogenicity and other pregnancy complications with statin use [14,15]. From a pathophysiological perspective, statin-mediated unfavorable effects on pregnancy are traditionally attributed to the essential role of cholesterol in metabolic pathways regulating morphogenesis [16] as well as the implantation process [17]. Nonetheless, it is of note that in animal studies reporting an excess of congenital anomalies, the administered doses of statins were significantly higher as compared to those commonly prescribe to human subjects [18]. In addition, a number of clinical studies have questioned the safety concerns regarding statin use during gestation, showing a non-clear relationship between statin therapy and adverse pregnancy outcomes [18–24]. Finally, there is evidence from some preclinical studies and clinical trials that statin use may be even beneficial to prevent some pregnancy complications, including preeclampsia and preterm delivery [25,26]. Due to such an inconsistency regarding the unsafety of statins during gestation, in the last years there have been some systematic review and meta-analysis of both human and animal studies objectively assessing the effects of statins during pregnancy [18–22]. Overall, while a clear relationship has emerged between statin exposure and risk of abortion, the impact of statins on congenital abnormalities has been reported to be significant in animal studies but not in clinical studies [18–22].

Therefore, as to whether the use of statins may have an overall detrimental impact on pregnancy or not remains an open question. A solution to such a dilemma may be of particular relevance in clinical practice to guide not only the interruption of statin therapy at the time of conception, but also the prescription of statins in premenopausal women. Indeed, young women with hypercholesterolemia are candidates to receive an effective cholesterol-lowering treatment for the prevention of cardiovascular risk [13]. Nonetheless, an unlimited prescription of statins in premenopausal women may significantly raise the risk of statin exposure in pregnancy, as a great amount of pregnancies are not planned [27]. Therefore, if the use of statins is overall harmful in pregnancy, statin prescription should be well-rationalized in women of childbearing age.

Evidence from randomized clinical trials would be crucial to further elucidate the relationship between statins and different pregnancy outcomes. However, no randomized clinical trial had been published when the aforementioned systematic reviews and meta-analysis were performed. Therefore, we aimed to perform an updating systematic review and meta-analysis of clinical studies on the effects of statin exposure in pregnancy.

2. Materials and methods

2.1. Search strategy

The search of MEDLINE was performed through the PubMed interface, Scopus, and Web of Sciences for original articles concerning "the effects of exposure to statins during pregnancy on outcomes of pregnancy and childbirth" published until May 16, 2020. The search strategy involved the following two search components: statins and pregnancy. Each component included MESH terms, entry terms, and keywords selected by experts. The complete search strategy was: *(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) AND (pregnancy OR pregnan* OR gestation* OR conception)*.

2.2. Inclusion and exclusion criteria

Published papers fulfilling the following criteria were included: (a) type of study: all original studies such as clinical trials, cohort studies, *registry-based cohort studies, case-control studies, case reports, and case series* meeting inclusion criteria were involved; (b) types of participants: only human studies were considered, whereas animal studies and *in vitro* investigations were removed; (c) types of interventions/comparisons: any type of exposure to any type of statins during any trimester of pregnancy was considered; (d) outcomes: outcomes related to pregnancy and childbirth that occurred during statin use, such as stillbirth rate, abortion rate, preterm delivery, birth weight and any other pregnancy-related outcomes found in the results of papers. Articles in languages other than English were removed.

2.3. Data abstraction

After the removal of duplicate articles, the initial output for the search was scrutinized by two separate researchers in terms of title and abstract, and the unrelated articles were deleted. The full text of the remaining articles was then examined. Articles that met the entry criteria were selected and other articles were deleted. In each case, the disputes between the two appraisers were resolved through discussion to reach a final joint opinion.

2.4. Data extraction

In order to extract the data of the papers in an integrated way, a data extraction tool was first designed by the research team, and data were extracted based on selected items. Items included first author name, year of publication, country, type of study, population, statin exposure group, control group, statin exposure time, statin type, and pregnancy outcomes.

2.5. Quality of the evidence

Two authors independently assessed the quality of the included studies. The risk of bias for clinical trials was evaluated using the criteria outlined in the Cochrane handbook for systematic reviews of interventions [28]. The National Institutes of Health (NIH) quality assessment tool was used for the appraisal of cohort studies [27]. 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.

2.6. Ethical considerations

The ethics committee's approval and consent were not required for this study because the data used in this systematic review and meta-analysis was obtained from previously published studies. In terms of adhering to ethical principles, the researchers tried to avoid any plagiarism and never deliberately manipulated data to achieve personal interests.

