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DRUGS IN PREGNANCY AND LACTATION

Sertraline use in the first trimester and risk of congenital anomalies: a systemic review and meta-analysis of cohort studies

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Keywords antidepressive agents, cohort studies, congenital anomalies, meta-analysis, pregnancy, sertraline

AIM

To perform a meta-analysis of available cohort studies on the association between sertraline use by pregnant women in the first trimester and the findings of congenital anomalies in infants.

METHODS

A comprehensive search of articles published from the index date up to 31st December 2015 investigating the aforementioned associations was conducted on PubMed and Web of Science. Mesh headings used included the terms "serotonin reuptake inhibitor," "sertraline," "congenital anomalies" and "obstetrical outcome."

RESULTS

Twelve cohort studies that involved 6 468 241 pregnant women were identified. We summarized odds ratios (ORs) and 95% confidence intervals (CIs) of congenital anomalies using the random-effects model. Pregnant women who used sertraline in the first trimester had a statistically significant increased risk of infant cardiovascular-related malformations (OR = 1.36; 95% CI = 1.06–1.74; I^2 = 64.4%; n = 12) as well as atrial and/or ventricular septal defects (OR = 1.36, 95% CI = 1.06–1.76; I^2 = 62.2%; n = 8). Additionally, positive but nonsignificant associations between sertraline use and congenital anomalies of the nervous system (OR = 1.39; 95% CI = 0.83–2.32; I^2 = 0%; n = 5), digestive system (OR = 1.23; 95% CI = 0.76–1.98; I^2 = 0%; n = 5), eye, ear, face and neck (OR = 1.08; 95% CI = 0.33–3.55; I^2 = 32.1%; n = 3), urogenital system (OR = 1.03; 95% CI = 0.73–1.46; I^2 = 0%; n = 5), and musculoskeletal system (OR = 0.97; 95% CI = 0.69–1.36; I^2 = 0%; n = 5) were observed.

CONCLUSION

This meta-analysis suggested that the use of sertraline use by pregnant women in the first trimester had an increased risk of cardiovascular-related malformations as well as atrial and/or ventricular septal defects in infants. Meanwhile, nonsignificant associations between sertraline use and other congenital anomalies were found. More cohort studies are warranted to provide detailed results of other congenital anomalies.

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Tables of Links

TARGETS
G protein-coupled receptors
5-HT_{2B} receptor

LIGANDS	
Citalopram	Paroxetine
Escitalopram	Serotonin
Fluvoxamine	Sertraline
Fluoxetine	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Introduction

Approximately 10% of pregnant women experience depression [3]. Among these women, 20% display signs of depression such as sleep disturbance, guilt and low energy [4]. Since exposure to untreated depression during pregnancy might be associated with serious adverse consequences for infants, including premature birth, low birth weight, and future behavioural disturbances [5, 6], prescription rate of antidepressant has showed an increasing trend upward. As first-generation antidepressants, tricyclics were popular for several decades until there was a drastic shift in the use of tricyclics in the 1980s to selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SSRIs) in the 1990s [7]. SSRIs (sertraline, fluoxetine, citalopram, paroxetine, fluvoxamine and escitalopram) are more valid and tolerable compared to first-generation antidepressants [8]; consequently, they have become the most frequently prescribed pharmacological treatment for depression during pregnancy [9, 10]. Several studies have demonstrated that the prescription rates of SSRIs were 3% and 4–10% in Europe and North America, respectively [11, 12]. By comparison, the prescription rates for tricyclics were only 0.14% in Denmark [13].

Among the SSRIs, sertraline is one of the most frequently used antidepressants worldwide [14]. *In vivo* and *in vitro* studies have suggested that [15] heart defects might be attributed to a mechanism of 5-HT playing a role in cardiac morphogenesis during endocardial cushion formation. Furthermore, Sari *et al.* [16] found that serotonin promoted the proliferation of foetal heart cells and abnormal serotonin levels or misuse of the serotonin-uptake blocker may change the heart development. However, epidemiological studies have provided controversial evidence of the association between sertraline use and the risk of cardiovascular malformations. Several studies [17–20] have suggested that sertraline could increase the risk of cardiovascular-related malformations in infants, while other studies [21–28] found no association at all. A recent meta-analysis [29] found that sertraline was not associated with the risk of heart defects. However, six cohort studies [18–20, 23, 26, 27] that reported the outcomes of cardiovascular-related malformations were excluded in that study. Moreover, several limitations of the previous meta-analysis were noted: (i) for the authors, journals or institutions of the publications, the process of data extraction and analyses were not blind; and (ii) the study lacked subgroup analyses based on important potential confounders. Except for cardiovascular-related malformations, very few studies provide evidence of sertraline use and malformations of other systems such as the nervous, digestive, eye, ear, face and neck, urogenital, and musculoskeletal systems.

Given the inconsistency of previous results, as well as to provide the best estimates of the effect of sertraline usage during first trimester of pregnancy, we performed this meta-analysis of cohort studies to investigate the association between sertraline use during the first trimester of pregnancy and selective congenital anomalies.

