Selective Serotonin Reuptake Inhibitors (SSRIs) and the Risk of Congenital Heart Defects: A Meta-Analysis of Prospective Cohort Studies

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Background—Recent studies have reported conflicting results on the association between selective serotonin reuptake inhibitors (SSRIs) and the risk of heart defects. We aimed to assess the association between SSRIs in pregnant women during the first trimester and the risk of congenital heart defects.

Methods and Results—PubMed and EMBASE up to July 2014 were searched for population-based cohort studies that reported SSRIs in pregnant women during the first trimester and live infants' heart defects at follow-up. A meta-analysis of published data was undertaken primarily by means of fixed-effects models. Four cohort studies including 1 996 519 participants were included with a mean follow-up period ranging from discharge to 72 months. SSRIs were not associated with increased risks of heart defects 1.06 (95% confidence interval: 0.94 to 1.18).

Conclusions—SSRIs during the first trimester in pregnant women were not associated with increased risks for newborn heart defects. (*J Am Heart Assoc*. 2015;4:e001681 doi: 10.1161/JAHA.114.001681)

Key Words: antidepressant • congenital • heart defects • meta-analysis • pregnant • SSRIs

D epression affects up to 15% of pregnant women.[1] Selective serotonin reuptake inhibitors (SSRIs) were the most commonly prescribed antidepressant drugs during pregnancy.[2] In 2005, considering its risk for heart defects, the use of paroxetine during pregnancy was warned by the U.S. Food and Drug Administration.[3] However, recent studies have reported conflicting results on the association between SSRIs and the risk of heart defects. Some studies reported a positive association,[4–6] whereas most studies reported no association.[7–11] Moreover, A recent large epidemiological study by Huybrechts et al. in 949 504 pregnant women revealed that

SSRI use was positively associated with heart defects in unadjusted analysis, but the correlation turned to be nonsignificant in the fully adjusted analysis restricted to women with depression.[12] The discrepancy may be owing to varying sample size, diagnostic criteria for congenital heart defects, follow-up duration, and confounders in the studies. Whether SSRIs in pregnant women during the first trimester were associated with congenital heart defects has not reached consensus.

We hypothesized that SSRI use would not be associated with an increased risk of infants' cardiac malformations. Therefore, we performed a meta-analysis of cohort studies to investigate the relationship between SSRI use in pregnant women during the first trimester and the risk of congenital heart defects.

Methods

Guidelines

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses framework guidelines.[13]

Studies' Eligibility Criteria

Articles were considered for inclusion in this meta-analysis if: (1) the authors reported data from an original, peer-reviewed

study; (2) the study was a population-based cohort study consisting of pregnant women who took SSRIs during the first trimester; (3) the outcome was cardiac malformations in the offspring; (4) adjusted relative risk (RR) or adjusted odds ratio (OR) of the SSRIs mother of having a newborn with congenital heart defects was available, if more than 2 OR values were stated in the study, the OR most related to the study main conclusion was selected; and (5) the study was the most relevant and most recent if subjects/populations overlapped. Exclusion criteria were: (1) animal studies; (2) case report, books, comments, letter to the editor, cross-sectional studies, randomized, control clinical trial, longitudinal case-control comparative studies, or population-based cohort study in liveborn children whereas information on pregnant women could not be retrieved; (3) no or insufficient data including OR or adjusted OR value could not be retrieved, combined data of first trimester with other trimesters, and combined data of all congenital malformations without separate data of congenital heart defects; (4) the same data overlapped another eligible larger or more recent study; and (5) non-English publications. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Search Method

Published studies were identified through a computer-based search (up to July 16, 2014) of PubMed and EMBASE for relevant literatures on the associations between antidepressant and heart defects by using a combination of terms: ("Serotonin Uptake Inhibitors"[Mesh] OR "selective serotonin uptake inhibitors"[tiab] OR "selective 5-HT uptake inhibitors"[tiab] OR "paroxetine"[tiab] OR "sertraline"[tiab] OR fluoxetine[tiab] OR citalopram[tiab] OR fluvoxamine[tiab] OR escitalopram[tiab]) AND ("Heart Defects, Congenital"[Mesh] OR "cardiac defect*" [tiab] OR "congenital malformation*"[tiab] OR "cardiac malformation*" [tiab] OR "heart defect*" [tiab] OR "birth defect*" [tiab] OR "congenital heart disease*"[tiab] OR outcome* [tiab]) AND (pregnancy[tiab] OR pregnant[tiab]). In addition, PubMed option "Related Articles" was used, and the references of identified studies were reviewed to search for potentially relevant articles. Only articles published in the English language were considered.

