

The risk of major cardiac malformations associated with paroxetine use during the first trimester of pregnancy: a systematic review and meta-analysis

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AIMS

The aim of this study was to perform an up-to-date meta-analysis on the risk of cardiac malformations associated with gestational exposure to paroxetine, taking into account indication, study design and reference category.

METHOD

A systematic review of studies published between 1966 and November 2015 was conducted using EMBASE and MEDLINE. Studies reporting major malformations with first trimester exposure to paroxetine were included. Potentially relevant articles were assessed and relevant data extracted to calculate risk estimates. Outcomes included any major malformations and major cardiac malformations. Pooled odds ratios and 95% confidence intervals were calculated using random-effects models.

RESULTS

Twenty-three studies were included. Compared with non-exposure to paroxetine, first trimester use of paroxetine was associated with an increased risk of any major congenital malformations combined (pooled OR 1.23, 95% CI 1.10, 1.38; $n = 15$ studies), major cardiac malformations (pooled OR 1.28, 95% CI 1.11, 1.47; $n = 18$ studies), specifically bulbus cordis anomalies and anomalies of cardiac septal closure (pooled OR 1.42, 95% CI 1.07, 1.89; $n = 8$ studies), atrial septal defects (pooled OR 2.38, 95% CI 1.14, 4.97; $n = 4$ studies) and right ventricular outflow tract defect (pooled OR 2.29, 95% CI 1.06, 4.93; $n = 4$ studies). Although the estimates varied depending on the comparator group, study design and malformation detection period, a trend towards increased risk was observed.

CONCLUSIONS

Paroxetine use during the first trimester of pregnancy is associated with an increased risk of any major congenital malformations and cardiac malformations. The increase in risk is not dependent on the study method or population.

Introduction

Up to one-fifth of women of childbearing age experience moderate to severe depressive symptoms [1]. Pregnancy may be a time of risk for both new onset and reoccurrence of depression, with prevalence rates of depression ranging from 7% to 20% [2–5]. Depression during pregnancy is associated with poor maternal nutrition, inadequate weight

gain, smoking, alcohol and other substance intake, and increased risk of post-partum depression [6–10]. Antidepressant prescribing during pregnancy has increased up to four-fold between 1992 and 2006 with a total of 4.8% of women receiving a prescription in the months prior to pregnancy in the UK [11]. Prevalence rates are estimated to be 4.5% (2009) in Canada and up to 13% (2007) in the US [12, 13]. The most frequently used treatment for

depression in pregnant women is selective serotonin re-uptake inhibitors (SSRIs) [14, 15], accounting for approximately 80% of prescribed antidepressants during pregnancy [11, 12, 15–18]. The widespread use of antidepressants during pregnancy makes it essential to understand the safety and the risk of adverse outcomes in the fetus.

Up until 2005 paroxetine was considered to be safe for use during pregnancy [19–23]. However, following results from a small unpublished study conducted by the manufacturer, there were suggestions of an increase in the risk of cardiac malformations in infants with *in utero* exposure to paroxetine, compared with those unexposed to paroxetine. This resulted in a modification of the product label to include warnings of the risk of cardiac malformations with antenatal exposure to paroxetine [24]. At the same time, the US FDA changed the classification of paroxetine from pregnancy category C (human data lacking: animal studies positive or not done) to category D (human data show risk, but benefit may outweigh). Subsequent to these changes, numerous studies using various study designs with the use of different populations across Europe and North America have been published. Some supported statistically significant association of the risk of congenital malformations with first trimester exposure of paroxetine [25–31]. Conversely, findings from other studies showed conflicting results in terms of statistical significance, although a trend remained towards an increased risk.

Paroxetine and other SSRIs are known to cross the maternal placental barrier [32, 33] and significant concentrations of antidepressants have been found in the amniotic fluid [34]. It is thought that SSRIs may affect fetal cardiovascular and central nervous system development through interference with the serotonin 5-HT_{2B} receptor [35]. In addition, physiological systems such as the sleep-wake cycle, circadian rhythms and hypothalamic-pituitary-adrenal axis are affected by increased serotonergic neurotransmission [36].

As more studies have been conducted overtime, a number of meta-analyses have been performed in order to find more conclusive answers to the question of teratogenicity associated with paroxetine and/or other SSRIs. Earlier meta-analyses, that reported an increased risk of cardiac defects associated with paroxetine had methodological limitations such as using studies that did not adjust for all potential risk factors for malformations (confounders) [37, 38]. Wurst *et al.* [38] have performed a meta-analysis showing that paroxetine use during pregnancy was increasing the risk of cardiac defects. However, some studies were not considered and only studies up to 2009 were used. In an attempt to categorize studies in terms of their quality (by using quality tools), Girgordiadis *et al.* [39] conducted a meta-analysis using 19 studies on SSRIs as a class, with a sub-analysis of individual SSRIs. They found an increased risk of congenital cardiac malformations, but major

malformations as a whole were not associated with paroxetine exposure. Myles *et al.* [40] conducted another meta-analysis of 16 studies also investigating SSRIs as a whole but excluded studies with any antidepressant medications in the comparator group. Paroxetine was associated with an increase in the risk of major malformations and cardiac malformations. However, some relevant studies were not included in Myles *et al.* [40], and the majority of studies used did not distinguish between the potential effect of depression (the underlying condition) and the drug (paroxetine) on the risk of major and cardiac malformations.

There is a strong recommendation for studies to include untreated patients with depression and/or other psychiatric diagnoses [41]. Recent studies have attempted to overcome this by including a comparison group of untreated depressed patients [16, 42–44], some of which were not considered in previous meta-analyses. In light of new publications and recent recommendations, we aimed to conduct a meta-analysis incorporating more recent findings, stratifying on types of comparison groups to update current understanding of paroxetine and major congenital malformations, with a particular focus on cardiac defects. The impact of study designs, methodologies and comparator groups (reference category) on the quantification of the effect were also studied.

Method

Electronic and hand searches

A systematic electronic literature search of English and French language publications, indexed in MEDLINE and EMBASE databases between 1966 to the 10 November 2015, was conducted by three individual reviewers independently (AB, NI, SC) using a broad combination of search terms. The search strategy was written in Ovid and run in each database (Supplementary file S1). Strategies were based on the subject headings specific to the individual databases searched, combined with appropriate keywords and phrases. After exclusion of duplicates, full text of potentially relevant studies was retrieved and examined. The reference list of manuscripts included in the analysis, were manually searched for additional relevant publications. Corresponding authors of studies that contained information on SSRIs, but not specifically on paroxetine, as an individual drug, were contacted for additional information. Information available in previous meta-analyses that were obtained by investigators from the corresponding authors was also used [38, 40].