Methods

Eligibility criteria, information sources, search strategy

We followed the Meta-analysis of Observational Studies in Epidemiology guideline [30] and Preferred Reporting Items for Systematic reviews and Meta-analyses guideline [31] to perform and report our meta-analysis. A systematic literature search of PubMed (1964 to 31st December 2015) and Web of Science (1992 to 31st December 2015) databases was independently conducted by two investigators, for all correlative studies with respect to the effect of the maternal use of sertraline in the first trimester of pregnancy on the risk of congenital anomalies in infants. We carried out searches using the following keywords and medical subject heading terms including (serotonin reuptake inhibitors OR SSRI OR fluoxetine OR paroxetine OR citalopram OR sertraline OR fluoxamine) AND (malformations OR birth outcomes OR obstetrical outcome OR congenital abnormalities). Additionally, the references cited in retrieved articles were scrutinized by manual search.

Study selection

Studies were considered for inclusion if they: (i) were cohort studies; (ii) defined the exposure period of sertraline as occurring in the first trimester of pregnancy; (iii) defined the non-exposed group as pregnant women who did not use any kind of antidepressants; (iv) reported usable risk estimates (e.g., odds ratio, relative risk or risk ratio with 95% confidence intervals or indispensable data to calculate) of the association between sertraline exposure and congenital anomalies; and (v) were published in English.

Studies were excluded if they met the following criteria: (i) were review articles, systemic reviews and meta-analyses, commentaries, editorials or meeting abstracts; (ii) used other

study designs (e.g., case–control study, descriptive study, randomized controlled trial etc.); (iii) included pregnant women who were exposed to more than two kinds of antidepressant simultaneously; and (iv) defined the exposure period as throughout or another trimester of pregnancy other than the first.

When the results from the same study were reported in different manuscripts, only the newest or most complete study with the largest number of the cohort or cases at the endpoint of our interest was included. The selection and exclusion of studies were previewed by two investigators (T.-N.Z. and Z.-Q.S.). Disagreements were resolved by a third author (Q.-J.W.) through discussion.

A quality assessment of the included studies was conducted by two independent researchers (T.-N.Z. and S.-Y.G.) based on the Newcastle–Ottawa Scale for cohort studies [32]. The scale consists of eight items, and all of the items were available to our study question. The items are separated into three domains (selection, comparability and outcome). We applied these Newcastle–Ottawa Scale parameters to evaluate the studies rather than scoring them or categorizing them into high or low quality on the basis of the scores.

Data extraction

Data were extracted independently by a standardized form by two reviewers (T.-N.Z. and Z.-Q.S.). Dissenting opinions were resolved through discussion. The following data were abstracted from each study: the name of the first author; year of publication; country; number of cases; number of cohorts; study design; exposure time; outcome with their risk estimates and 95% confidence intervals (CIs); plus adjustment confounders. Since the limited number of studies of several outcomes (e.g. conotruncal and major arch anomalies, transposition of great arteries etc.), we only summarized and presented the outcomes of cardiovascular anomalies, cardiac malformations and septal defects. If there were multiple estimates of the association, we extracted the estimate that was adjusted for the largest number of potential confounders. If there was no adjusted estimate in the study, we used the crude estimate.

As for the studies [17–28] reporting the results of cardiovascular anomalies as other outcomes but with similar definition (e.g., as specific heart anomalies, any cardiac defects, cardiac malformations, congenital cardiovascular defects, congenital heart malformation, all major cardiovascular anomalies and other congenital anomalies of the heart), we extracted these data to calculate the summarized odds ratio (OR) of overall cardiovascular-related malformations. Similar patterns are also carried out in the analysis of the studies [17–19, 21, 22, 25, 26, 28] reporting the outcomes as atrial septal defect (ASD), ventricular septal defect (VSD), septal defect, atrioventricular septal defect, in addition to ASD and/or VSD. We extracted these data to calculate summarized OR of ASD and/or VSD events. Additionally, for the studies [18, 21, 23, 25, 26] reporting results of defects of genital organs, defects of external genital organs, defects of internal urinary system, defects of urinary system, and urogenital malformation, the data were extracted to calculate the summarized OR of urogenital malformations [33].

Data synthesis

Since congenital anomaly is a relatively rare event, we assumed that ORs were comparable estimates of the risk ratios (RRs). However, if the study did not provide the estimate, we calculated it through raw data in the study [27]. For studies that separately reported the risk estimates of sertraline, we used the effective count method proposed by Harmling *et al*. [33] to recalculate the effect estimate [34–38]. Random-effects models by DerSimonian and Laird [39] were applied to obtain summarized OR estimates across the included studies. We calculated the I^2 statistic to quantify the magnitude between-study heterogeneity, and assigned values of 50% or less, 51%–75%, and 76% or more for low-, moderate- and high- heterogeneity, respectively [40–46]. Subgroup analysis was carried out based on geographic location (Europe, North America and other regions). Furthermore, a heterogeneity analysis was also conducted to assess the effect of adjustment of confounders, such as maternal age, socioeconomic situations, smoking or drinking situations, body mass index, pregnancy outcomes, and parity. In addition, a sensitivity analysis was conducted and the summarized OR was computed with the omission of one study at a time to detect whether results were strongly influenced by a specific study [42, 47–49]. Finally, we evaluated publication bias through Egger's linear regression [50], Begg's rank-correlation methods [51] (publication bias considered present if $P \leq 0.10$) and visual inspection of funnel plots. All analyses were performed using Stata software, version 12.1 (StataCorp LP, College Station, Texas).

Results

Study selection

We identified a total of 1874 papers (1437 and 437 studies from PubMed and Web of Science, respectively) via the search strategy. Of these studies, 1841 of them were excluded on the basis of titles and abstracts. The remaining 33 studies were considered of interest and full-text studies were retrieved for detailed evaluation, 21 of these studies were subsequently excluded. Finally, 12 studies [17–28] were eligible for inclusion in the meta-analysis, representing a total of 6 468 241 individuals (Figure 1).