2.7. Statistical analyses

All analyses were conducted with STATA16 (StataCorp, College Station, Texas, USA). The reporting of the study was adopted based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [29]. Random effect meta-analyses were conducted using the restricted maximum likelihood method [30]. The between study heterogeneity was evaluated using the Cochran Q test, the Tau-squared, the H-Squared statistics and the I-Squared statistics [31]. The funnel plots, the regression-based Egger's [32] and the nonparametric rank correlation based Begg's tests [33] were used to explore the

presence of small-study effects which are often associated with publication bias. No "trim and fill" was conducted since there was no publication bias [34]. The common effect sizes were calculated as Odds Ratios (ORs) and their 95% confidence interval (CI) for each main outcome. The results were presented by forest plots reporting both the individual effect sizes and the overall effect size (ES), their confidence intervals (CIs), heterogeneity statistics, and the test of significance for the ES. Additionally, predetermined subgroup analyses were conducted by type of abortion.

3. Results

A total count of 2127 publications was obtained from the initial search. As the PRISMA flow chart shows (Fig. 1), 107 articles were evaluated after the initial screening process and 18 studies were systematically reviewed. The characteristics of the totality of the studies systematically reviewed are shown in Table 1. These studies included 7 cohort studies [35–41], 2 clinical trials [42,43], 3 case reports [44–46], and 6 case series [47–52]. Four studies were performed on women at risk for preeclampsia or those with it [42–44,47], and one study on pregnant women with antiphospholipid syndrome refractory to antithrombotic therapy [35]. Statins included atorvastatin, simvastatin, lovastatin, pravastatin, cerivastatin, fluvastatin, and rosuvastatin. Three studies were conducted in the United States [42,48,51] and the United Kingdom [40,43,50], two in Canada [37,39], and one in South Africa [36], Japan [47], India [46], Germany [45], Norway [38], Greece [35], Serbia [52], and Poland [44]. Manson and Winterfeld's studies [41,49] were multinational. The studies were published between 1996 and 2019.

3.1. Results of quality assessment

The quality of the cohort studies that were critiqued with the NIH instrument was fair to good (28.6% had the fair quality and 71.4% had good quality). Both clinical trials were of good quality. They scored on most of the domains of the Cochran's appraisal instrument but did not provide any data on the concealment of the randomization.

3.2. Results of the meta-analysis

Nine studies were meta-analyzed. Five studies were applied for the effect of statin exposure in pregnancy on rate of stillbirth (involving 2350 women), six studies (11 arms) on fetal abortion (involving 8422 women), and 4 studies on rate of preterm delivery (involving 483 women).