Inclusion and exclusion criteria

Studies were included if 1) they investigated paroxetine use during the first trimester of pregnancy (if the study investigated SSRIs as a class, it was only included if individual data or a sub-analysis for paroxetine use alone was available), 2) they had a comparator group, 3) they

reported an effect measure such as odds ratio (OR), risk ratio (RR) or there were enough information to calculate an unadjusted OR and 4) the outcomes investigated included any major congenital malformations, and/or major cardiac malformations and/or sub-categories of cardiac defects. Studies were excluded if 1) exposure consisted of SSRIs and/or other antidepressants combined or 2) exposure did not occur during the first trimester of pregnancy. Additionally, if the data source of two or more studies overlapped with each other (time period, population, inclusion and exclusion criteria), the most recent study was included (Supplementary file S2).

Data extraction

Data were extracted from each study independently by two reviewers using a standardized extraction form. Disagreements of data collected were resolved by re-examining the data by a third reviewer.

Meta-analysis

Since the prevalence of major congenital malformations is less than 10%, we have assumed that the OR is equivalent to the RR and will refer to the effect measure as OR throughout [45]. If the effect size was not reported in the study, we calculated the unadjusted OR and their 95% confidence intervals (95% CI) from the raw data. We used the adjusted ORs in preference to unadjusted ORs, and estimates related to all infants in preference to estimates from subgroups only. Due to the differences in methods between study populations, a random effects model was used to calculate a pooled OR for each outcome in our meta-analysis [46]. In order to evaluate publication bias in our main meta-analysis, we inspected a funnel plot (eye ball test). However, given the inherent subjectivity of a graphical assessment, the Egger test and trim and fill methods were used to adjust for a potential publication bias [47]. Also, abstract data were combined with the included studies in a sensitivity analysis. The I-squared (I^2) test was used to assess the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance).

In an attempt to explain possible heterogeneity between studies, we conducted several sub-group analyses by study design (cohort/case control), continent (North America, Europe, Australia), type of comparator groups, time to defect ascertainment (less than 1 year/up to 1 year and more), definitions of first trimester exposure, type of data source (administrative claims data/prescription databases linked to registries, clinical data linked to registries and teratogen information services) and timing of the exposure. We also restricted the main analysis to the use of only adjusted OR estimates (no unadjusted values), studies that specified excluding chromosomal and/or genetic defects and other teratogenic substances, studies that adjusted for depression or consisted of a depressed cohort and studies that excluded or adjusted analyses for

individuals with epilepsy or hypertension. In addition, sensitivity analyses using fixed effects were performed to ensure the robustness of our results. All pooled ORs were calculated using STATA software (version 11).

Results

After screening abstracts and titles, 53 articles were identified as potentially relevant studies and full texts were obtained (Figure 1). In addition, nine articles were identified through hand searching references. Twenty-three studies in total were included in the meta-analysis, 16 with a result on major malformations [16, 19, 20, 23, 24, 26–28, 30, 41, 47, 48, 50–52, 54] and 19 with a result on cardiac malformations [16, 19, 23, 24, 26–30, 41, 43, 47–52, 54, 55]. Thirty of the potentially relevant articles were excluded in the analysis because they did not investigate the outcome of interest (major congenital malformations, major cardiovascular malformations) ($n = 5$), exposure time window was not in the first trimester ($n = 4$), exposure group of interest contained other SSRIs or antidepressants ($n = 8$), overlapped with a previous study/and or combined previously published results/updated later ($n = 3$), contained a control group from a different population ($n = 1$), were abstracts ($n = 7$) or a commentary ($n = 1$) (Supplementary file S2). Relevant results available from abstracts were not included in the main analysis. However four were added to the sub-analyses [56–59].

Three authors were contacted for additional information [44, 61, 62]. Two authors could not give specific information for paroxetine and the studies were not included in the analysis [60, 61]. One author provided additional information and the study was included [44]. Further information on studies published in previous meta-analyses that were obtained through author contact was also included in our meta-analysis [19, 20, 38, 40].

Characteristics of studies included

Included studies contained data collected from Australia, Canada, Denmark, Israel, Italy, The Netherlands, Sweden, United Kingdom and United States. Four studies used a case-control design [27, 29, 30, 51] and the remaining 15 used cohort study designs. Study populations ranged from 534 subjects to 949 504 in size. The most common data sources were prescription databases linked to birth registries. Other sources included claims and administrative databases, active surveillance cohorts and teratogen information service data (Table 1).

In order to include prescriptions received immediately before pregnancy and potentially used during pregnancy (duration overlaps with the start of pregnancy), the majority of studies defined the exposure time window as 30 days prior to conception date until the end of the first trimester (14 weeks of gestation; nine

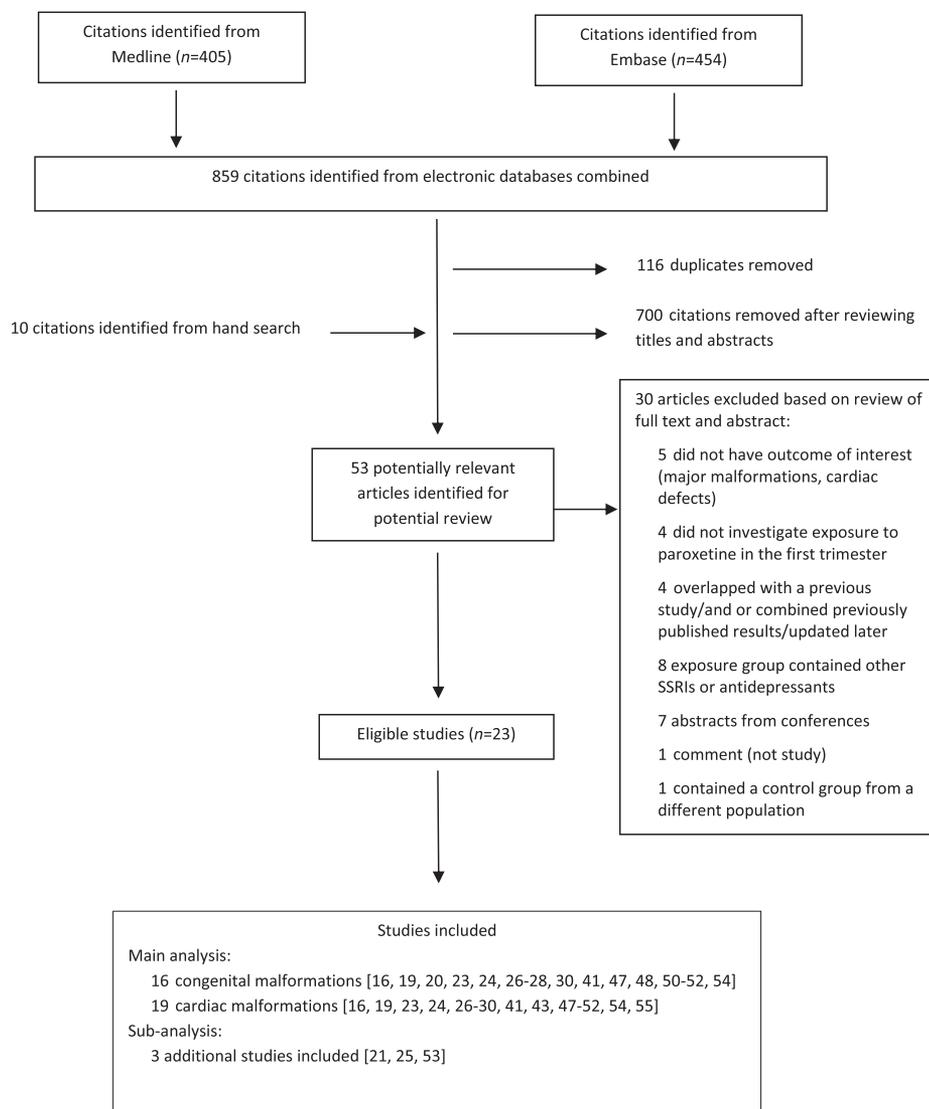


Figure 1

Flow diagram of study selection in the systematic review and meta-analysis of the effect of paroxetine use during pregnancy on the risk of major malformations and cardiac malformations. [Indexed from 1966 to November 10th, 2015].