Study characteristics

Characteristics of all 12 studies [17–28] are shown in Table 1. Among the 12 studies, 10 were prospective cohort studies [17–23, 25, 27, 28] and two were retrospective cohort studies [24, 26]. These studies were published between 2007 [28] and 2015 [21, 22], which covered a study period from 1990 to 2010. The number of participants in each study ranged from 18 493 [21] to 2 303 647 [22], and the number of cases ranged from 515 [27] to 26 854 [22]. The studies were generally from European countries (n = 7), North America (n = 3), and one study each were conducted in Australia and Israel. Many studies (n = 9) adjusted for potentially important confounders: maternal age (n = 9); smoking and drinking situation (n = 7); parity (n = 7); pregnancy complication (n = 5); socioeconomic

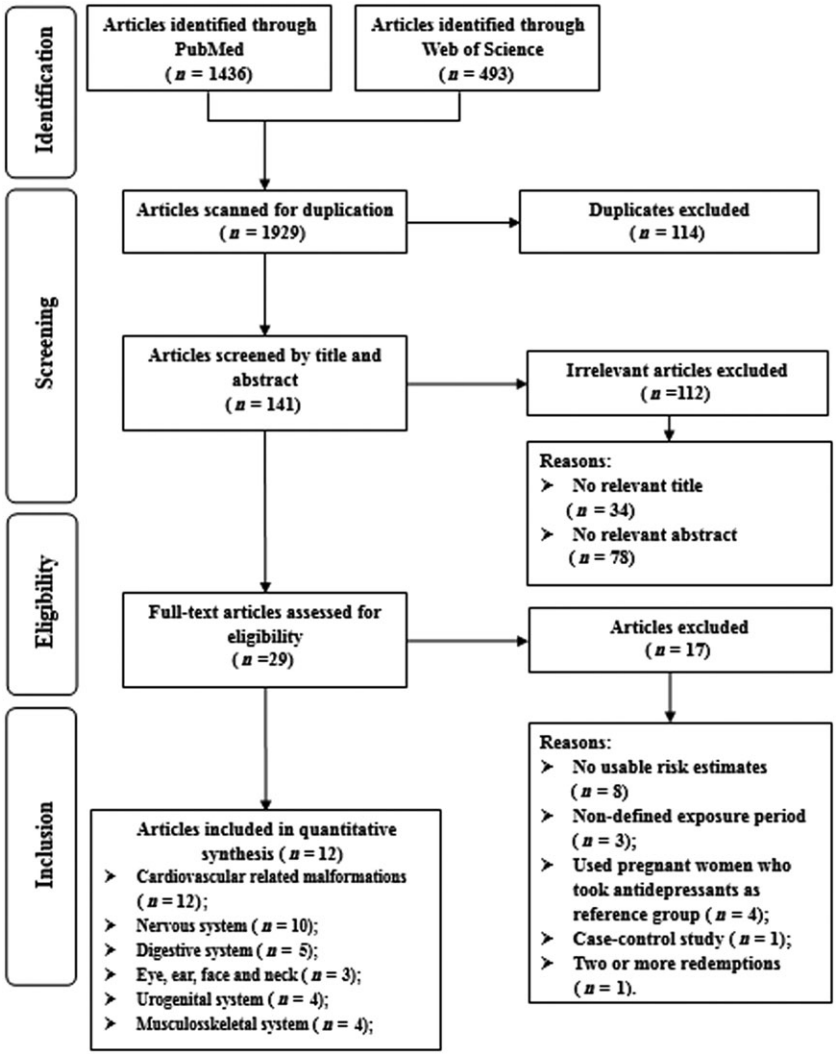

Figure 1
Flow-chart of study selection

situation ($n = 2$); and body mass index ($n = 1$), with the exception of three studies.

Quality assessment

Table 2 presents the results of the quality assessment based on the Newcastle–Ottawa Scale. All studies satisfied adequate quality. Meanwhile, in the classification of 'control for important factor or additional factor', six studies were not assigned to two scores because they adjusted for fewer than two important confounders. Moreover, in the classification of 'follow-up long enough for outcomes to occur' and 'adequacy of follow-up of cohorts', five studies were not assigned any score because they did not mention follow-up in their studies.

Cardiovascular-related malformations

Twelve studies [17–28] evaluated the relationship between sertraline use in the first trimester of pregnancy and any cardiovascular-related malformations in infants. After summarizing all of the studies, pregnant women exposed to sertraline in the first trimester had a statistically significant increased risk of cardiovascular-related malformations occurring in their infants (OR = 1.36, 95% CI = 1.06–1.74; Figure 2). Moderate heterogeneity was noted ($I^2 = 64.4\%$, $P = 0.01$). Publication bias was not detected by Egger's tests ($P = 0.421$), Begg's tests ($P = 0.631$) and visual inspection of the funnel plot was symmetric. A total of five studies [17, 19, 21, 22, 28] reported the relationship between sertraline use and risk of cardiac malformations. The summarized OR was 1.20 (95% CI = 0.94–1.53; $I^2 = 59.2$; $P = 0.04$). Eight studies [17–19, 21, 22, 25, 26, 28] reported ASDs and/or VSDs. The results suggested that exposure to sertraline use had 36% statistically significant increased risk of ASDs and/or VSDs in infants (95% CI = 1.06–1.76; Figure 3). I^2 was 62.2%, which suggest a moderate degree of heterogeneity between studies ($P < 0.01$).