Data Extraction, Evaluation, and Synthesis

Two reviewers (S.W. and L.Y.) independently reviewed the abstracts and titles identified by the database searches and together decided which articles should be retrieved. These retrieved articles were reviewed by both authors to identify eligible studies. Discrepancies were resolved by the third reviewer (L.W.). Reviewers were not blinded to study authors

and results. All data were independently abstracted in duplicate by means of a standardized data collection form. We also contacted authors to request additional information. The following information was extracted from the eligible articles: study characteristics (study title, authors, year of publication, journal, study site, follow-up duration, and sample size); demographic characteristics (mean age or age range); number of subjects with SSRIs and no antidepressant use or no SSRIs use; infants' heart defects; diagnosis criteria for heart defects; and covariates included in the models.

Quality assessment was performed with the Newcastle-Ottawa Assessment Scale for Cohort Study; a study with at least 8 stars was considered to be a high-quality study.

Statistical Analysis

Adjusted OR was used to evaluate the relationship of SSRIs with heart defects. Heterogeneity across studies was evaluated by means of Q and I^2 statistics.[14] $I^2 \geq 50\%$ was considered as significant heterogeneity. We calculated the pooled risk estimates using either fixed-effects models or, in the presence of heterogeneity, random-effects models. Weights for the pooled analysis were derived from the Mantel-Haenszel method.

Because characteristics of cohorts, diagnostic criteria for congenital heart defects, and adjustments for confounding factors were not consistent among studies, we further performed sensitivity analysis to explore possible explanations for heterogeneity and examine how the various exclusion criteria affect the overall results. We also evaluated the influence of a single study on the overall risk estimate by deleting each study in turn.

The potential for publication bias was investigated using visual assessment of the funnel plot. Given that publication bias may lead to asymmetrical funnel plots,[15] we visually assessed publication bias based on funnel plots with a study number ≥ 5.

We used STATA 12.0 (StataCorp LP, College Station, TX) for the statistical analyses and considered $P < 0.05$ as statistically significant.