studies). Comparison groups consisted of unexposed to any antidepressants (non-medicated depressed and non-depressed women), those unexposed to SSRIs (non-SSRI treated patients or other antidepressant treated patients, non-medicated depressed patients, non-depressed women) and unexposed to paroxetine (can be exposed to other SSRIs or non-SSRI antidepressants). Two studies used non-medicated controls with a diagnosis of depression [42, 50] and the control groups in two studies consisted of all subjects treated with other antidepressants [28, 29]. Oberlander *et al.* [53] and Nordeng *et al.* [52] adjusted for depression in their analyses. Knudsen *et al.* [44] and Jimenez-Solem *et al.* [16] included an exposure group of women who stopped SSRIs treatment 3 to 12 months before the last menstrual period, did not use their SSRIs during pregnancy but restarted taking the same SSRIs after pregnancy. Most studies adjusted for maternal age. Other

confounding factors that were adjusted for included smoking, alcohol use, folic acid intake, year of birth, parity, presence of chronic diseases, body mass index, education, other medications, income and maternal depression (Table 1).

Major congenital malformations

Based on 15 studies using women unexposed to paroxetine as reference category (women could be using other antidepressants including other SSRIs), the use of paroxetine was associated with a statistically significant 23% increased risk of major congenital malformations (pooled OR 1.23, 95% CI 1.10, 1.38) [16, 19, 20, 25, 27–29, 31, 42, 48, 49, 51–53, 55] (Figure 2A). After restricting the analysis to studies that compared women using paroxetine with women unexposed to SSRIs, the ORs remained similar (Table 2, Figure 2).

Table 1

Characteristics of included studies

Study	Study period	Country and data source	Study design	Exposure (first trimester)/ sample size	Comparison group	Relevant congenital malformations	Relevant findings (paroxetine use only)
Furu et al. [23]	1996–2010	Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) Nationwide health registers	Cohort	SSRIs as a class and individually Total n = 2 303 647 Paroxetine: 2879	Unexposed to any antidepressant	Major congenital malformations Cardiovascular defects Atrial and ventricular septal defects Right ventricular outflow tract obstructions Conotruncal and major arch defects	Adjusted OR 1.16, 95% CI 0.95, 1.41 Adjusted OR 1.30, 95% CI 0.96, 1.75 Adjusted OR 1.37, 95% CI 0.96, 1.95 Adjusted OR 2.54, 95% CI 1.31, 4.90 Adjusted OR 2.27, 95% CI 1.01, 5.07
Ban et al. [42]	1990–2009	UK The Health Improvement Network	Cohort	SSRIs as a class and individually Total n = 349 127 Paroxetine: 1200	1) Depressed untreated 2) No depression (unexposed to any antidepressant)	Major congenital defects Cardiovascular defects	Adjusted OR 1.08, 95% CI 0.77, 1.50 Adjusted OR 1.79, 95% CI 1.09, 2.89
Huybrechts et al. [50]	2000–2007	US Medicaid Analytic eXtract	Cohort	All antidepressants Total n = 949 504 Paroxetine: 11 126	Unexposed to antidepressant (depressed or not depressed)	Any cardiac malformation	Adjusted OR 0.94, 95% CI 0.73, 1.21
Knudsen et al. [44]††	1995–2008	Denmark Medical Birth Registry; National Hospital Register; National Prescription Registry, Statistic Denmark	Cohort	SSRIs as a class and individually Total n = 72 280 Paroxetine: 131*	Unexposed to SSRI (not treated with SSRI from 1 year before to 1 year after pregnancy)	Congenital heart defects*	Adjusted OR (total congenital heart defects) 1.01, 95% CI 0.14, 7.22
Jimenez-Solem et al. [16]	1997–2009	Denmark (Nationwide) Danish Medical Birth Registry, Danish Hospital register, Register of Medicinal Product Statistics	Cohort	SSRIs as a class and individually Total n = 848 786 Paroxetine: 568 Paused exposure (women with exposure to an SSRI 3 to 12 months before conception and 1 to 12 months after giving birth)	Unexposed to SSRI	Major congenital malformations Cardiovascular defects Bulbus cordis anomalies and anomalies of cardiac septal closure	Adjusted OR 1.25, 95% CI 0.84, 1.85 Adjusted OR 1.54, 95% CI 0.77, 3.10 Adjusted OR 1.89, 95% CI 0.85, 4.23
Nordeng et al. [52]	1999–2005	Norway Norwegian Mother Child Cohort (information from hospital lists and questionnaires)	Cohort	SSRIs as a class and individually Total n = 63 395 Paroxetine: 76	Non-exposed to any antidepressants (6 months before pregnancy)	Major congenital malformations	Unadjusted OR 1.70, 95% CI 0.55, 5.63
Colvin et al. [48]	2002–2005	Australia Western Australia Data Linkage System; hospital mortality data; national pharmaceutical claims dataset	Cohort	SSRIs as a class and individually Total n = 96 968 Paroxetine: 572	Non-exposed to SSRI (can be exposed to other antidepressants)	Major congenital malformations Bulbus cordis anomalies and anomalies of cardiac septal closure	Adjusted OR 0.99, 95% CI 0.65, 1.51 Unadjusted OR 1.76, 95% CI 0.83, 3.72

(Continues)

Table 1
(Continued)

