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REVIEW ARTICLE

Risk of cardiovascular malformations after exposure to paroxetine in pregnancy: meta-analysis

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Aims and method To examine the association between the use of paroxetine during pregnancy and the risk of cardiovascular defects in the newborn. A systematic review of nine electronic databases was carried out and bibliographies were hand-searched for other relevant articles. Inclusion criteria for studies were the use of selective serotonin reuptake inhibitors in the first trimester of pregnancy, with separate data available for paroxetine and cardiovascular defects in newborn babies. A random-effect model was used to combine the data.

Results A total of 11 studies were included in the analysis, concerning 4515 offspring who were exposed to paroxetine in the first trimester and 1 469 302 controls. In pooled analysis, paroxetine in the first trimester of pregnancy was slightly, but significantly, associated with a risk of cardiovascular malformations in the offspring (relative risk = 1.25, 95% CI 1.01–1.54). Separate analyses of case–control and cohort studies made this difference non-significant.

Clinical implications This meta-analysis supports current guidelines advising not to use paroxetine in early pregnancy.

Declaration of interest P.S. received a research grant as a principal investigator from Eli Lilly for a project that was completed about 6 months prior to his involvement in this study.

Depression during pregnancy is a major public health concern. It is highly prevalent and causes considerable suffering and impairment to the mother and has possible adverse consequences for the newborn.[1–4] Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants during pregnancy[4] and until recently were considered safe in this period.[5] However, database and case–control studies have reported an association between SSRIs and anencephaly, cranio-synostosis, omphalocele and persistent pulmonary hypertension in newborn children, although these associations have not been replicated in other studies.[4,6] First-trimester exposure to paroxetine has been associated with cardiovascular malformations in some studies,[7,8] however, other studies have failed to replicate this finding.[4,9]

We have conducted a meta-analysis with the aim of examining the suggested association between the use of paroxetine during pregnancy and the risk of cardiovascular defects in newborn children.

Method

We used the search engine Dialog™ (formerly, DataStar®) provided by the National Library of Health that includes the following databases: PubMed, Embase, PsycINFO, Social Sciences Citation Index (SSCI), King's Fund, DH-Data, CINAHL, Allied and Complementary Medicine Database (AMED) and British Nursing Index (BNI). Combinations of the terms 'SSRI', 'selective serotonin reuptake inhibitor(s)', 'SRI', 'serotonin reuptake inhibitors', 'paroxetine', 'pregnancy', 'congenital malformation(s)', 'congenital defect(s)', 'cardio-vascular malformation(s)', 'cardiac defect(s)', 'cardiovascular defect(s)', 'fetal malformation(s)' and 'fetal anomalies' were used for the search. The search was restricted to articles published in English but there was no exclusion on the basis of country, ethical approval, etc. No grey literature was searched for this review. Each abstract/title and article was scrutinised by two of the authors (N.P. and R.P.) and the differences between them were resolved by consensus. Relevant articles were hand-searched for cross-references. The GlaxoSmithKline website was searched for recent data on paroxetine. To exclude repetitive data-sets, only the study with the most updated data was taken up for analysis. A repeat data search was done in August 2012, after the first review of this article, and results were updated.

Inclusion and exclusion criteria

We included studies that met the following criteria:

1 use of SSRIs in the first trimester of pregnancy, with separate data available for paroxetine

2 control group of unexposed women available for comparison
3 as an outcome, separate data available for congenital cardiovascular defects in newborns, for instance conotruncal heart defects, septal heart defects, ventricular outflow tract obstruction.

Exclusion criteria were:

1 papers published on repeat data
2 studies with no control group for comparison
3 no cardiovascular defect in both study and control group.

Excluded studies are presented in online Table DS1.

The modified QUOROM Flow Chart[10] (Fig. 1) was used to show the study search process.

Outcome measure

The outcome measure for this review was cardiovascular malformation in the newborn.