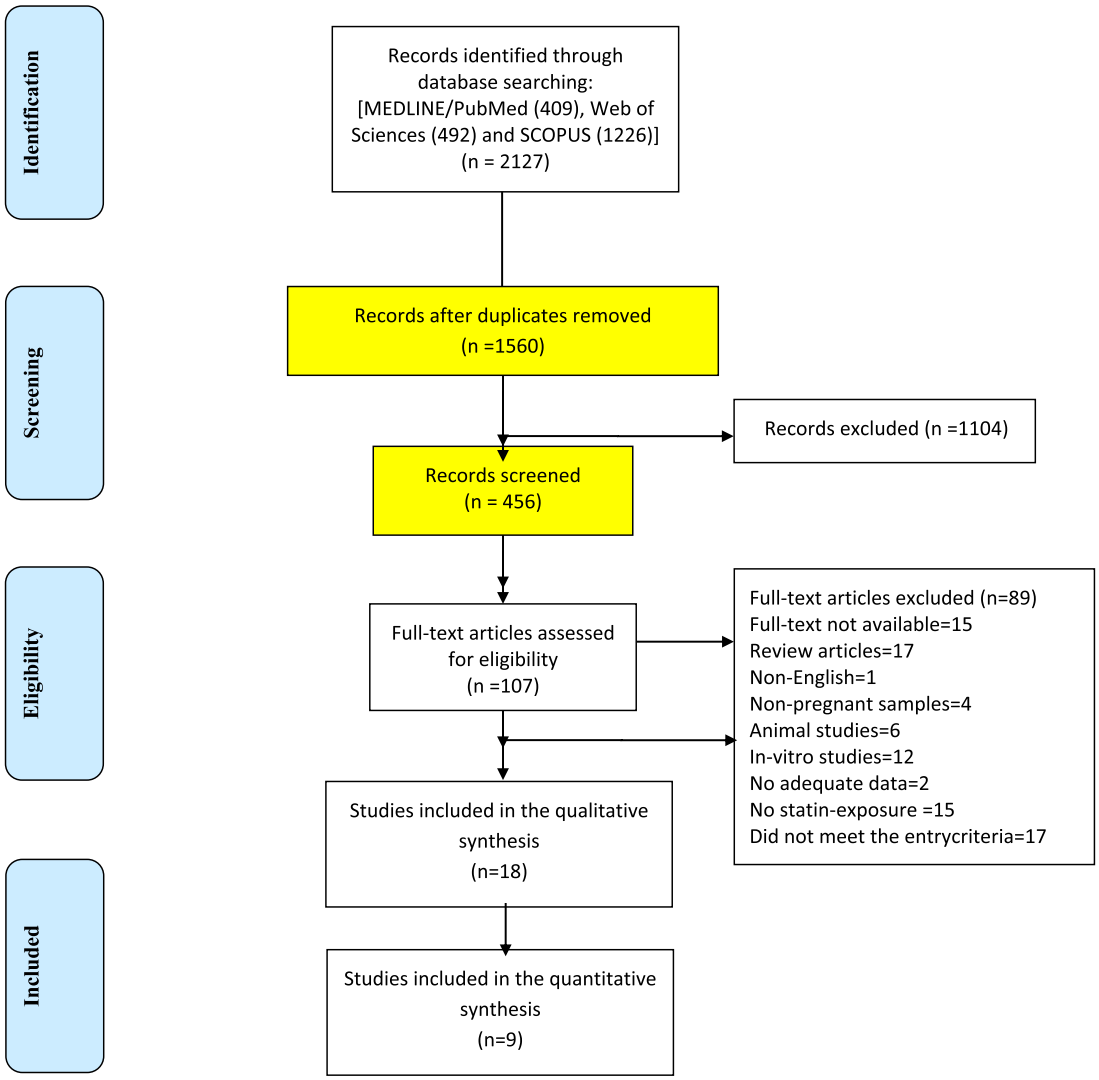


Fig. 1. PRISMA flow chart of inclusion and exclusion.

Table 1
Characteristics of the included studies.

First author, (year)	Country	Type of study	Population (number of subjects)	Statin exposure	Control	Trimester	Outcomes
Ahmed, A (2020) [43]	United Kingdom	Randomized controlled trial	62 pregnant women with early-onset preeclampsia	30 women used pravastatin	32 women used placebo	Second and third	No significant differences between groups in factors associated with the severity of preeclampsia Duration of pregnancy following randomization was the same in the two groups There were no serious adverse reactions considered attributable to statin
Botha, T.C (2018) [36]	South Africa	Cohort	39 pregnancies with homozygous familial hypercholesterolaemia	18 women exposed to statin. The most common statins used was atorvastatin	21 women used no statin	Before conception, first and second trimesters	There were no statistical differences in the rate of elective cesarean, abortion, congenital malformations, and birth weight between the statin exposed and unexposed groups The preterm delivery rate was 11.1% in the statin group *vs.* 4.7% in the control group
Brownfoot, F·C (2015) [47]	Japan	Case series	4 pregnant women affected by preeclampsia at 23–30 weeks of gestation	Pravastatin (n = 4)	None	Second and third	Pravastatin decreased maternal serum sFlt-1 levels and stabilized blood pressure, proteinuria, and serum uric acid levels There were no obvious statin-related side effects There was no neonatal death
Costantine, M.M (2016) [42]	United States	A pilot randomized controlled trial	20 women at high risk for preeclampsia	10 women used daily pravastatin	Placebo (n = 10)	Second and third	Four subjects in the placebo group developed preeclampsia (with 3 of 4 having a severe disease) compared with none in the pravastatin group There were no significant differences between two groups in the mean of birth weight of neonates, rate of maternal, fetal, or infant death, and neonatal respiratory distress syndrome The rate of preterm delivery in the statin group was 10% *vs.* 50% in the control group
Edison, R.J (2004) [48]	United States	Case series	Pregnant women with statin exposure during pregnancy	178 women who used cerivastatin, simvastatin, lovastatin, atorvastatin	No control	First	There were 46 elective and 42 spontaneous abortions, 15 pregnancy losses due to maternal illness, 3 fetal genetic disorders, and 5 transient neonatal disorders
Jurisic, A (2018) [52]	Serbia	Case series	Five twin pregnant women with abnormal umbilical artery dopplers	Pravastatin and L-arginine from 23 weeks of gestation until the end of the pregnancy	–	Second and third	There was a significant improvement in the umbilical artery blood flow two weeks after onset of treatment There was a significant weight gain in all fetuses No cases of fetal death were reported Pregnancies survived 9 weeks after the first time that abnormal umbilical artery blood flow was detected

(*continued on next page*)

Table 1 (*continued*)