We carried out subgroup analyses stratified by geographic locations in analysis of cardiovascular malformations. Significant results were only observed in North American populations (summarized OR = 1.26; 95% CI = 1.06–1.49).

Table 1

Characteristics of cohort studies in the meta-analysis

First author (ref), year, location	Studyperiod	No. of cohort/case	Outcomes	Risk estimates (95% CI)	Adjusted factors
Furu *et al.* [22], 2015, Europe	1996–2010	2 303 647		Odds ratio	Maternal age, year of birth, birth order, smoking, maternal diabetes, country and use of other prescribed drugs.
		26 854	Any cardiac defects	1.13 (0.93–1.38)	
		17 573	Atrial and ventricular septal defect	1.05 (0.82–1.35)	
		1079	Atrioventricular septal defect	1.81 (0.80–4.06)	
		2231	Conotruncal and major arch anomalies	1.02 (0.48–2.15)	
		2599	Left ventricular outflow tract obstruction	0.82 (0.37–1.84)	
		2720	Right ventricular outflow tract obstruction	1.40 (0.81–2.42)	
Berard *et al.* [21], 2015, North America	1998–2010	18 493		Risk ratio	Maternal age, welfare status, other diabetes, hypertension, asthma, and medication use.
		354	Cardiac malformations	1.16 (0.62–2.19)	
		281	Ventricular/ atrial septal defect	1.34 (1.02–1.76)	
		122	Nervous system	1.67 (0.68–4.13)	
		87	Eye, ear, face and neck	0.46 (0.06–3.32)	
		181	Digestive system	1.13 (0.46–2.77)	
		164	Genital organs	0.97 (0.34–2.75)	
		144	Urinary system	0.86 (0.27–2.72)	
		635	Musculoskeletal system	1.04 (0.63–1.72)	
Ban *et al.* [23], 2014, Europe	1990–2009	349 127		Odds ratio	Maternal age at the end of pregnancy, year of childbirth, Townsend deprivation quintile, maternal smoking history, body mass index before pregnancy, and maternal diabetes, hypertension, asthma and epilepsy in the year before conception or during pregnancy.
		N/A	MCAs	1.27 (0.85–1.89)	
		N/A	Specific heart anomalies	1.52(0.78–2.96)	
		N/A	Genital system	0.32 (0.04–2.40)	
		N/A	Urinary system	0.54 (0.08–3.76)	
		N/A	Nervous system	1.79 (0.42–7.54)	
		N/A	Musculoskeletal system	2.13 (0.51–8.90)	
		N/A	Digestive system	2.69 (0.67–10.76)	
Huybrechts *et al.* [17], 2014, North America	2000–2007	949 504		Odds ratio	N/A
		6532	Cardiac malformations	1.27 (1.07–1.52)	
		3275	Ventricular septal defect	1.24 (0.96–1.59)	
		1062	Right ventricular outflow tract obstruction	1.03 (0.64–1.66)	
		3280	Other cardiac defect	1.39 (1.10–1.76)	

(*Continues*)

Table 1

(Continued)

First author (ref), year, location	Studyperiod	No. of cohort/case	Outcomes	Risk estimates (95% CI)	Adjusted factors
Jimenez-Solem *et al.* [18], 2012, Europe	1997–2009	848 786		Odds ratio	Mother's age, parity, income, education, smoking and year of conception.
		N/A	Congenital malformation of the heart	2.73 (1.75–4.26)	
		N/A	Septal defects	3.09 (1.82–5.25)	
		N/A	Ventricular septal defects	3.60 (1.86–6.96)	
		N/A	Atriventricular septal defects	2.85 (1.35–5.99)	
		N/A	Nervous system	0.85 (0.12–6.07)	
		N/A	Eye	1.05 (0.15–7.45)	
		N/A	Ear, face and neck	6.13 (0.85–44.05)	
		N/A	Digestive system	1.43 (0.36–5.74)	
		N/A	Internal urinary system	0.44 (0.06–3.11)	
		N/A	External genital organs	0.41 (0.06–2.93)	
		N/A	Musculoskeletal system	0.83 (0.12–5.90)	
Nordeng *et al.* [24], 2012, Europe	1999–2009	63 395		Odds ratio	Maternal depression, maternal age at delivery, parity and use of psychotropic drugs during pregnancy.
		542	Cardiovasular malformation	1.15 (0.16–8.28)	
Colvin *et al.* [25], 2011, Western Australia	2002–2005	123 405		Odds ratio	N/A
		672	Cardiovascular anomalies	1.74 (0.96–3.17)	
		N/A	Ventricular septal defect	0.49 (0.07–3.50)	
		289–294	Nervous system	1.08 (0.35–3.38)	
		224–229	Ear, face and neck	0.46 (0.07–3.31)	
		1330	Urogenital system	1.27 (0.07–2.09)	
		539	Digestive system	0.97 (0.40–2.36)	
		1059	Musculoskeletal system	0.69 (0.33–1.46)	
Malm *et al.* [26], 2011, Europe	1996–2006	635 583		Odds ratio	Maternal age at the end of pregnancy, parity, year of pregnancy ending, marital status, smoking any time during pregnancy, other reimbursed psychiatric drug purchases and entitlement for special reimbursement for prepregnancy diabetes.
		8146	All major cardiovascular anomalies	0.65 (0.34–1.25)	
		1281	Atrial septal defect	0.93 (0.23–3.76)	
		5470	Ventricular septal defect	0.53 (0.22–1.29)	
		435	Conotruncal heart defect	1.27 (0.18–9.15)	
		239	Transposition of great arteries	2.55 (0.35–18.62)	
		N/A	Central nervous system	1.35 (0.50–3.64)	
		N/A	Digestive system	1.09 (0.35–3.41)	
		N/A	Urogenital system	1.22 (0.55–2.74)	
		N/A	Musculoskeletal system	0.97 (0.50–1.88)	