Data collection and analysis

We collected data from the studies that met the selection criteria. The quality of studies was assessed by criteria adapted from Centre for Reviews and Dissemination guidelines.[11] Descriptive data were mainly expressed in actual numbers of exposed mothers and controls. Where exact numbers were not available, frequencies were changed into actual numbers (described odds ratios (ORs) were used to resolve doubts). Results were presented in terms of risk ratio (RR) with 95% confidence intervals. A funnel plot was used to assess publication bias and heterogeneity among studies was analysed by the χ^2-test. A random-effect model was applied to combine the data. Subgroup analysis was carried out for cohort and case–control studies separately. Sensitivity analysis was carried out by the sequential removal of studies with maximum weight. Data analysis was performed with Review Manager (RevMan 5.0) for Windows. A checklist recommended by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group[12] was used.

Results

The systematic search identified 29 relevant studies. Only 11 studies[6,8,9,13–19,21] could be included in the analysis, 7 cohort [6,14–17,19,21] and 4 case–control studies[8,9,13,18] (Table 1). The total number of individuals included in the meta-analysis was 4514 in the paroxetine group and 1 469 302 in the control group.

Quality analysis

As shown in Table 1, the studies that met the selection criteria were from all grades except grade B and the lowest grade E on the Centre for Reviews and Dissemination hierarchy of observational studies.[11]

Publication bias

The funnel plot (Fig. 2) shows the relative absence of small-sample sized studies which showed teratogenic effect of paroxetine. In trim-and-fill analysis, three studies on the left side of the plot were trimmed, but the adjusted risk ratio for the main analysis remained significant (RR = 1.23, 95% CI 1.05–1.42).

Test of heterogeneity

Examination of the χ^2 distribution showed that there was significant heterogeneity between the studies included in the main analysis (Q = 14.34, d.f. = 10, $P = 0.1$). In the subgroup analysis, there was no significant heterogeneity within case–control (Q = 0.4, d.f. = 3, $P = 0.9$) and cohort (Q = 8.22, d.f. = 6, $P = 0.2$) studies.

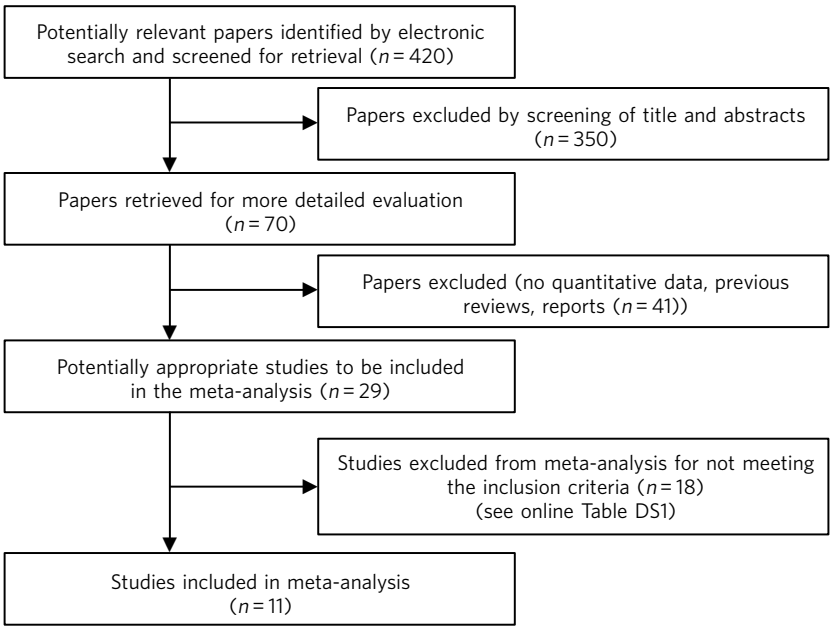

Fig 1 Modified QUORON flow chart[10] describing the search process.