First author, (year)	Country	Type of study	Population (number of subjects)	Statin exposure	Control	Trimester	Outcomes
Kozłowski, S (2017) [44]	Poland	Case report	An obsessed preeclamptic woman with four previous pregnancy losses and with a history of chronic hypertension, hypothyroidism, polycystic ovarian syndrome, with insulin resistance	Pravastatin from 17 weeks of gestation until delivery	–	Second and third	Increased pulsatility index in the umbilical artery was found at 33 weeks of gestation There were fetal growth restriction and decreasing volume of amniotic fluid at 33 weeks of gestation
Lefkou, E (2016) [35]	Greece	Cohort	21 pregnant women with antiphospholipid syndrome who developed preeclampsia and/or intrauterine growth restriction during treatment	11 subjects used pravastatin in addition to aspirin and heparin	Aspirin and heparin (n = 10)	Not clearly reported	There was an improvement in maternal blood pressure, uterine artery blood flow, duration of pregnancy after the initial diagnosis, neonatal outcomes, and neonatal survival rate 30% stillbirth was found in the control group *vs.* 0% in the statin group There was 100% preterm delivery in the control group *vs.* 27.2% in the statin group
Manson, J.M (1996) [49]	Multinational study (12 countries)	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	There was no relationship between exposure to statins during pregnancy and the occurrence of adverse pregnancy outcomes such as spontaneous abortion, elective abortion, fetal death/stillbirth, and miscellaneous adverse outcomes
McElhatton, P (2008) [50]	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 were 18 live-born, 2 neonatal problems, 5 spontaneous abortions, and 2 elective terminations of pregnancy
McGrogan, A (2017) [40]	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 conception and/or during the first trimester	The rate of induced abortion in the control group was higher than in the statin group (0.68% *vs.* 0.36%) and the rate of spontaneous abortion in the statin group was higher than in the control group (25% *vs.* 20%) The rate of stillbirth in the statin group was higher than in the control group (2.6% *vs.* 1.6%)
Ofori, B (2007) [39]	Canada	Cohort	259 women prescribed statins during or before pregnancy	153 women exposed to atorvastatin, pravastatin, and simvastatin during pregnancy	106 women exposed to statins between a year before and a month before pregnancy	First trimester	21% of induced abortions occurred in the statin exposure group compared to 10% in the control group 34% of miscarriage/ stillbirth/unspecified abortion occurred in the statin exposure group compared to 27% in the control group
Otten, L.A (2017) [45]	Germany	Case report	A 40 year old pregnant with a 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	The course of pregnancy was uncomplicated, and a healthy appropriate for gestational age neonate was delivered at term
Pollack, P.S (2005) [51]	United States	Case series	477 reports of exposure to statins during pregnancy	386 prospective and 91 retrospective	–	First trimester exposure was	Pregnancy consequences such as miscarriage, congenital anomalies in

(*continued on next page*)

Table 1 (*continued*)

First author, (year)	Country	Type of study	Population (number of subjects)	Statin exposure	Control	Trimester	Outcomes
				reports of exposure to simvastatin and/or lovastatin		reported in 162 subjects	the statin group and the general population were not different
Singh, N (2013) [46]	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	At week of 36, a cesarean was performed due to a Bishop score of 4 and a healthy neonate was born
Taguchi, N (2008) [37]	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 were no differences in the rate of spontaneous and therapeutic abortions, and stillbirths between the statin group and the comparison group Neonatal birth weights were lower in the statin group (p=0.01)
Toleikyte, L (2011) [38]	Norway	Cohort	1093 familial hypercholesterolemia women with 2319 births	16 cases used a statin during pregnancy. The type of statins was not mentioned	General population (n = 2304067)	Not mentioned	The frequency of prematurity and birth weights did not change significantly from the period before (years 1979–1991) to the period after (years 1992–2006) statin introduction among the study population
Winterfeld, U (2013) [41]	Multinational (11 centers in Europe)	Cohort	598 pregnant women	249 pregnant women who used simvastatin (n = 124), atorvastatin (n = 67), pravastatin (n = 32), rosuvastatin, (n = 18), fluvastatin (n = 7), and cerivastatin (n = 1)	249 pregnant women used no statins	First trimester in 86% of cases	No difference was found in the birth weight between the statin-exposed and the control groups (p= 0.95) Premature birth (p= 0.019) and miscarriage or fetal death (p=0.016) were more frequent in exposed pregnancies

3.3. Effect of statin exposure in pregnancy on stillbirth rate

3.3.1. Common effect size

The OR from 5 studies was 1.30 (95% CI = 0.56 to 3.02, p=0.54) based on a random effect model, with non-significant heterogeneity between studies ($\tau^2 = 0.0$, $I^2 = 00.0\%$, $H^2 = 1.0$, $Q_{(df=4)} = 4.66$, $p_Q = 0.32$) (Fig. 2A shows the forest plot of individual effect sizes within each study).

3.3.2. Bias assessment

Assessment for bias by Egger's test (p=0.249) and Begg's (p=0.147) test showed no significant small-study effects. Further visual inspection of the funnel plot suggested no publication bias (Fig. 2B). Therefore, we did not extend the results of the analyses for nonparametric "trim and fill" method of accounting for publication bias.