Study	Study period	Country and data source	Study design	Exposure (first trimester)/ sample size	Comparison group	Relevant congenital malformations	Relevant findings (paroxetine use only)
Malm et al. [31]	1996–2006	Finland Drugs and pregnancy project database (Registries for Medical Birth, Congenital Malformations, Drug reimbursement)	Cohort	SSRIs as a class and Individually Total n = 635 583 Paroxetine: 968	Unexposed to SSRI in analysis of all SSRIs; For paroxetine SSRIs: Unexposed to paroxetine (includes other SSRIs)	Major congenital malformations Cardiovascular defects	Adjusted OR 1.22, 95% CI 0.91, 1.64 Adjusted OR 1.09, 95% CI 0.66, 1.79
Bakker et al. [30]	1997–2006	Netherlands Eurocat Northern Netherlands database	Case–control	Paroxetine Total n = 1293 (678 cases, 615 controls) Paroxetine: 16	Unexposed to any SSRIs	Congenital heart defects Bulbus cordis anomalies and anomalies of cardiac septal closure	Adjusted OR 1.5, 95% CI 0.5, 4.0 Adjusted OR 1.6, 95% CI 0.4, 5.6
Reis et al. [25]	1995–2007	Sweden (birth register)	Cohort	SSRIs as a class and paroxetine individually Total n = 15 017 infants Paroxetine: 1208	Unexposed to an antidepressant	'Relatively severe' malformation Cardiovascular defects	Adjusted OR 1.20, 95% CI 0.90, 1.61 Adjusted OR 1.67, 95% CI 1.09, 2.53
Pedersen et al. [54]†	1996–2003	Denmark Birth registry, fertility database, hospital register, medicinal product statistic	Cohort (population based)	SSRIs as a class and Individually Total n = 493 113 Paroxetine: 299	Unexposed to an antidepressants	Any malformations	Adjusted OR 1.41, 95% CI 0.79, 2.51
Diav-Citrin et al. [55]	1994–2002	Israel, Italy, Germany Teratology information service	Prospective cohort	Paroxetine and fluoxetine individually Total n = 2191 Paroxetine: 463	Unexposed to SSRIs or known teratogens (n = 1467)	Any malformations† Cardiovascular defects	Adjusted OR 2.14, 95% CI 1.19, 3.82 Adjusted OR 2.66, 95% CI 0.80, 8.90
Einarson et al. [56]	Not specified	Italy; Switzerland; Australia; Germany; Israel; Finland Teratology information services	Case–control	Paroxetine 1174 exposure to Paroxetine identified from the TIS2061 exposures from published studies, not used in analysis	Unexposed to known teratogens with similar clinic characteristics to women with case infants	Cardiovascular defects	Adjusted OR 1.11, 95% CI 0.36, 2.78
Oberlander et al. [53]	1998–2001	Canada Administrative databases (British Columbia registry of births, hospital separation records, PharmCare registry, Medical Services Plan, PharmNet)	Cohort (population based)	SRI monotherapy SRIs and benzodiazepines Total n = 119 547 Paroxetine (monotherapy): 993	Unexposed to SRIs and benzodiazepines	Major congenital malformations† Cardiovascular malformation†	Unadjusted OR 0.93, 95% CI 0.64, 1.35 Unadjusted OR 1.48, 95% CI 0.70, 3.10
Alwan et al. [27]	1997–2002	US NBDPS surveillance study	Retrospective Case–control (population bases)	SSRIs Total n = 13 714 (9622 cases, 4092 controls) Paroxetine: 88	Controls: Infants with no birth defects Comparison: Unexposed to SSRIs	Major congenital malformations Cardiovascular defects	Adjusted OR 1.60, 95% CI 0.90, 2.77 Adjusted OR 1.70, 95% CI 0.92, 3.16

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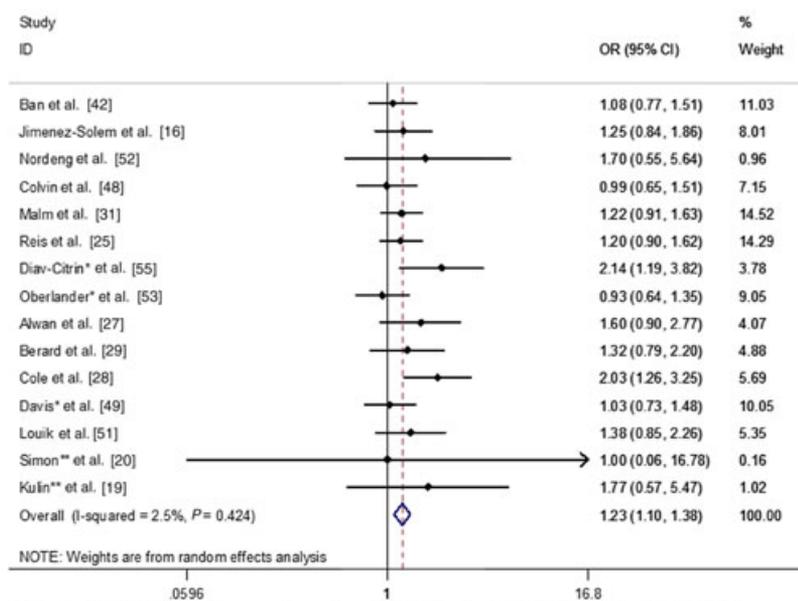
Table 1
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Study	Study period	Country and data source	Study design	Exposure (first trimester)/ sample size	Comparison group	Relevant congenital malformations	Relevant findings (paroxetine use only)
Berard et al. [29]	1997–2003	Canada Québec databases (Quebec Pregnancy Cohort)	Nested case-control (population based)	Paroxetine Total n = 1403 (101 cases, 1302 controls) Paroxetine: 542	Exposure to non-SSRI antidepressants	Bulbus cordis anomalies and anomalies of cardiac septal closure Major congenital malformations major cardiac malformations Bulbus cordis anomalies and anomalies of cardiac septal closure	Adjusted OR 1.70, 95% CI 0.8, 3.5 Adjusted OR 1.32, 95% CI 0.79, 2.20 Adjusted OR 1.38, 95% CI 0.49, 3.94 Unadjusted OR 1.14, 95% CI 0.44, 2.99
Cole et al. [28]	1995–2004	US United Healthcare Claims database	Cohort	Paroxetine Total n = 5752 Paroxetine: 815	Exposed to other antidepressants as monotherapy or polytherapy.	Any congenital malformation Cardiovascular malformations	Adjusted OR 2.03, 95% CI 1.28, 3.25 Adjusted OR 1.46, 95% CI 0.74, 2.89
Davis et al. [49]	1996–2000	US HMO research network program administrative databases)	Cohort (population based)	SSRIs as a class and individually Total n = 805 Paroxetine: 182	Unexposed to SSRIs	Congenital anomalies Cardiac defects†	Unadjusted OR 1.03, 95% CI 0.73, 1.48 Unadjusted OR 1.03, 95% CI 0.45, 2.32
Kallen et al. [26]*	1995–2004	Sweden Swedish medical birth register, birth defects register and hospital discharge, register	Cohort	SSRIs as a class and individually Total n = 860 215 Paroxetine: 959	Unexposed to any antidepressant	Major congenital malformations Cardiac malformation Bulbus cordis anomalies and anomalies of cardiac septal closure	Adjusted OR 1.03, 95% CI 0.76, 1.8 Adjusted OR 1.63, 95% CI 1.05, 2.53 Unadjusted OR 1.81, 95% CI 0.96, 3.09
Louik et al. [51]	1993–2004	US The birth defects study (population based)	Retrospective Case-control	SSRIs Total n = 15 709 (9849 cases, 5860 controls) Paroxetine: 97	Controls: Infants with no birth defects Comparison: Unexposed to antidepressants	Major congenital malformations [38] Any cardiac defect Bulbus cordis anomalies and anomalies of cardiac septal closure	Adjusted OR 1.38, 95% CI 0.85, 2.27 Adjusted OR 1.40, 95% CI 0.79, 2.46 Adjusted OR 0.8, 95% CI 0.3, 2.2
Malm et al. [21]§	1996–2001	Finland Drugs and pregnancy project database (Registries for Medical Birth, Congenital Malformations, Drug reimbursement)	Cohort (Population based)	SSRIs Total n = 1920 Paroxetine: 149	Women with no drug purchases	Major congenital malformations Cardiac malformations	Adjusted OR 0.4, 95% CI 0.1, 3.3 Adjusted OR 0.66, 95% CI 0.09, 4.95
Simon et al. [20]	1986–1998	US Group Health Cooperative (claims database)	Retrospective Cohort	SSRIs as a group TCAs Total n = 787 Paroxetine: 38	Unexposed to SSRIs	Major and minor malformations¶	Unadjusted OR 1.00, 95% CI 0.06, 16.78
Kulin et al. [19]	Not specified	Canada, US Teratogen information service (Motherisk Program)	Controlled cohort	SSRIs as a group Total n = 534 Paroxetine: 97	Unexposed to known teratogenic agents	Major congenital malformations¶ Cardiac malformations¶	Unadjusted OR 1.77, 95% CI 0.57, 5.47 Unadjusted OR 0.77, 95% CI 0.09, 6.89