Table 1 Characteristics of included studies

Study	Design and quality[a]	Description of study	Study group	Control group	Results	Comments
Alwan *et al*[9]	D	Data from National Birth Defects Prevention Study (USA)	9622 infants with major birth defects	4092 infants with no major birth defects	No significant association between maternal use of SSRIs and congenital heart defects	Odds ratio adjusted for race/ethnicity, obesity, smoking and income
Bakker *et al*[13]	D	Birth defects registry (The Netherlands)	678 infants with isolated heart defects	615 controls with a genetic disorder with no heart defect	Paroxetine associated with increased risk of atrium septum defects	No increased risk for heart defects overall
Berard *et al*[8]	D	Data from Quebec Pregnancy Registry (Canada) Women on antidepressants during first trimester (excluding those on known teratogens) were included	101 infants with major congenital malformations	1302 infants without congenital malformations	Exposure to paroxetine above 25 mg/day associated with major congenital and cardiac malformations	Odds ratio adjusted for gestational and maternal age, diabetes, hypertension, depression, medications, number and types of antenatal visits and other sociodemographic variables
Davis *et al*[14]	C	Pregnancy outcomes from five managed-care organisations (USA)	1441 full-term infants exposed to antidepressants	49 663 full-term infants not exposed to antidepressants	SSRIs and tricyclic antidepressants did not have a consistent link with congenital anomalies 182 infants exposed to paroxetine did not have an increased risk of cardiac septal defects	Controls could be on other possible teratogenic medicines, no adjustment for confounders
Diav-Citrin *et al*[15]	A	Teratology information services from Israel, Italy and Germany	410 first-trimester paroxetine-exposed pregnancies	1467 women on non-teratogenic drugs	Twofold increase in overall rate of congenital anomalies in paroxetine group Main risks applied to cardiovascular anomalies	After adjusting for various confounders significance disappeared
Einarson *et al*[16]	A	From teratology information centres around the world	1174 infants exposed to paroxetine	Equal number of demographically and clinically matched women on non-teratogenic drugs	The rates of cardiac defects in the paroxetine group and in the unexposed group were both 0.7% (odds ratio 1.1, 95% CI 0.36–2.78)	For meta-analysis actual numbers were derived from frequency and odds ratio
Reis & Kallen[17]	C	Swedish Medical Birth Register	15 017 infants exposed to antidepressants	General population	Association between paroxetine and congenital heart defects was verified	Adjustments were made for year of delivery, maternal age, parity, smoking and BMI

continued

Table 1 Characteristics of included studies *(continued)*

Study	Design and quality[a]	Description of study	Study group	Control group	Results	Comments
Louik *et al*[18]	D	Slone Epidemiology Center Birth Defects Study (USA)	9849 infants with birth defects	5860 infants without birth defects	Sertraline and paroxetine significantly associated with cardiac defects	Reference group was all the women not exposed to any antidepressants Odds ratio adjusted for maternal age, race/ethnicity, education, year of last menstrual period, study centre, smoking, alcohol, history of birth defect in first-degree relative, BMI, parity, seizure, diabetes, hypertension, infertility and folic acid use
Malm *et al*[19]	C	Finnish data	1782 women with at least one purchase of SSRI Women with chronic illnesses were excluded	1782 matched controls, as per year of pregnancy, age, geographic area and social status with no drug purchase	Major malformations were not more common in infants of women with SSRI purchase	For meta-analysis, data for paroxetine were extrapolated from Einarson *et al*[20]
Vial *et al*[21]	A	French data	500 women exposed to paroxetine	500 controls	Incidence of major malformations was 3.6% after paroxetine exposure, compared with 1.8% (RR = 2.03, 95% CI 0.79–5.58) Two major cardiac malformations in each group	Only abstract is available
Wogelius *et al*[6]	C	Data from Danish Medical Birth Registry	1051 women who filled prescription for SSRIs	Reference cohort of 150 780 women with no SSRI prescriptions	Increased risk of congenital malformations after exposure to SSRIs Among offspring of SSRI users, 1.4% had cardiovascular malformation (1% in controls)	Relative risk adjusted for smoking, birth order, maternal age, birth year, county and prescriptions for anti-epileptics, NSAIDs and antidiabetics Data for paroxetine were extrapolated from Einarson *et al*[20]

BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.
a. Adapted from Centre for Reviews and Dissemination guidelines:[11] A (highest quality): cohort (prospective study) with concurrent controls, B: cohort (prospective study) with historical controls, C: cohort (retrospective study) with concurrent controls, D: case–control (retrospective) study, E: observational study without control groups or large differences from comparisons between times and/or places.