3.4. Effect of statin exposure in pregnancy on type and rate of fetal abortion

3.4.1. Common effect size

The OR from six studies (11 arms) was 1.37 (95% CI = 1.15 to 1.65, $p < 0.001$) based on a random effect model, with non-significant heterogeneity between studies ($\tau^2 = 0.0$, $I^2 = 43.0\%$, $H^2 = 1.0$, $Q_{(df=10)} = 10.16$, $p_Q = 0.43$) (Fig. 3A shows the forest plot of individual effect sizes within each study).

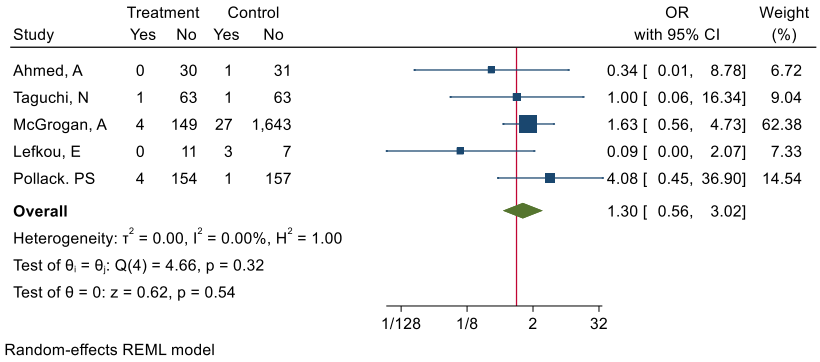
3.4.2. Bias assessment

Assessment for bias by Egger's test (p=0.385) and Begg's (p=0.640) test showed no significant small-study effects. Further visual inspection of the funnel plot suggested no publication bias (Fig. 3B). Therefore we did not extend the results of the analyses to nonparametric "trim and fill" method of accounting for publication bias.

3.5. Subgroup analysis

The forest plot of individual ORs of the predetermined subgroup analysis by type of abortion is presented in Fig. 4. The results indicate a non-significant effect in the induced abortion type [OR (95% CI) = 2.08 (0.81, 5.36)] and in the elective abortion type [OR (95% CI) = 1.37 (0.68, 2.76)], but a significant effect in induced abortion type [OR (95% CI) = 1.36 (1.10, 1.68)], so that the test assessing subgroup differences showed a non-significant difference among subgroups ($Q_{(df=2)} = 0.74$, $p_Q = 0.69 > 0.05$). Additionally, no significant heterogeneity was observed among subgroups (all $p > 0.05$).

A



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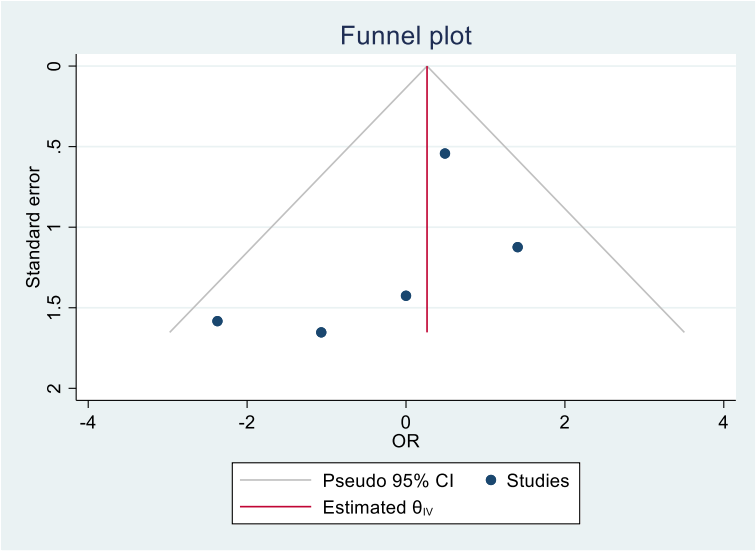


Fig. 2. (A) Forrest plot for odds ratio of statin exposure in pregnancy on rate of stillbirth. (B) Funnel plot for publication bias of statin exposure in pregnancy on rate of stillbirth.

3.6. Effect of statin exposure in pregnancy on rate of preterm delivery

3.6.1. Common effect size

The OR from 4 studies was 0.47 (95% CI = 0.06 to 3.70, p=0.47) based on a random effect model, with non-significant heterogeneity between studies ($\tau^2 = 3.20$, $I^2 = 76.35\%$, $H^2 = 4.23$, $Q_{(df=3)} = 12.0$, $p_Q = 0.01$) (Fig. 5A shows the forest plot of individual effect sizes within each study).