*Information obtained from authors. †Potential overlap of data with Jimenez-Solem et al. [16]. However overlap is minimal and therefore considered as an independent study. ‡Unadjusted OR (calculated via a 2 by 2 table). §This study overlaps with Malm et al. [31]; used when restricting comparison group to: unexposed to all antidepressants. ¶Unadjusted OR (obtained via previous meta-analysis). **Overlaps with Reis et al. [25]; used in sub-analysis. ††Potential overlap of data with Jimenez-Solem et al. [16]. However overlap is minimal and therefore considered as an independent study. Data set is smaller but includes still births, and terminations, not available in Jimenez-Solem et al. [16].

A. Major malformations

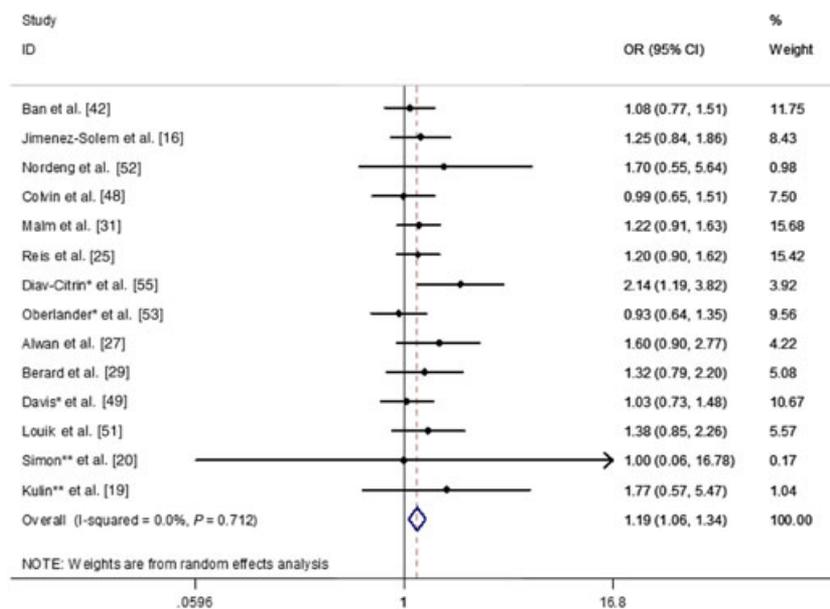
Comparison: unexposed to paroxetine



**Unadjusted OR (obtained from previous meta-analysis); *Unadjusted OR (obtained via a 2 by 2 table)

B. Major malformations

Comparison: unexposed to SSRIs



**Unadjusted OR (obtained from previous meta-analysis); *Unadjusted OR (obtained via a 2 by 2 table)

Figure 2

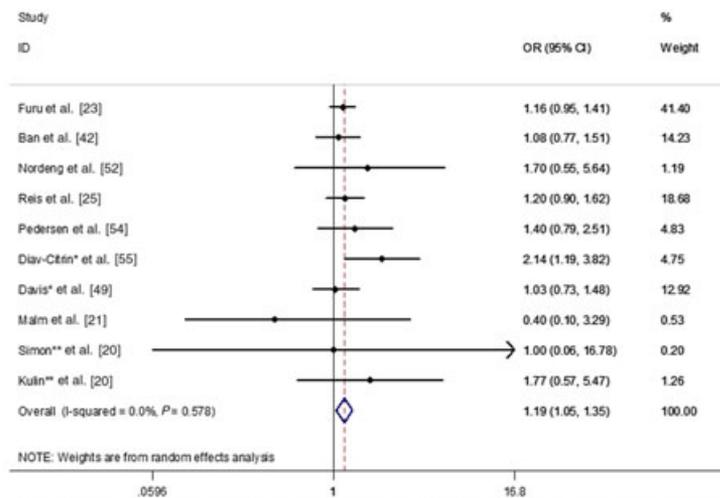
Forest plots and pooled measures of risks for overall malformation and cardiac malformation according to the comparator group. (A) Major malformations, comparison: unexposed to paroxetine, (B) major malformations, comparison: unexposed to SSRIs, (C) major malformations, comparison: unexposed to any antidepressants, (D) cardiac malformations, Comparison: unexposed to paroxetine, (E) cardiac malformations, comparison: unexposed to SSRIs, (F) cardiac malformations, comparison: unexposed to any antidepressants.

The risk estimates were slightly higher in subgroups using different data sources such as clinic surveillance linked to registries (pooled OR 1.49, 95% CI 1.05, 2.12; $n = 3$ studies) (Table 2).

The estimate was higher (pooled OR 1.66, 95% CI 1.09, 2.53; $n = 2$ studies) when the comparison group was restricted to women prescribed a non-paroxetine antidepressant. However, a higher inter-study heterogeneity

C. Major malformations

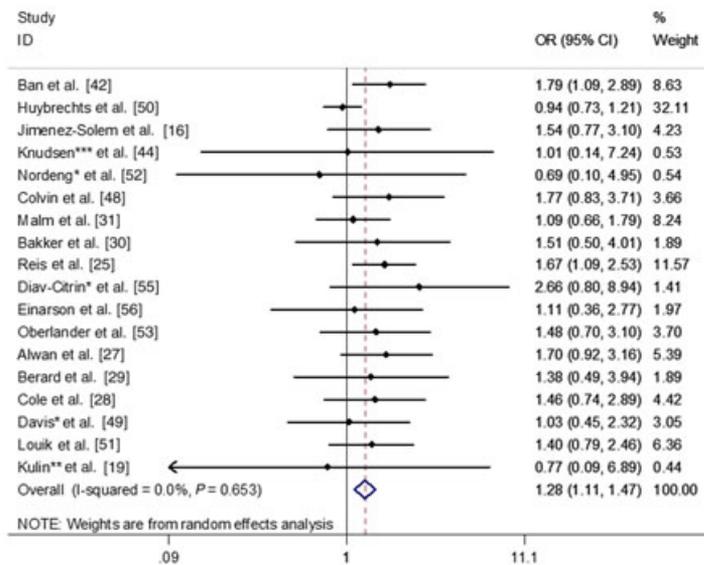
Comparison: unexposed to any antidepressants