(*Continues*)

Table 1
(Continued)

First author (ref), year, location	Studyperiod	No. of cohort/case	Outcomes	Risk estimates (95% CI)	Adjusted factors
Kornum *et al.* [19], 2010, Europe	1991–2007	216 042		Odds ratio	Maternal smoking status, maternal age, birth order and birth year.
		1410	Cardiac malformations	3.0 (1.4–6.4)	
		N/A	Septal heart defect	3.3 (1.5–7.5)	
Merlob *et al.* [20], 2009, Israel	2000–2007	67 871		Relative risk	N/A
		1084	Congenital heart malformation	8.78 (1.08–71.42)	
Oberlander *et al.* [27], 2008, North America	1998–2001	11 957		Odds ratio	N/A
		515	Cardiovascular congenital defects	1.03 (0.33–3.23)	
Kallen *et al.* [28],2007, Europe	1995–2004	880 431		Odds ratio	Year of birth, maternal age, parity, smoking and ≥3 previous miscarriages.
		11 384	Any cardiac defect	0.76 (0.47–1.23)	
		7174	VSD and/or ASD	1.06 (0.63–1.77)	
		1218	Unspecified cardiac defect	0.55 (0.01–3.06)	

CI, confidence interval; ASD, atrial septal defect; MCA, major congenital anomalies; N/A, not available; VSD, ventricular septal defect

Additionally, when stratified by whether adjustment potential confounders, although the directions of the result of subgroup analyses were consistent with the main findings, not all of them showed statistical significance. Moreover, no statistically significant source of heterogeneity was identified in a metaregression analysis of these subgroups (Table 3).

In the sensitivity analysis, which omitted one study at a time and calculated a summarized OR for the remainder of the studies, the estimated OR in this sensitivity analysis ranged from 1.22 (95% CI = 0.99–1.51) after omission of the study by Jimenez-Solem *et al.* [18] to 1.45 (95% CI = 1.13–1.87) after omission of the study by Kallen and Otterblad [28].

Congenital anomalies of the nervous system, digestive system, eye, ear, face and neck, urogenital system, and musculoskeletal system

The association between sertraline exposure in the first trimester and congenital anomalies of the nervous system was explored by five studies [18, 21, 23, 25, 26]. The summarized OR was 1.43 (95% CI = 0.88–2.32; $P = 0.98$ for heterogeneity; $I^2 = 0.0$). The tests for publication bias showed that there was no publication bias (Begg's test = 0.221, Egger's test = 0.195). Sensitivity analyses showed that none of the individual studies greatly influenced the summarized OR (OR range from 1.27 [95% CI = 0.68–2.38] to 1.48 [95% CI = 0.83–2.64]).

Five studies [18, 21, 23, 25, 26] reported the relation of sertraline exposure and congenital anomalies of the digestive system, the summarized OR was 1.23 (95% CI = 0.76–1.98) without heterogeneity ($I^2 = 0.0\%$, $P = 0.81$). The results of the tests for publication bias (Begg's test = 0.086 and Egger's test = 0.166), suggest the existence of some publication bias through Begg's test. To assess whether any one study had a dominant effect on the summarized OR, each study was excluded one at a time and we evaluated the effect on the main summary estimate. The results showed that no study obviously affected the summarized estimate (OR range from 1.10 [95% CI = 0.66–1.84] to 1.35 [95% CI = 0.76–2.39]).

Three studies [18, 21, 25] reported estimates for congenital anomalies of the eye, ear, face and neck; the summarized OR was 1.08 (95% CI = 0.33–3.55; $I^2 = 32.1\%$; $P = 0.22$). We also conducted tests for publication bias (Begg's test = 0.734, Egger's test = 0.883), which suggested no publication bias existed.

Four prospective cohort studies [18, 21, 23, 25] and one retrospective cohort [26] study reported the relation of sertraline exposure and congenital anomalies of the urogenital system. When we summarized these studies, we found that sertraline exposure was not associated with such anomalies (OR = 1.03 95% CI = 0.73–1.46). I^2 was 0 ($P = 0.76$), which suggested a low degree of heterogeneity. In addition, there was indication of a publication bias by using Begg's test ($P = 0.002$) or Egger's test ($P < 0.001$). Furthermore, sensitivity analysis presented that none of the individual studies evidently affected the summarized OR (OR range from 0.85 [95%CI = 0.52–1.38] to 1.10 [95% CI = 0.76–1.57]).