3.6.2. Bias assessment

Assessment for bias by Egger's test (P=0.178) and Begg's (P=0.064) test showed no significant small-study effects. Further visual inspection of the funnel plot suggested no publication bias (Fig. 5B). Therefore, we did not extend the results of the analyses to nonparametric "trim and fill" method of accounting for publication bias.

3.7. Other outcomes

3.7.1. Influence on birth weight

Based on the data from four studies, we did not observe any significant difference in birth weight between neonates of statin exposure and the control groups [36,38,41,42]. However, in the study by Taguchi et al., the neonatal weight in the statin group was 3140 ± 680 gr and in the control group was 3450 ± 420 gr (p=0.01) [37]. In the study by Lefkou et al., the median of birth weight in the statin and control groups was 2390 gr and 900 g, respectively. It should be noted that all subjects who took statins delivered at 36 weeks or later, while in the control group 100% of deliveries occurred preterm [35]. In Botha's study, two premature infants in the statin exposure group had low birth weight (2400 gr) [36].

3.7.2. Effect on the risk of preeclampsia

In a case series on five twin pregnant women with abnormal umbilical artery Dopplers, who took pravastatin and L-arginine from the 23rd week of gestation, a significant improvement in the umbilical artery blood flow was found two weeks after onset of treatment. Pregnancies survived 9 weeks after the first time that abnormal umbilical artery blood flow was detected [52]. Increased pulsatility index in the umbilical artery was found in a preeclamptic woman who used pravastatin from the 17th week of gestation to delivery [44]. There was an

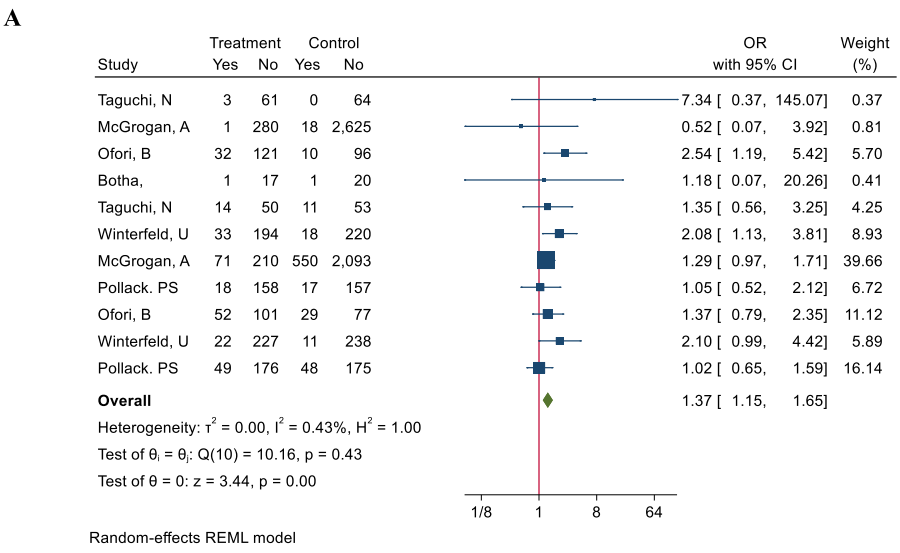


Fig. 3. (A) Forrest plot for odds ratio of statin exposure in pregnancy on overall fetal abortion. (B) Funnel plot for publication bias of statin exposure in pregnancy on fetal abortion.

improvement in maternal blood pressure and uterine artery blood flow when pravastatin was added to aspirin and heparin in the treatment of pregnant women with antiphospholipid syndrome, who developed preeclampsia and/or intrauterine growth restriction [35]. Otten et al. reported an uncomplicated course of pregnancy in a 40-year old pregnant woman with a history of severe recurrent early-onset HELLP syndrome, who used pravastatin at 13 weeks of gestation until delivery [45]. In another case report in India, a pregnant woman with familial hypercholesterolemia and cardiomyopathy, who used a statin until week 24 of an unplanned pregnancy, delivered a healthy neonate at week 36 [46]. Ahmed et al. reported no significant differences in factors associated with the severity of preeclampsia between statin exposure and control groups. Preeclamptic women who used pravastatin had a similar length of pregnancy compared with the control group [43]. In a case series on 4 pregnant women with preeclampsia presenting at 23–30 weeks of gestation, pravastatin decreased maternal serum sFlt-1 levels and stabilized blood pressure, proteinuria, and serum uric acid levels [47].

4. Discussion

In this systematic review and meta-analysis, we evaluated the effects of statins on three major outcomes related to pregnancy, that is abortion (i.e., pregnancy interruption before the 20th week), stillbirth (i.e., death of fetus after the 20th week of pregnancy or during delivery), and preterm delivery (i.e., labor before the 37th week of pregnancy). Another important outcome of pregnancy that is affected by the use of statins is preeclampsia, which has already been fully discussed and therefore will not be mentioned here [53].