**Unadjusted OR (obtained from previous meta-analysis); *Unadjusted OR (obtained via a 2 by 2 table)

D. Cardiac malformations

Comparison: unexposed to paroxetine



***Adjusted OR (obtained from authors); *Unadjusted OR (calculated via a 2 by 2 table)

Figure 2

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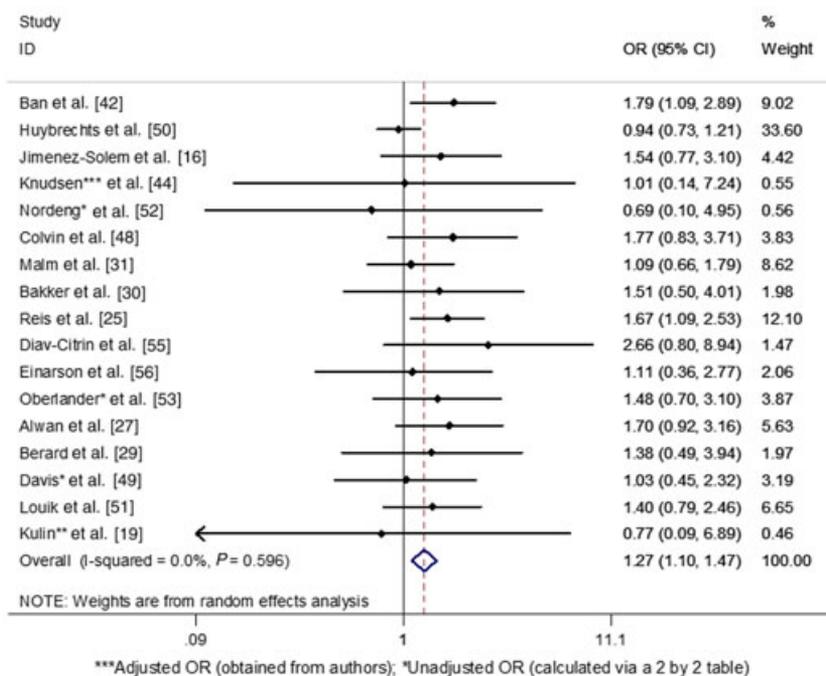
was observed in this latter subgroup ($I^2 = 30.9\%$) (Table 2). It remained nevertheless that the inter-study heterogeneity was null or very low in the majority of combinations.

Cardiac malformations

An aggregated outcome for all cardiac malformations was reported in 19 studies with a total of 20251 women exposed to paroxetine (Figure 2). The estimate for all major cardiac malformations in women exposed to paroxetine compared with non-paroxetine exposure (can be exposed to other antidepressants) was pooled OR 1.28 (95% CI 1.11, 1.47; $n = 19$ studies) (Table 2, Figure 2D). This

estimate was similar when the comparison group was restricted to women with no antidepressant use (Table 2, Figure 2F). The risk estimate increased slightly when the analysis was restricted to studies with adjusted estimates (pooled OR 1.35, 95% CI 1.23, 1.62; $n = 13$ studies) (Table 2). Estimates varied amongst different data sources; i.e. lower pooled risk was seen in studies conducted with data from administrative databases (pooled OR 1.00, 95% CI 0.79, 1.25; $n = 4$ studies). A higher risk was seen in studies conducted with data obtained in Europe (pooled OR 1.40, 95% CI 1.06, 1.84; $n = 7$ studies) (Table 2).

E. Cardiac malformations
Comparison: unexposed to SSRIs



F. Cardiac malformations
Comparison: unexposed to any antidepressants

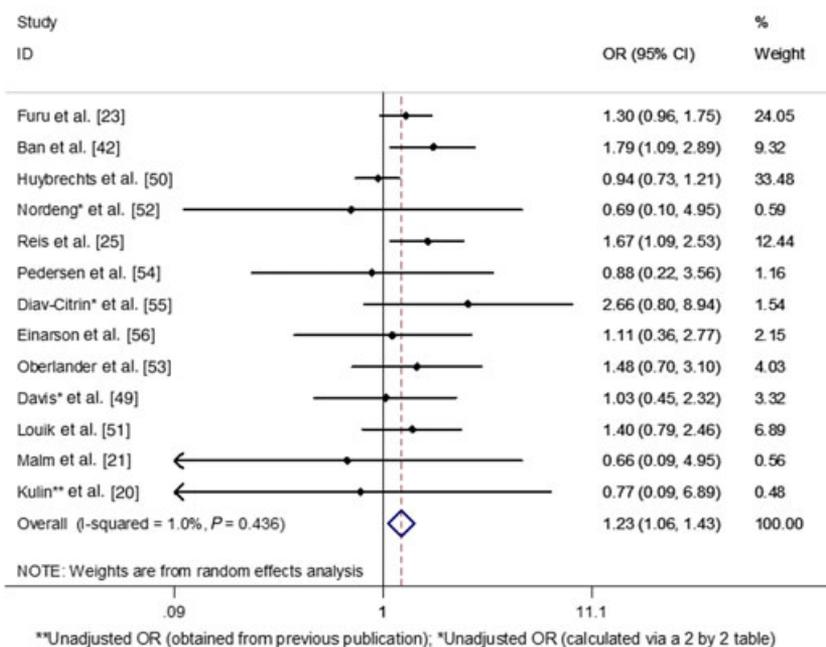


Figure 2

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Specific cardiac malformations

Table 3 presents the specific cardiac malformations reported. Compared with women not exposed to paroxetine, the use of paroxetine was associated with an increased risk of bulbus cordis anomalies and anomalies

of cardiac septal closure (pooled OR 1.42, 95% CI 1.07, 1.89; $n = 8$ studies), atrial septal defects (pooled OR 2.38, 95% CI 1.14, 4.97; $n = 4$ studies) and right ventricular outflow track obstruction defects (pooled OR 2.29, 95% CI 1.06, 4.93; $n = 4$ studies). One study reported the risk