Four prospective cohort studies [18, 21, 23, 25] and one retrospective cohort study [26] reported the relation of sertraline exposure and congenital anomalies of the musculoskeletal system. The summarized OR was 0.97 (95%CI = 0.69–1.36; $P = 0.72$ for heterogeneity; $I^2 = 0.0\%$). There was no indication

Table 2

Methodological quality of cohort studies included in the meta-analysis

First author (reference), publication year	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor/ additional factor[a]	Assessment of outcome	Follow-up long enough for outcomes to occur[b]	Adequacy of follow-up of cohorts[c]	Total scores
Furu *et al.* [22], 2015	*	*	*	*	**	*	*	*	9
Berard *et al.* [21], 2015	*	*	*	*	*	*	*	*	8
Ban *et al.* [23], 2014	*	*	*	*	**	*	-	-	7
Huybrechts *et al.* [17], 2014	*	*	*	*	-	*	*	*	7
Jimenez-Solem *et al.* [18], 2012	*	*	*	*	**	*	*	*	9
Nordeng *et al.* [24], 2012	*	*	*	*	*	*	-	-	6
Colvin *et al.* [25], 2011	*	*	*	*	-	*	*	*	7
Malm *et al.* [26], 2011	*	*	*	*	**	*	-	-	7
Kornum *et al.* [19], 2010	*	*	*	*	**	*	*	*	9
Merlob *et al.* [20], 2009	*	*	*	*	-	*	*	*	7
Oberlander *et al.* [27], 2008	*	*	*	*	-	*	-	-	5
Kallen *et al.* [28], 2007	*	*	*	*	**	*	-	-	7

A study could be awarded a maximum of one star for each item except for the item *Control for important factor or additional factor*. The definition/explanation of each column of the Newcastle–Ottawa Scale is available from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[a]A maximum of two stars could be awarded for this item. Studies that controlled for age received one star, whereas studies that controlled for other important confounders such as smoking and/or alcohol using received an additional star

[b]A cohort study with a follow-up time > 9 months was assigned one star

[c]A cohort study with a follow-up rate > 75% was assigned one star

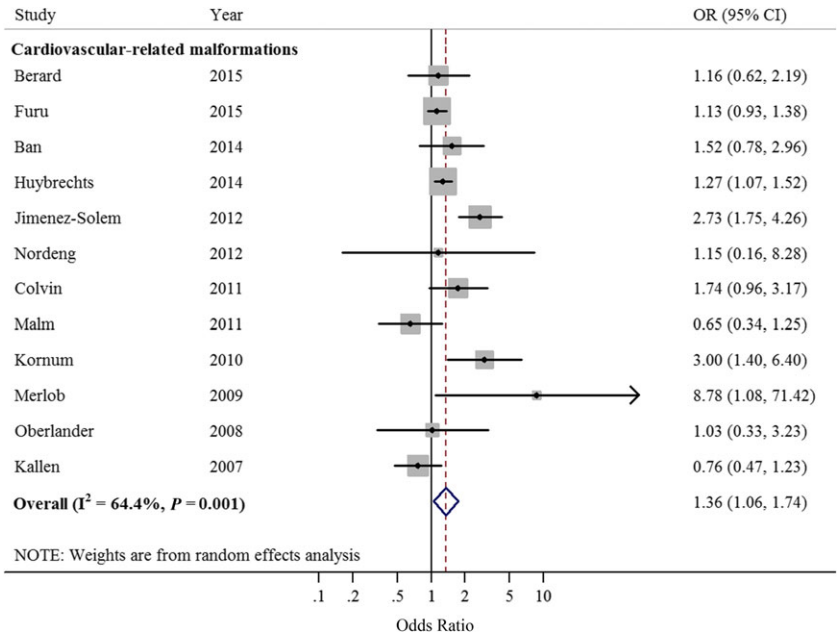

Figure 2

Forest plots of the relationship between sertraline use and risk of cardiovascular-related malformations. Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates the summary odds ratio with its 95% CI. OR: odds ratio

of a publication bias using Begg's test (P = 0.806) or Egger's test (P = 0.685). The tests for sensitivity analysis showed OR range from 0.92 (95%CI = 0.58–1.44) to 1.06 (95% CI = 0.73–1.55).

Discussion

Main findings

To our knowledge, this is the first meta-analysis to review systematically the relationship between sertraline use in the first trimester of pregnancy and selective congenital anomalies. After summarizing the results from 12 cohort studies, we found that sertraline use had 36% and 35% statistically significant increased risks of the cardiovascular-related malformations as well as ASDs and/or VSDs, respectively. However, nonsignificant associations between sertraline use and congenital anomalies of the nervous system, digestive system, eye, ear, face and neck, urogenital system, and musculoskeletal system were observed.

The specific biological mechanisms on sertraline use and selective congenital anomalies remain unclear. However, several possible mechanisms may partly explain the aforementioned associations, especially for cardiovascular-related malformations. *In vivo* study [52] showed that serotonin might play an important role in cardiac morphogenesis during endocardial cushion formation in the mouse embryo. Besides, sertraline could inhibit proliferation of cardiac mesenchyme, endocardium, and myocardium. Subsequently, Nebigil *et al*. [53] demonstrated that 5-HT was a crucial regulator in the process of cardiomyocyte proliferation and differentiation via 5-HT_{2B} receptor. Additionally, other studies [16] indicated that the blockade of 5-HT uptake decreased the number of heart cells, which might alter heart development. Considering that there is little information on molecular mechanisms in the cells and tissues level, further experimental studies should be conducted to investigate the potential mechanisms between sertraline and cardiovascular-related malformations.