In line with results of previous studies [18–21], our pooled analysis shows that statin exposure is associated with an increased rate of unspecified abortion. In addition, in the subgroup analysis by type of abortion, it emerges a significant association between statin therapy and spontaneous abortion.

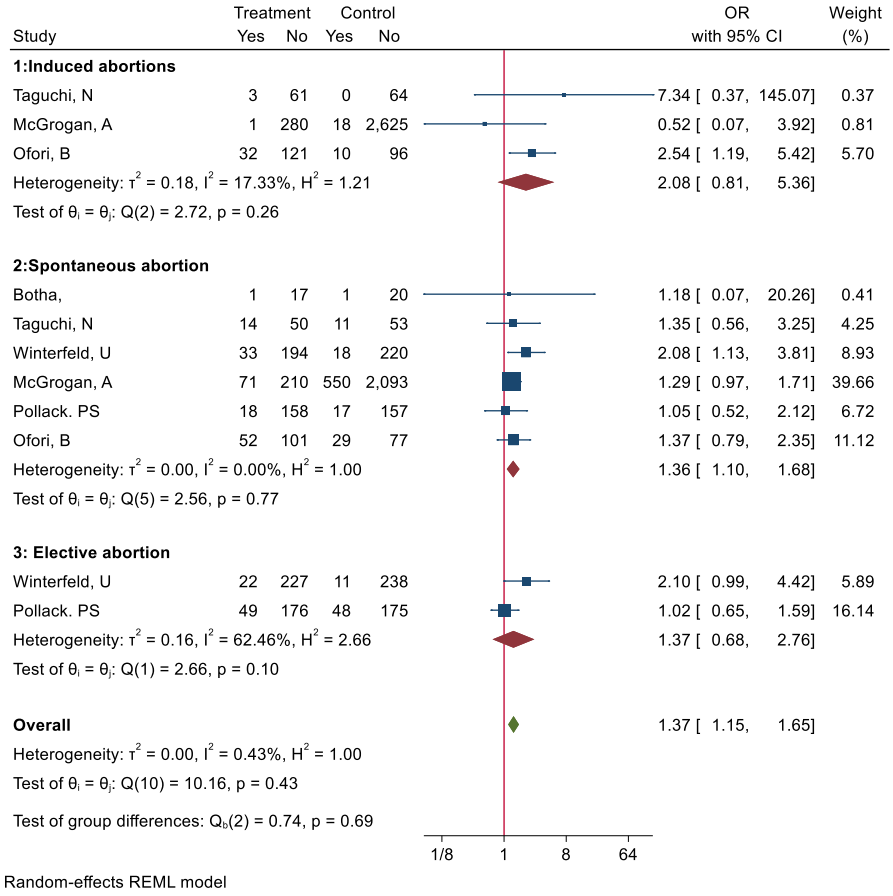


Fig. 4. Forrest plot for odds ratio of statin exposure in pregnancy on type and rate of fetal abortion.

Overall, these results strongly suggest the notion that statin therapy may have an unfavorable impact on the early phases of gestation. Nonetheless, some caution is needed in interpreting the observed effect size of statin exposure on abortion, either unspecified or spontaneous, for different reasons. First, most of the studies included both in the pooled analysis and in the spontaneous abortion-restricted analysis were observational studies [35–37,39–41], which may have the intrinsic limitation of the lack of appropriate and well-balanced comparator groups. Second, the study participants of some of the included studies cannot be considered representative of the general population of pregnant women. Thus, for instance, in some studies participants had medical conditions (*i.e.*, antiphospholipid syndrome, hypercholesterolemia, high risk of preeclampsia), which may themselves influence pregnancy outcomes [54–56]. Third, it cannot be excluded that statin use in the early phase of pregnancy may be a proxy of the coexistence of clinical conditions (*e.g.*, older age, cardiovascular risk factors) exposing women to a higher risk of abortion [57–60]. Thus, as to whether the observed association between statins and abortion may be in part attributed to the underlying medical conditions rather than to statins may be a matter of debate.

Noteworthy, in the subgroup analysis by type of abortion, a non-significant trend emerges towards a direct association between statin exposure and either induced or elective abortion (*i.e.* planned pregnancy termination due to medical/non-medical and non-medical reasons, respectively). This results suggests that statin therapy may influence, albeit non-significantly, the occurrence of intentional pregnancy interruption.