Results

Study Selection

The search process is presented in Figure 1. A total of 384 potentially relevant citations were initially identified. After the first-round screening based on titles and abstracts, 18 articles were included for further evaluation. After examining those articles in more detail, 14 articles were excluded. In total, 4 articles were included into the meta-analysis.
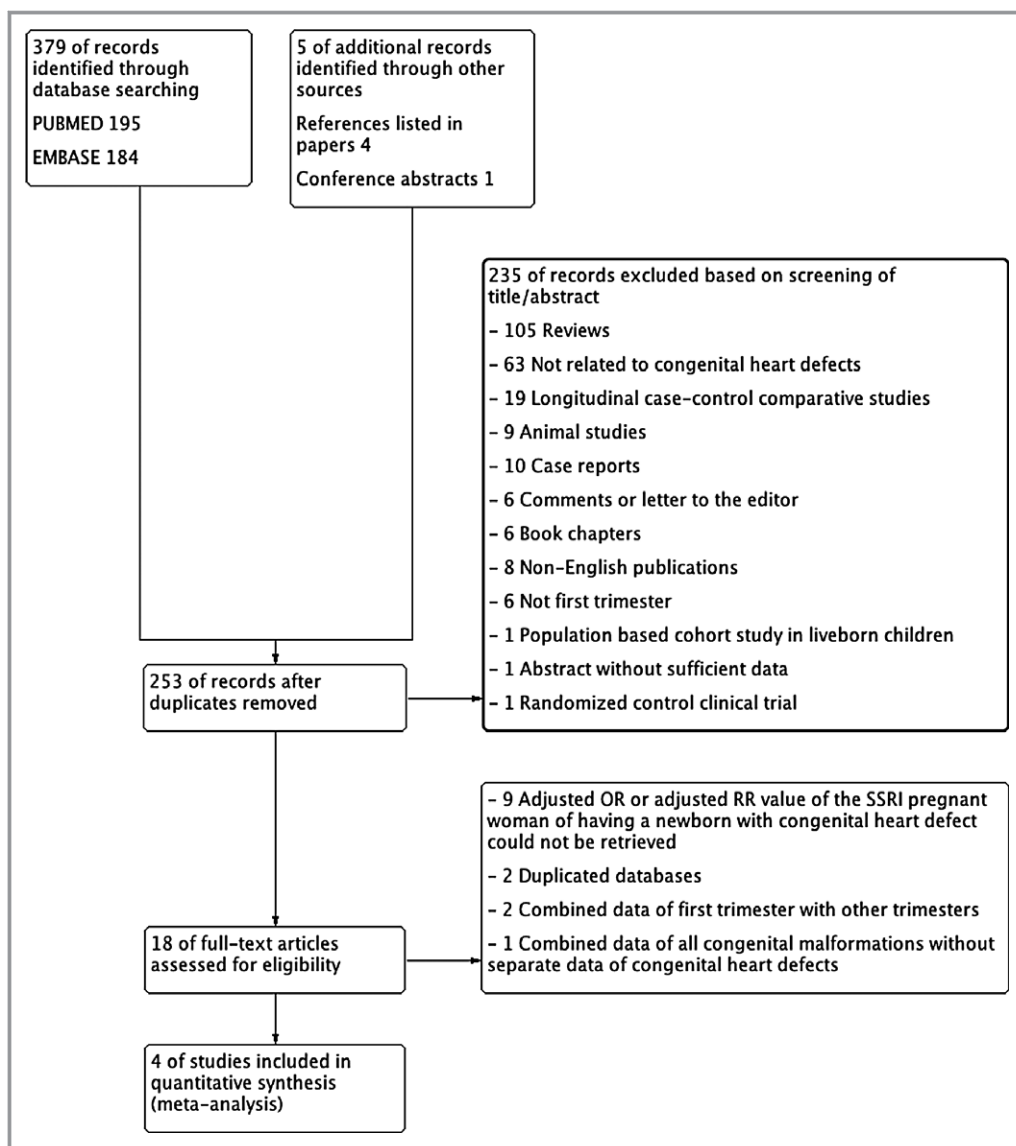
Figure 1. Flow chart of study selection. OR indicates odds ratio; RR, relative risk; SSRI, selective serotonin reuptake inhibitor.

Study Characteristics

Characteristics of the selected studies are shown in Table 1. Of the 4 studies, 2 were conducted in Europe, 1 in the United States, and 1 in Australia.

The total number of pregnant women included in this meta-analysis was 1 996 519, ranging from 63 395 in the smallest study to 949 504 in the largest study. The diagnosis of heart defects was based on the International Classification of Diseases (ICD)-9 in 2 studies and the ICD-10 in 1 study. Follow-up duration for diagnosis of heart defects was reported in all studies, ranging from discharge after delivery to 6 years after delivery. Three studies retrieved data from electronic medical records and 1 study used self-administrated

questionnaires for SSRIs use. Three studies defined exposure as any SSRI use in gestational week 0 to 4, and only 1 study defined exposure of SSRI from 14 to 104 days after last menstrual period, or to the end of the pregnancy event. Two studies defined nonexposure as no SSRI use during the first trimester, whereas 1 study defined nonexposure as no antidepressants in the 6 months before or during pregnancy, and 1 study defined nonexposure as no use of any antidepressant in the first trimester. Regarding types of cardiac malformations included in the studies, 2 studies excluded minor defects and anomalies related to prematurity, whereas another 2 studies included all cardiac malformations. All studies included citalopram, fluoxetine, paroxetine, sertraline, escitalopram, and fluvoxamine in the analyses. Only 1 study