Comparing this information to cardiovascular-related malformations, we failed to find any significant association between sertraline use and other selective congenital anomalies (Table 3), which might be due to the limited number of studies. However, there were several possible mechanisms to explain the potential relevance. A genetic study in mice [54] that focused on the development of the nervous system showed that disruption of serotonin signalling during the period of pre- and postnatal development could lead to long-term behavioural abnormalities. Additionally, an *in vitro* study [55] found that serotonin could inhibit osteoblast proliferation, differentiation and mineralization at a low concentration. Moreover, as an important transmitter in the gut, serotonin plays an important role in vasodilation, epithelial secretion, stimulation of propulsion and segmentation motility patterns [56]. Despite the fact that pre-existing studies could partly explain the associations between sertraline use and other congenital anomalies, further animal models are needed to investigate the specific role of sertraline on embryo development.

In the subgroup analyses stratified by geographic location, a statistically significant association was only found for populations in North America. This pattern could be partly attributed to the different prescription rates of sertraline among different geographical populations. For example, the average prescription rates were 2.86% (range 1.48–5.10%)

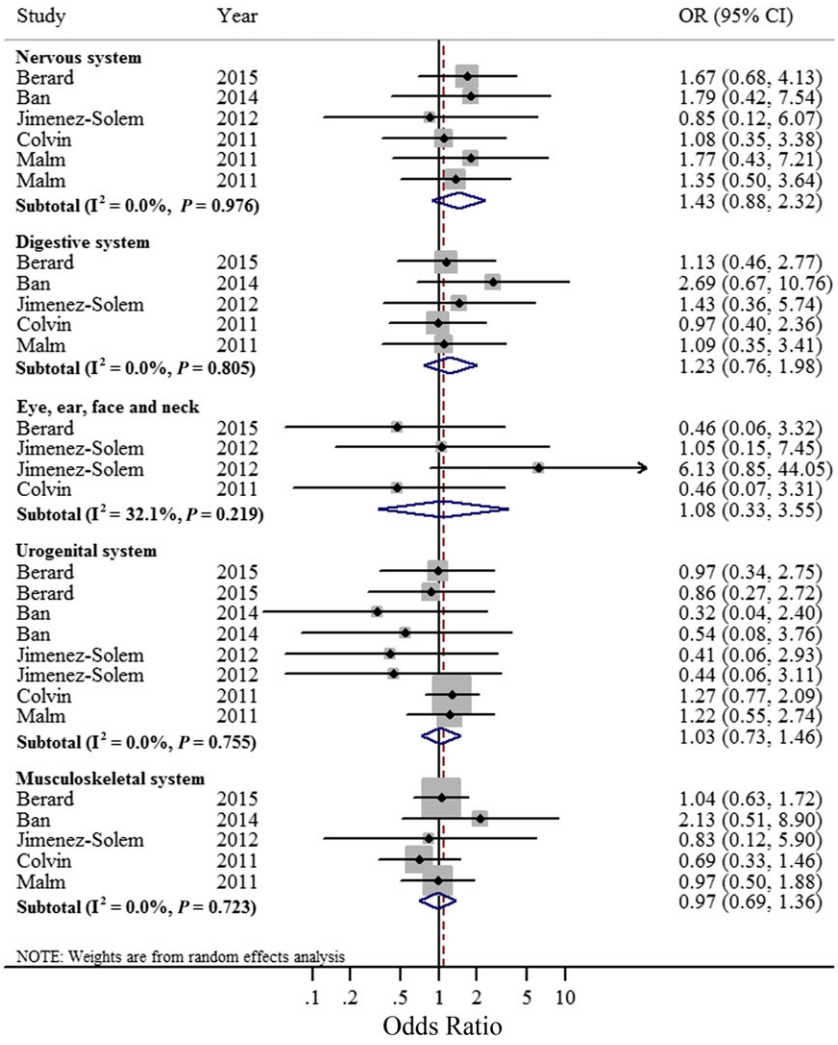

Figure 3

Forest plots of the relationship between sertraline use and congenital anomalies of the nervous system, digestive system, eye, ear, face and neck, urogenital system, and musculoskeletal system. Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates the summary odds ratio with its 95% CI

and 0.19% (range 0.10–0.31%) in North America and Europe, respectively. By contrast, we could not rule out the possibility of chance finding since there were only three studies in North America and two studies total in Australia and Israel investigating the aforementioned association.

Strengths and limitations

Our study has several strengths. Firstly, to the best of our knowledge, this is the first comprehensive and the most current meta-analysis that has evaluated the association between sertraline use in the first trimester of pregnancy and congenital anomalies. Secondly, our meta-analysis included 12 cohort studies with a total number of 6 468 241 participants, which provided sufficient power to detect modest associations. Thirdly, because we only included cohort studies, the influence of biases such as recall bias and selection bias could be minimized. Finally, numerous subgroup and sensitivity analyses were carried out to explore the heterogeneity.