Table 2

Sub-analyses of major malformations and cardiac malformations

	Major malformations (all/aggregate)			Cardiac malformations (all/aggregate)		
	Number of studies	Effect size Pooled OR (95% CI)	Between-sample heterogeneity I ² (P value)	Number of studies	Effect size Pooled OR (95% CI)	Between-sample heterogeneity I ² (P value)
Comparison group						
Unexposed to paroxetine (unadjusted or adjusted ORs combined)	15	1.23 (1.10, 1.38)	1.8% (0.431)	18	1.28 (1.11, 1.47)	0.0% (0.653)
Unexposed to paroxetine (adjusted ORs only)	10	1.26 (1.11, 1.43)	0.0% (0.615)	13	1.35 (1.23, 1.62)	8.5% (0.361)
Unexposed to SSRIs (unadjusted or adjusted ORs combined)	14	1.19 (1.06, 1.34)	0.0% (0.722)	17	1.27 (1.10, 1.47)	0.0% (0.596)
Unexposed to SSRIs (adjusted ORs only)	9	1.21 (1.06, 1.38)	0.0% (0.936)	11	1.36 (1.09, 1.56)	21.2% (0.241)
Unexposed to any antidepressants (unadjusted or adjusted ORs combined)	10	1.19 (1.05, 1.35)	0.0% (0.578)	13	1.23 (1.06, 1.43)	1.0% (0.436)
Unexposed to any antidepressants (adjusted ORs only)	6	1.21 (1.03, 1.43)	17.5% (0.300)	8	1.27 (1.03, 1.56)	27.1% (0.212)
Exposed to antidepressants other than paroxetine	2	1.66 (1.09, 2.53)	30.9% (0.229)	2	1.44 (0.81, 2.54)	0.0% (0.925)
Diagnosed with depression and/or anxiety (exposed or unexposed to an antidepressant other than paroxetine)	3	1.28 (0.74, 2.22)	81.4% (0.005)	4	1.33 (0.87, 1.71)	38.4% (0.181)
Diagnosed with depression and/or anxiety but not exposed to any antidepressant	1	-	-	2	1.20 (0.69, 2.08)	73.1% (0.051)
Addition of other data						
Addition of data from abstracts and unpublished studies	18	1.26 (1.11, 1.42)	16.2% (0.260)	21	1.27 (1.10, 1.46)	0.0% (0.585)
Study design						
Case-control	3	1.42 (1.05, 1.91)	0.0% (0.879)	4	1.51 (1.01, 2.17)	0.0% (0.972)
Cohort	13	1.21 (1.06, 1.38)	15.2% (0.295)	15	1.23 (1.01, 1.45)	0.0% (0.449)
Where study took place						
North America	8	1.28 (1.04, 1.58)	21.1% (0.262)	9	1.23 (1.01, 1.5)	8.0% (0.369)
Europe	6	1.19 (1.01, 1.41)	0.0% (0.946)	7	1.40 (1.06, 1.84)	0.0% (0.808)
Australia	1	-	-	1	-	-
More than one continent	1	-	-	2	1.6 (0.69, 3.79)	16.2% (0.275)
Time to malformation ascertainment						
Less than 1 year of age	4	1.69 (1.22, 2.3)	0.0% (0.532)	4	1.04 (0.84, 1.29)	0.0% (0.438)
Up to 1 year or beyond	5	1.27 (1.01, 1.61)	10.5% (0.346)	6	1.10 (0.66, 1.86)	50.7% (0.07)
Not specified	7	1.41 (0.99, 1.31)	0.0% (0.800)	9	1.51 (1.22, 1.87)	0.0% (0.895)
Data source						
Administrative/claims database	4	1.39 (0.78, 2.49)	61.1% (0.077)	4	1.00 (0.79, 1.25)	0.0% (0.491)
Prescription database and/or linked to birth registry	6	1.21 (0.96, 1.30)	0.0% (0.804)	7	1.46 (1.13, 1.89)	0.0% (0.884)
Clinic/surveillance and/or link to registries	3	1.49 (1.05, 2.12)	0.0% (0.901)	4	1.48 (1.02, 2.17)	0.0% (0.846)
Teratogen information services	3	1.50 (0.99, 2.26)	37.9% (0.200)	4	1.62 (1.21, 2.32)	0.0% (0.646)
Inclusions and exclusions						
Studies excluded chromosomal and/or genetic defects	5	1.28 (1.05, 1.55)	21.5% (0.277)	6	1.25 (0.93, 1.68)	43.8% (0.113)
Studies excluded or adjusted for the use of teratogenic drugs	6	1.23 (1.01, 1.52)	20.0% (0.283)	8	1.18 (0.94, 1.48)	14.0% (0.320)
Covariates adjustments						
Adjusted for maternal chronic diseases	7	1.25 (1.01, 1.54)	32.9% (0.189)	10	1.16 (0.97, 1.38)	0.0% (0.476)
Adjusted for depression or used a cohort of depressed pregnant women	5	1.26 (0.95, 1.69)	45.3% (0.120)	6	1.25 (0.93, 1.67)	27.5% (0.229)
Definition of first trimester exposure						
At least 30 days before to end of first trimester	8	1.15 (1.00, 1.33)	0.0% (0.681)	10	1.49 (1.20, 1.85)	0.0% (0.958)
Not specified	5	1.27 (0.98, 1.63)	17.7% (0.302)	5	1.50 (1.08, 2.09)	0.0% (0.623)

OR odds ratio; 95% CI 95% confidence interval.

Table 3

Meta-analysis of specific cardiac malformations

	Number of studies	Effect size Pooled OR (95% CI)	I ² (P value)
Specific cardiac defects			
Bulbus cordis anomalies and anomalies of cardiac septal closure	8	1.42 (1.07, 1.89)	0.0% (0.756)
Ventricular septal defect	5	1.26 (0.69, 2.32)	59.1% (0.044)
Atrial septal defect	4	2.38 (1.14, 4.97)	65.8% (0.032)
Ventricular and atrial septal defects combined	1	1.37 (0.96, 1.95)	-
Other cardiac defects/other congenital anomalies of heart	4	1.28 (0.96, 1.69)	0.0% (0.254)
Left ventricular outflow tract obstruction	2	1.00 (0.38, 2.61)	0.0% (0.387)
Right ventricular outflow tract obstruction	4	2.29 (1.06, 4.93)	81.0% (0.001)
Conotruncal heart defects including tetralogy of Fallot, interrupted aortic arch, ventricular septal defect and persistent truncus arteriosus	3	1.77 (0.96, 3.26)	0.0% (0.875)

OR, odds ratio; 95% CI, 95% confidence interval.

of pulmonary valve defect (unadjusted OR 1.84, 95% CI 0.75, 4.54) [48], left-sided defects (adjusted OR 2.1, 95% CI 0.5, 8.7) [30] and the risk of other anomalies of the peripheral vascular system (unadjusted OR 2.91, 95% CI 1.82, 4.65) [48]. There was higher heterogeneity between studies with the reporting of specific individual cardiac outcomes.

Impact of study design, methodology and adjustment for indication bias

Study designs, inclusion and exclusion criteria, exposure time window definitions, duration/time period of malformation ascertainment, adjustment for confounders including the indication and whether abstracts without full length paper data were considered had minimal impact on the pooled estimates (Table 2). Paroxetine use during the first trimester of pregnancy was always increasing the risk of malformations and cardiac malformations specifically.

Publication bias

A publication bias was present in the meta-analysis on the risk of major congenital malformations ($n = 16$ studies) (Supplementary file S3) and cardiac malformations ($n = 19$ studies). We performed an adjustment for publication bias using the trim and filled method [47] which imputed four theoretical missing estimates for major congenital malformations and three for cardiac malformations. The revised pooled, estimates taking into account publication bias, were pooled OR_{adjusted for publication bias} 1.16 (95% CI 1.01, 1.33) for major malformations and pooled OR_{adjusted for publication bias} 1.20 (95% CI 1.05, 2.69) for cardiac malformations, compared with the pooled ORs of 1.23 (major malformations) and 1.28 (cardiac malformations) before adjustment. Publication bias of the eight studies on bulbus cordis anomalies and anomalies of cardiac septal closure was not present (Egger >0.05). The fit

and trim method did not impute any hypothetical 'missing' studies for analyses on this specific defect.