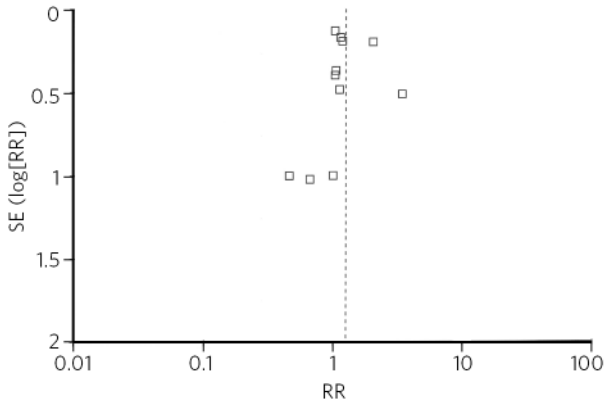

Fig 2 Funnel plot of studies included in the meta-analysis. RR, risk ratio; SE, standard error.

Pooled results

Paroxetine use in the first trimester of pregnancy was found to be significantly associated with cardiovascular malformations, compared with unexposed controls (RR = 1.25, 95% CI 1.01–1.54) (Fig. 3).

Subgroup analysis

Risk of cardiovascular malformation with paroxetine group became non-significant when data were pooled separately for case–control (RR = 1.09, 95% CI 0.91–1.30) and cohort (RR = 1.52, 95% CI 0.98–2.34) studies.

Sensitivity analysis

In sequential removal of studies with maximum effect sizes, the difference between paroxetine and the unexposed control remained significant after excluding the studies by Alwan *et al*[9] and Louik *et al*[18] (RR = 1.38, 95% CI 1.02–1.86). Individually, exclusion of studies by Bakker *et al*[13] (RR = 1.27, 95% CI 0.98–1.64), Louik *et al*[18] (RR = 1.28, 95% CI 0.98–1.66) or Reis & Kallen[17] (RR = 1.11, CI 0.94–1.31) made the pooled result non-significant.

Discussion

The validity of meta-analysis of observational studies has always been debated, as observational studies are more prone to biases when compared with the gold-standard randomised controlled trials.[22] However, a meta-analysis of observational studies seems justified for assessing the teratogenic effect of medications used during pregnancy because experimental studies cannot be conducted and large samples are required to observe rare events such as specific congenital malformations. In recognition of the limitations of meta-analysis of observational studies, we applied a random-effect model (rather than a fixed-effect model) to combine the results, as it can be applied irrespective of the level of heterogeneity of studies. Combining case–control and cohort studies is a well-recognised practice in meta-analysis of epidemiological studies,[12,23] although we also carried out a subgroup analysis for case–control and cohort studies separately. Further, we performed a sensitivity analysis to assess the robustness of results. For quality analysis of the studies, the key components of design were considered, as this method has been found to be more appropriate for meta-analysis of observational studies.[12] In general, the study met the requirements of the MOOSE guidelines.[12]

Although more than half of the identified studies were excluded from the analysis, most of them presented repeat data; thus, the combined results can be taken as a fair representation of the identified studies. There may be some doubts as to the reliability of actual numbers, as in some studies numbers were extrapolated from the frequencies and odds ratios; however, this should not affect the results considerably bearing in mind the large size of the collective sample. The apparent discrepancy between sample size and weight for each study (Fig. 1) corroborates the fact that in meta-analysis, weight given to a particular study depends not only on the sample size, but also on the variance of the data.