Table 1. Summary of the Included Studies

Source	Colvin et al[4]	Huybrechts et al[12]	Kallen and Otterblad Olausson[16]	Nordeng et al[17]
Study Participants	Pregnant women in Australia	Pregnant women in USA	Pregnant women in Swedish	Pregnant women in Norway
Sample size	123 405	949 504	873 876	63 395
Years covered	2002–2005	2000–2007	July 1, 1995–2004	1999–2005
Mean/median age of mothers, y	30	25	No mean reported	No mean reported
Diagnosis of heart defects	ICD-9	ICD-9	ICD, but no information on the version	ICD-10
Follow-up duration	Six years after delivery	The first 90 days after delivery	Discharge after delivery	Discharge after delivery
Definition of exposure	Any SSRI dispensed from 14 days to 104 days after last menstrual period, or to the end of the pregnancy event	At least one prescription for any SSRI from the date of last menstrual period through day 90 of pregnancy	Any SSRI use in early pregnancy up to the first antenatal visit (in 90% before the end of week 12)	Any SSRI use in gestational week 0 to 4
Definition of non-exposure	No SSRI dispensed from 14 days to 104 days after last menstrual period, or to the end of the pregnancy event	No use of any antidepressant in the first trimester	No SSRI use in early pregnancy up to week 12	No reported use of any antidepressants in the 6 months before or during pregnancy
Types of cardiac malformations included	Major cardiac defects, muscular ventricular septal defects and small arterial septal defects were excluded	Any cardiac malformations but anomalies related to prematurity (e.g., patent ductus arteriosus, pulmonary-valve stenosis, and anomalies of the pulmonary artery in preterm infants)	Ventricular septal defects and/or atrial septal defects, endocardial cushion defects, tetralogy of Fallot, coaractation of the aorta, pulmonary artery stenosis, pulmonary valve stenosis, and an unspecified defects in cardiac septa	All cardiovascular malformations classified with ICD-10 code Q20 to 28
Individual drugs included	Citalopram, fluoxetine, paroxetine, sertraline, escitalopram and fluvoxamine	Citalopram, fluoxetine, paroxetine, sertraline, escitalopram and fluvoxamine	Fluoxetine, citalopram, paroxetine, sertraline, escitalopram and fluvoxamine	Citalopram, fluoxetine, paroxetine, sertraline, escitalopram and fluvoxamine
Whether elective terminations and stillbirths were included	No	No	No	Yes
Controlled variables	Gestation age	Sociodemographic information, known or suspected risk factors for congenital heart defects, and chronic maternal illness, multiple gestation, and use of other psychotropic medications, etc.	Year of birth, maternal age, parity, smoking and more than or equal to 3 previous miscarriages	Maternal depression, maternal age at delivery, parity, and use of psychotropic drugs during pregnancy
Conclusion	SSRIs were associated with cardiovascular defects.	No substantial increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester. (The results extracted correspond to a sub-analysis in women with depression)	SSRIs were not associated with an increased risk of cardiovascular defects.	Exposure to SSRIs during the first trimester was not associated with increased risk of cardiovascular malformations.

Table 2. Quality of the Studies Included in the Meta-analysis

Study	Selection				Comparability		Outcomes	
	Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Exposure	Demonstration That Outcome Was Not Present at Start of Study	Comparability of Cohorts	Assessment of Outcome	Was Follow-up Long Enough (≥1 Year)	Adequacy of Follow-up Cohorts
Colvin et al.[4]	★	★	★	★	★	★	★	★
Huybrechts et al.[12]	★	★	★	★	★★	★	—	★
Kallen and Otterblad Olausson[16]	★	★	★	★	★★	★	—	★
Nordeng et al.[17]	★	★	★	★	★★	★	—	★

included elective terminations and stillbirths. The studies varied with regard to controlled variables in the multivariate models; 1 study only controlled for the gestation age.