Discussion

Main findings

Our systematic review and meta-analysis showed a 23% increased risk of any major congenital malformations and a 28% increased risk of major cardiac malformations associated with paroxetine exposure during the first trimester of pregnancy. This risk of major congenital malformations increased to 42% when only case-control studies were considered, to 69% in studies that followed up infants for ascertaining outcomes less than 1 year after birth and to 49% when clinic or surveillance data were linked to registry. The risk of major cardiac malformations increased to 51% when only case-control studies were considered and to 62% when teratogen information services were used as a data source. The use of paroxetine during the first trimester of pregnancy was associated with a two-fold increased risk of atrial septal defects and right ventricular outflow tract obstruction compared with non-use of SSRIs during pregnancy. Although there was a clear overall increase in the risk of major and cardiac malformations overall, these findings highlight the influence of different aspects of the study design, the data source used, and the exposure and outcome time window of ascertainment when studying the use of antidepressant drugs during pregnancy and the risk of major congenital malformations.

The risk of any major malformations or cardiac malformations differs according to the comparison group used. In our meta-analysis, the highest risk estimates were obtained when the comparator included women exposed to a non-paroxetine antidepressant, hence women who might be treated with other SSRIs or other antidepressants. These studies are therefore adjusting for the indication per design. The most used

comparison group included women unexposed to any antidepressant. Although choice of comparator group varied the risk estimate, it remains that there was a general trend towards increase in risk.

Comparison with existing reviews

The increases in the risk of major and cardiac malformations in this meta-analysis coincide with earlier meta-analyses. Indeed, initial meta-analyses conducted in 2007 and 2010 [38, 63], reported pooled risk estimates for cardiac malformations of 1.72 (95% CI, 1.22, 2.42) [63] and 1.46 (95% CI 1.17, 1.82) [38]. The most recent meta-analysis conducted by Myles *et al.* [40] estimated the risk of cardiac malformations in association with paroxetine use during pregnancy to be 1.44 (95% CI 1.12, 1.86). Our meta-analysis included subsequently published studies with significantly larger population sizes, with data originating from different countries such as the UK and Australia [16, 42, 48, 50]. The 28% increased risk of major cardiac malformations in our meta-analysis is concordant with the 44% increased risk of major cardiac malformations following paroxetine use obtained from a previous meta-analysis [40]. The adjustment for publication bias did not change our conclusion on the risk of any major congenital malformations and major cardiac malformations.

Effect of methodological parameters on risk estimates

Restricting findings according to different data sources showed higher risk estimates in studies using teratogen information services, and lower estimates in studies using administrative and claims data sources, which is important in interpreting findings from studies. Potential bias from information services may exist, as mothers who feel the need to call and enquire may be more likely to be at higher risk than those who have no concerns. In addition there is a risk of recall bias. Many of the claims databases estimated the start of the first trimester and subsequent exposure by using algorithms based on the delivery date to backdate to time of conception, potentially leading to exposure misclassification. Indeed, this is not as accurate as using ultrasound and the date of the last menstrual period, which is used in sources linked to registries and hospital records [28]. In addition, the risk was lower in the pooled estimate of studies that reported time to ascertainment of defect to be less than 1 year. This factor is particularly important in defects such as atrial septal defects, which can remain undetected until later on in life.

Previous literature emphasizes the need to correct for confounding by indication (i.e. to separate the effects of depression from the potential effect of paroxetine). In order to address the potential confounding by indication (effect of depression on the risk estimates), we restricted our analyses to include studies that used women

diagnosed with depression and/or anxiety in their comparison group. This was further limited to include studies with depressed women unexposed to any antidepressant in the comparison group. Although this had an impact on the estimates, it did not change the overall finding of an increased risk. This can be explained by the fact that the majority of studies already adjust for maternal depression in their multivariate analyses.

Clinical implications

In practice, the main question that physicians are faced with when treating depressed women during pregnancy is whether the risk to the fetus after continuing antidepressant therapy, such as paroxetine, is lower or greater than the risk associated with the depression itself or to the risk from other similar treatments (other SSRIs or antidepressants). Due to changes in metabolism during pregnancy, SSRIs are often cleared from the body at a faster rate and hence the concentration of paroxetine in the blood may be reduced to below the therapeutic optimum [64, 65]. In addition, given that pregnant women usually decrease or maintain pre-pregnancy dosage during gestation, it is hypothesized that antidepressants, and paroxetine specifically, put mothers and unborn children at greater risks, which is highlighted in this meta-analysis.

Strengthens and limitations

We carried out several sub-analyses in order to consider different aspects of study designs and data sources that may influence study results. Although variations in estimates were seen depending on the populations, study designs and comparator groups, it remained that there was a constant trend in showing an increasing risk of major malformation and cardiac malformations. We also performed a sub-analysis, which used only adjusted estimates, as malformations have several risk factors. However, some prevalence of specific defects are small and thus are more difficult to study, partly explaining why they are less likely to be reported in individual studies.

Conclusions

Paroxetine is associated with a significantly increased risk of major malformations, and cardiac malformations specifically cardiac septal and atrial septal defects, and right ventricular outflow tract obstruction. Studies consisting of a depressed cohort or comparing paroxetine exposure to clinically depressed unexposed pregnant women showed similar risk estimates. Few studies controlled for indication by using depressed non-treated women in the comparison group but the majority took into account maternal depression in the multivariate analyses. Our meta-analysis is novel because it includes up to date

findings, and mostly because it has studied the effect of methodological choices on the reported outcome and adjusted pooled estimates for publication bias. Given the increased metabolism during gestation and thus the decrease of benefit at comparable dosage, it is believed that paroxetine bears more risks than benefits when used during organogenesis. The baseline risk of major malformations is 3% and of cardiac malformations is 1%. However, given that the benefit of using these medications during pregnancy is debatable, any increase in risk is significant. Hence, regardless of the size of the risk, it is essential to disseminate these findings given that they should be used to change practice and impact appropriate antidepressant use during pregnancy.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare AB is a consultant for plaintiffs in the litigation involving antidepressants and birth defects. All other authors report no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Author Contributions

Anick Bérard had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

- Study concept and design: AB, NI, SC, FTM, BT, JPZ
- Acquisition of data: AB, NI, SC, FTM, BT, JPZ
- Analysis and interpretation of data: AB, NI, SC, FTM, BT, JPZ
- Drafting the manuscript: AB, NI, JPZ
- Critical revision of the manuscript and important intellectual content: AB, NI, SC, FTM, BT, JPZ
- Obtained funding: AB
- Study supervision : AB

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S1

Example of the electronic search strategy in Embase with the predefined key words

S2

Articles excluded from the analyses

S3

Assessment of publication bias