However, several potential limitations of this study also need to be acknowledged. First, the summarized ORs might be overestimated because mothers who have been treated for depression are more likely to receive elaborate examinations, which might lead to the possible detection of some less severe congenital anomalies [57] and thus cause information bias. For instance, infants of women exposed to selective serotonin reuptake inhibitors had approximately twice as many echocardiograms in the first year of life compared with infants of unexposed women [57]. Also, more frequent echocadiograms may lead to a higher rate in the detection of heart defects; hence, infants of women who used that drug would more likely be detected. As well, since four studies [17, 19, 25, 27] conducted their investigations by means of record linkage, there was a limitation that drug compliance and length of exposure timing could not be assured, which might result in an overestimation of summarized ORs. However, there have been many studies [58] indicating that the majority of redeemed prescriptions were taken by the pregnant

Table 3

Summary risk estimates of the association between sertraline use and congenital anomalies

	No. of study	Summary OR95% CI	I^2(%)	*P**	*P***[a]
Cardiovascular-related malformation	12	1.36 (1.06–1.74)	64.4	0.01	
Atrial and/or ventricular septal defect	8	1.36 (1.06–1.76)	62.2	<0.01	
Cardiac malformation	5	1.20 (0.94–1.53)	59.2	0.04	
Nervous system	5	1.39 (0.83–2.32)	0.0	0.95	
Digestive system	5	1.23 (0.76–1.98)	0.0	0.81	
Eye, ear, face and neck	3	1.08 (0.33–3.55)	32.1	0.22	
Urogenital system	5	1.03 (0.73–1.46)	0.0	0.76	
Musuloskeletal system	5	0.97 (0.69–1.36)	0.0	0.72	
Subgroup analysis[a]					
Geographic location					0.53
North America	3	1.26 (1.06–1.49)	0.0	0.91	
Europe	7	1.35 (0.88–2.06)	77.2	<0.01	
Others	2	2.83 (0.66–12.08)	52.8	0.15	
Adjustment for potential confounders					
Age					0.68
Yes	8	1.32 (0.91–1.91)	73.4	<0.01	
No	4	1.43 (0.98–2.07)	30.6	0.23	
Socioeconomic status					0.32
Yes	2	1.84 (0.80–4.24)	78.8	0.03	
No	10	1.23 (0.98–1.56)	51.9	0.03	
Smoking or alcohol drinking					0.88
Yes	6	1.36 (0.87–2.11)	81.0	<0.01	
No	6	1.30 (1.11–1.53)	0.0	0.48	
Pregnancy body mass index					0.86
Yes	1	1.52 (0.78–2.96)	N/A	N/A	
No	11	1.35 (1.03–1.75)	67.3	<0.01	
Pregnancy complications					0.21
Yes	4	1.10 (0.87–1.38)	14.3	0.32	
No	8	1.62 (1.09–2.42)	70.4	<0.01	
Parity					0.77
Yes	6	1.32 (0.81–2.15)	80.7	<0.01	
No	6	1.31 (1.12–1.53)	0.0	0.46	

CI, confidence interval; N/A, not available; OR, odd ratio

*P** for heterogeneity within each subgroup

*P*** for heterogeneity between subgroups with metaregression analysis

[a]Subgroup analyses were only carried out for cardiovascular-related malformation

women. When treating chronic illnesses, drug compliance was especially high during pregnancy [59].

Second, our meta-analysis did not take malformations leading to an elective termination of pregnancy or miscarriage into consideration. This missing information could disguise a possible teratogenic effect of the sertraline. This results could occur if pregnant women exposed to sertraline had a higher rate of elective abortions or miscarriages due to severe malformation, it would create an underestimation of the risk.

Third, we acknowledge important confounders that may cause similar results; however, we cannot account for unknown confounders. Since previous studies [59] have reported that smoking, alcohol, drug use, poor maternal diet,

obesity, and chronic conditions were all frequently seen in patients with depression more so than in those without depression, all of those factors could be considered potential risk factors for congenital anomalies. However, these potential confounders were not consistent in each study. For instance, some studies [17, 20, 25, 27] did not adjust for any confounder, while seven studies [18, 19, 21–23, 26, 28] adjusted for more than three confounders. Because we did not have access to the primary data of these included studies, future cohort studies are warranted to report analyses stratified by possible risk factors that fully adjust for the potential confounders in order to rule out residual confounders.

Although numerous subgroup and sensitivity analyses were carried out, heterogeneity still existed in our study. Hence heterogeneity could be a concern when interpreting the findings of this study. As suggested previously, significant heterogeneity could potentially be induced by factors such as differences in the assessment of exposure timing, drug compliance, study location or differing covariate adjustment. We conducted many subgroup analyses with the expectation of detecting potential factors for such considerable heterogeneities; however, it appears that in numerous subgroups the heterogeneity remains relatively high. Therefore, further studies are warranted to validate our findings and better characterize the relationship.

Finally, there was a limitation with the review in that there were very few studies focusing on systems other than cardiovascular. For example, just five studies [18, 21, 23, 25, 26] mentioned these anomalies. As for congenital anomalies of the eye, ear, face and neck, the numbers were even fewer [18, 21, 25]. Out of the studies, only three reported the risks, and we could not rule out that our results could derive from chance finding. Hence, future studies are still required to investigate the association between sertraline use and congenital anomalies of other systems.

Conclusions

In conclusion, in this original and comprehensive meta-analysis, we found that pregnant women who were exposed to sertraline during the first trimester of pregnancy had an increased risk of cardiovascular-related malformations as well as ASDs and/or VSDs in infants. Further investigations are warranted to provide more detailed results of the association between sertraline use and other congenital anomalies.

Competing Interests

There are no competing interests to declare.

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Contributors

Q.-J.W. and D.L. designed research; T.-N.Z., S.-Y.G., Z.-Q.S. and Q.-J.W. conducted literature search; T.-N.Z., S.-Y.G., Z.-Q.S. and Q.-J.W. analysed data; Z.-Q.S., S.X.L., D.L. and Q.-J. W. wrote the draft; all authors read, reviewed and approved the final manuscript. Q.-J.W. and D.L. had primary responsibility for final content.

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