Risk of Bias in Included Studies

Quality of the studies included in the meta-analysis was high; all had 8 stars (Table 2). Three studies' follow-up durations were not long enough (>1 year); 1 study was 90 days, whereas the other 2 studies were followed up to discharge after delivery. Overall, the risk of bias of the included population-based cohort studies was low.

SSRIs and the Risk of Heart Defects

Three studies reported no association between SSRIs and the risk of congenital heart defects, whereas 1 study reported a

positive association. The pooled adjusted OR was 1.06 (95% confidence interval [CI], 0.94 to 1.18) with no significant heterogeneity (I^2=27.9%; P=0.244; Figure 2).

Stratifying Analysis

In the subgroup analyses by individual SSRIs, no significant association was found between the risk of heart defects and the individual SSRIs (Table 3).

Dosage of SSRIs and the Risk of Heart Defects

One study reported that increased SSRI dose was not associated with an increased risk of heart defects. The adjusted ORs for heart defects were 1.10 (95% CI, 0.83 to 1.46), 1.12 (95% CI, 0.93 to 1.34), and 0.96 (95% CI, 0.69 to 1.35) in low-, medium-, and high-dose groups, respectively.
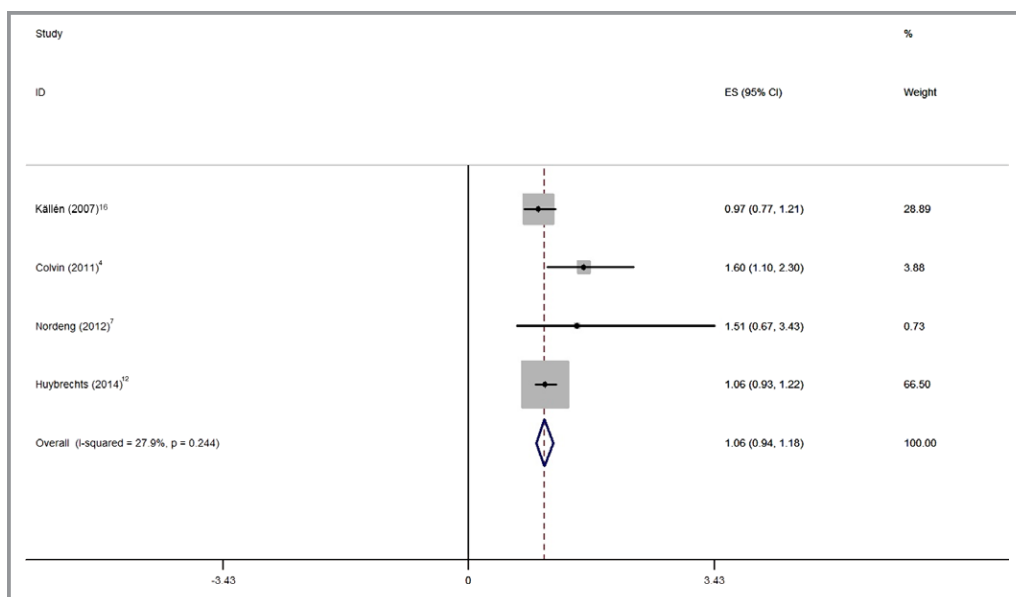

Figure 2. Association between selective serotonin reuptake inhibitors in pregnant women during the first trimester and the risk of congenital heart defects. References: Källén et al. (2007)[16], Colvin et al. (2011)[4], Nordeng et al. (2012)[17], Huybrechts et al. (2014)[12]. CI indicates confidence interval; ES, effect size.