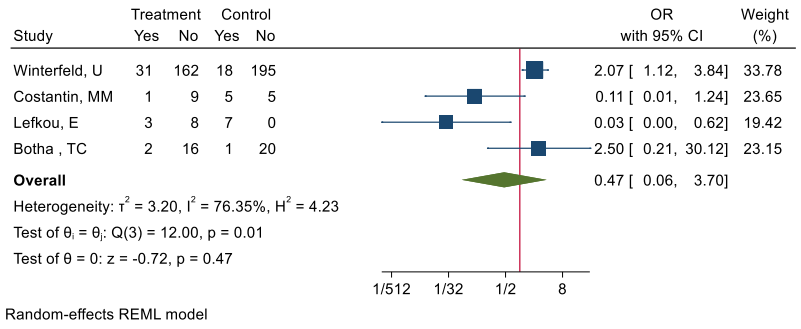
Our results also show that statin use is associated with a trend toward an increase of stillbirth rate, albeit not significant. By definition, stillbirth is a late-occurring event in pregnancy. Therefore, it might further support the notion that the deleterious effects of statins on pregnancy is restricted to the early gestational phases. However, it cannot be excluded that statin exposure restriction to the premature phases of gestation (i.e., pre-conception period and first trimester) in most of the pooled studies may mask a possible detrimental impact of statins on stillbirth [37,40,51]. In order to verify this hypothesis, it would be useful to evaluate results from clinical trials in which statin exposure occurs for all the pregnancy duration. However, such studies would not be ethical. Thus, it is unlikely that a better level of evidence would ever be reached on this issue.

Finally, a non-significant trend toward a decrease of preterm delivery in statin-treated women emerges in our study. Based on this result, a possible protective action of statins against preterm delivery cannot be excluded. Supporting this notion, emerging evidence from preclinical studies suggests a significant statin-mediated activity against pathophysiological mechanisms leading to preterm delivery [26,61]. Particularly, it has been speculated that statins, due to their pleiotropic effects, may reduce the risk of early labor by counteracting cervical remodeling and myometrial cell contraction [26,61].

Regarding the relationship between statin exposure during pregnancy and birth weight, great variability emerges from available studies, which does not allow to draw any conclusion. Instead, evidence from one cohort study, one randomized controlled trial, and one case series suggests a neutral or even protective impact of statins against pre-eclampsia [35,43,47].

As a limitation of the present study, no subgroup analyses were performed according to statin type. Nonetheless, it is conceivable that hydrophilic statins are less prone to affect cholesterol biosynthesis in the fetus, as compared to lipophilic ones [20]. Indeed, hydrophilicity may prevent statin transfer across membranes, including the placenta [20].

A



B

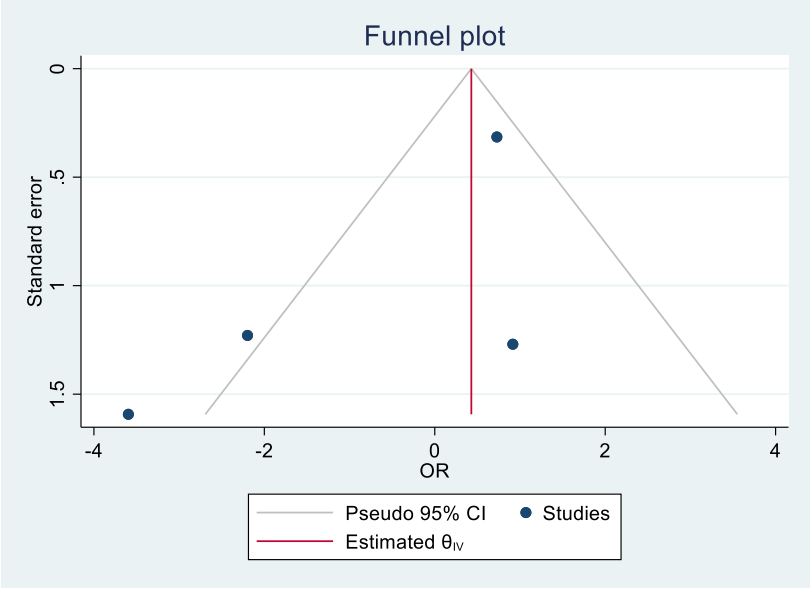


Fig. 5. (A) Forrest plot for odds ratio of statin exposure in pregnancy on rate of preterm delivery. (B) Funnel plot for publication bias of statin exposure in pregnancy on rate of preterm delivery.

Thus, it remains an open question as to whether the observed results could be generalizable to the entire drug class or not.

In conclusion, statin therapy seems to be safe as it was not associated with the stillbirth as well as induced and elective abortion rates. Significant increase after statin therapy was however observed for spontaneous abortion. These results needs to be further confirmed and validated in future studies in order to finally establish whether statin therapy might be useful in some strictly selected pregnant women patients, for whom potential benefit outweight the risk.

Author contributions

AV, AS and MB conceived and designed the study. VB, SM, SMM and MP were involved in preparing the initial draft. AVA, MB and AS critically revised the final version. All authors approved the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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