Underrepresentation of positive studies with small sample size in publication bias analysis could be a reflection of Type II error, a likely outcome in view of the rarity of the

Study or subgroup	Paroxetine Events	Paroxetine Total	Unexposed controls Events	Unexposed controls Total	Weight, %	Risk ratio M-H, random, 95% CI
Alwan *et al*[9]	32	70	4268	9622	23.7	1.03 (0.80, 1.33)
Bakker *et al*[13]	10	16	678	1277	16.6	1.18 (0.80, 1.73)
Berard *et al*[8]	10	552	24	1403	6.9	1.06 (0.51, 2.20)
Davis *et al*[14]	6	182	1594	49 654	6.1	1.03 (0.47, 2.26)
Diav-Citrin *et al*[15]	7	348	8	1359	4.0	3.42 (1.25, 9.36)
Einarson *et al*[16]	9	1174	8	1174	4.4	1.13 (0.44, 2.91)
Louik *et al*[18]	25	96	3601	15 709	18.9	1.14 (0.81, 1.59)
Malm *et al*[19]	1	149	18	1771	1.1	0.66 (0.09, 4.91)
Reis & Kallen[17]	24	1208	11 910	1 236 053	16.0	2.06 (1.39, 3.07)
Vial *et al*[21]	2	500	2	500	1.2	1.00 (0.14, 7.07)
Wogelius *et al*[6]	1	219	1508	150 780	1.2	0.46 (0.06, 3.23)
Total (95% CI)		4514		1 469 302	100.0	1.25 (1.01, 1.54)
Total events	127		23 619			

Heterogeneity: $\tau = 0.03$; $\chi^2 = 14.34$, d.f. = 10 ($P = 0.16$); $I^2 = 30\%$
Test for overall eect: $Z = 2.03$ ($P = 0.04$)

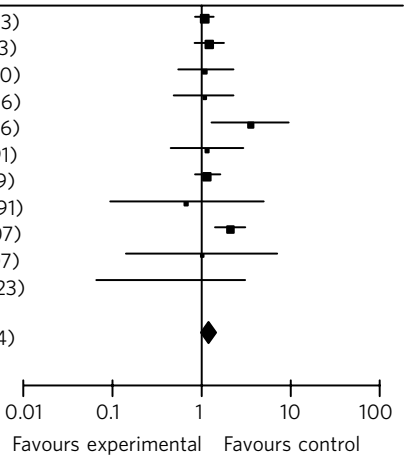

Fig 3 Risk of cardiovascular malformations with first-trimester use of paroxetine in comparison with unexposed controls (forest plot). M-H, Mantel–Haenszel method.

occurrence of cardiovascular defects. The trim-and-fill analysis only confirmed the limitation of this method, as it does not take into account the reasons for funnel plot asymmetry other than publication bias.

Our meta-analysis, based on largest collective data sample so far, suggests that offspring of women who are exposed to paroxetine in the first trimester of pregnancy are at a small but significant increased risk of cardiovascular malformations. However, subgroup analysis and sensitivity analysis shows the fragility of this association. It is also possible that the borderline significant results of our meta-analysis could disappear, if the crude numbers used for the combined analysis were adjusted for various confounders such as maternal age, race, smoking, medical comorbidities, concomitant use of possible teratogens, etc.

Results of our meta-analysis fall in line with two other meta-analyses.[24,25] O'Brien *et al*[24] separately analysed three case–control ($n = 30\,247$) and six cohort ($n = 66\,409$) studies and they did not find any significant association of cardiac malformation with paroxetine exposure. On the other hand, meta-analysis by Wurst *et al*[25] combined ten cohort and four case–control studies ($n = 109\,958$) and found an increased prevalence of cardiac defects with first-trimester paroxetine use (OR = 1.46, 95% CI 1.17–1.82). Whether it is the large sample size which overcomes Type II error and exposes the teratogenic potential of paroxetine or too much heterogeneity (for the sake of large sample size) that brings spurious association remains debatable. In future, an analysis with large but more homogeneous data might provide the answer. In the meantime, our meta-analysis suggests that there is a possibility that exposure to paroxetine could be significantly associated with cardiovascular malformations and in that sense it supports the existing guidelines,[4,26] which advise avoiding paroxetine use in early pregnancy.

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