Table 3. Stratification Analysis According to Individual SSRIs

Subgroups	Number of Studies	Adjusted OR (95% CI)	Heterogeneity		
			I^2	χ^2	P Value
Paroxetine	3	0.97 (0.75 to 1.19)	0%	1.39	0.499
Sertraline	3	1.00 (0.81 to 1.20)	43.10%	3.52	0.172
Fluoxetine	3	1.11 (0.87 to 1.35)	0%	0.56	0.755
Citalopram	3	0.86 (0.56 to 1.16)	0%	1.66	0.436

CI, indicates confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

Sensitivity Analyses

We conducted sensitivity analyses to explore potential sources of heterogeneity in the association between SSRIs and the risk of heart defects and examine the influence of various exclusion criteria on the overall risk estimate. We found that the Colvin study[4] accounted for the observed heterogeneity. When we omitted this study, the pooled adjusted OR was 1.04 (95% CI, 0.92 to 1.16) with no heterogeneity (I^2=0%; P=0.636). Further omission of any single study did not materially alter the overall combined adjusted OR, with a range from 1.05 (95% CI, 0.85 to 1.26) to 1.09 (95% CI, 0.95 to 1.23).

Analysis of Publication Bias

The potential for publication bias could not be investigated because the included number of studies was <5.

Discussion

Several large epidemiological and cohort studies that have examined the effect of SSRIs during the first trimester in pregnant women on the risk of heart defects have provided inconsistent findings. Using a meta-analysis of published population-based cohort studies, we found that SSRI use was not associated with an increased risk of congenital heart defects.

SSRIs are the most common prescribed antidepressant for depressive patients. It is critical whether SSRIs were associated with an increased risk of congenital heart defects in pregnant women during the first trimester. In our meta-analysis, 3 large population-based studies did not reveal a significant association, whereas the Colvin study[4] was the only one reporting a positive association between SSRI use during the first trimester and congenital heart defects. Its follow-up duration was much longer than other studies, which may increase the detection rate of congenital heart defects. However, the definition of exposure was any SSRI dispensed from 14 to 104 days after the last menstrual period, or to the end of the pregnancy event, which was also different from other studies. Moreover, the study only adjusted gestation age in the regression model, whereas other factors, such as smoking and more than or equal to 3 previous miscarriages, were not adjusted, which may undermine the significance of the result. Nevertheless, the sensitivity test after removing this study did not alter the combined OR value, and the conclusion was unchanged.

Previously, many meta-analyses on SSRIs and cardiac malformations have been published with diverse conclusions. Myles et al.,[18] Wurst et al.,[19] and Riggin et al.[20] found that first-trimester paroxetine use was associated with increased risk of cardiac malformations. These meta-analyses included cohort studies before 2013 or earlier, besides population-based cohort study in pregnant women, longitudinal case-control comparative studies and population-based cohort studies in liveborn children were also included. However, our study included the most up-to-date large population-based cohort studies in pregnant women; among them, the Huybrechts study[12] had the largest sample size and weighted the most with nonsignificant assocation between first-trimester paroxetine use and cardiac malformations. The reason why we excluded longitudinal case-control comparative studies was that the control group may be not from the same population, which could cause heterogeneity. Furthermore, the reason for exclusion of population-based cohort studies in liveborn children was that the interpretation of OR or RR was different from that in population-based cohort studies in pregnant women. Apart from these differences, Myles et al.[18] used raw OR values, which may overweight the influence of paroxetine on cardiac malformations. Consistent with Riggin et al.,[20] we also used the adjusted OR value in each study, which may reduce the impact of potential confounders in each study.

The strengths of our meta-analysis are that it included all published population-based cohort studies in pregnant women, the methodological quality of most studies was high, and the results of the nonsignificant associations between SSRIs and heart defects are consistent and robust with very low heterogeneity across studies, allowing for clinically meaningful insights.

However, there are several potential limitations. First, our meta-analysis was limited to English-language publications, raising the possibility of publication bias by failing to include unidentified unpublished reports and reports in other languages. Second, data extraction and analyses were not blinded to the authors, journals, or institutions of the publications, raising the possibility of assessor bias. Nevertheless, the literature screening and data extraction were performed independently by 2 investigators and discrepancies were resolved by the third investigator. Finally, the number of included studies was less than 5, which could not allow us to provide the information on publication bias.

Conclusion

SSRIs during the first trimester in pregnant women were not associated with increased risks for newborn heart defects.

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Disclosures

None.

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