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, craniosynostosis, 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)’, ‘cardiovascular 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.

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 1469 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.
The modified QUOROM Flow Chart10 (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. 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 $\chi^2$-test. A random-effect model was applied to combine the data. Subgroup 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 was used.

Results
The systematic search identified 29 relevant studies. Only 11 studies6,8,9,13-19,21 could be included in the analysis, 7 cohort and 4 case–control studies6,8,9,13,18 (Table I). The total number of individuals included in the meta-analysis was 4514 in the paroxetine group and 1469302 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 $\chi^2$ 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.

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Fig 1 Modified QUORON flow chart10 describing the search process.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design and quality</th>
<th>Description of study</th>
<th>Study group</th>
<th>Control group</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alwan et al</td>
<td>D</td>
<td>Data from National Birth Defects Prevention Study (USA)</td>
<td>9622 infants with major birth defects</td>
<td>4092 infants with no major birth defects</td>
<td>No significant association between maternal use of SSRIs and congenital heart defects</td>
<td>Odds ratio adjusted for race/ethnicity, obesity, smoking and income</td>
</tr>
<tr>
<td>Bakker et al</td>
<td>D</td>
<td>Birth defects registry (The Netherlands)</td>
<td>678 infants with isolated heart defects</td>
<td>615 controls with a genetic disorder with no heart defect</td>
<td>Paroxetine associated with increased risk of atrium septum defects</td>
<td>No increased risk for heart defects overall</td>
</tr>
<tr>
<td>Berard et al</td>
<td>D</td>
<td>Data from Quebec Pregnancy Registry (Canada) Women on antidepressants during first trimester (excluding those on known teratogens) were included</td>
<td>101 infants with major congenital malformations</td>
<td>1302 infants without congenital malformations</td>
<td>Exposure to paroxetine above 25 mg/day associated with major congenital and cardiac malformations</td>
<td>Odds ratio adjusted for gestational and maternal age, diabetes, hypertension, depression, medications, number and types of antenatal visits and other sociodemographic variables</td>
</tr>
<tr>
<td>Davis et al</td>
<td>C</td>
<td>Pregnancy outcomes from five managed-care organisations (USA)</td>
<td>1441 full-term infants exposed to antidepressants</td>
<td>49,663 full-term infants not exposed to antidepressants</td>
<td>SSRIs and tricyclic antidepressants did not have a consistent link with congenital anomalies</td>
<td>Controls could be on other possible teratogenic medicines, no adjustment for confounders</td>
</tr>
<tr>
<td>Diav-Citrin et al</td>
<td>A</td>
<td>Teratology information services from Israel, Italy and Germany</td>
<td>410 first-trimester paroxetine-exposed pregnancies</td>
<td>1467 women on non-teratogenic drugs</td>
<td>Twofold increase in overall rate of congenital anomalies in paroxetine group</td>
<td>After adjusting for various confounders significance disappeared</td>
</tr>
<tr>
<td>Einanson et al</td>
<td>A</td>
<td>From teratology information centres around the world</td>
<td>1174 infants exposed to paroxetine</td>
<td>Equal number of demographically and clinically matched women on non-teratogenic drugs</td>
<td>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)</td>
<td>For meta-analysis actual numbers were derived from frequency and odds ratio</td>
</tr>
<tr>
<td>Reis &amp; Kallen</td>
<td>C</td>
<td>Swedish Medical Birth Register</td>
<td>15,017 infants exposed to antidepressants</td>
<td>General population</td>
<td>Association between paroxetine and congenital heart defects was verified</td>
<td>Adjustments were made for year of delivery, maternal age, parity, smoking and BMI</td>
</tr>
</tbody>
</table>

Table 1 Characteristics of included studies
Table 1  Characteristics of included studies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and quality</th>
<th>Description of study</th>
<th>Study group</th>
<th>Control group</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louik et al 18</td>
<td>D</td>
<td>Slone Epidemiology Center Birth Defects Study (USA)</td>
<td>9849 infants with birth defects</td>
<td>5860 infants without birth defects</td>
<td>Sertraline and paroxetine significantly associated with cardiac defects</td>
<td>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</td>
</tr>
<tr>
<td>Malm et al 19</td>
<td>C</td>
<td>Finnish data</td>
<td>1782 women with at least one purchase of SSRI Women with chronic illnesses were excluded</td>
<td>1782 matched controls, as per year of pregnancy, age, geographic area and social status with no drug purchase</td>
<td>Major malformations were not more common in infants of women with SSRI purchase</td>
<td>For meta-analysis, data for paroxetine were extrapolated from Einarson et al 20</td>
</tr>
<tr>
<td>Vial et al 21</td>
<td>A</td>
<td>French data</td>
<td>500 women exposed to paroxetine</td>
<td>500 controls</td>
<td>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</td>
<td>Only abstract is available</td>
</tr>
<tr>
<td>Wogelius et al 6</td>
<td>C</td>
<td>Data from Danish Medical Birth Registry</td>
<td>1051 women who filled prescription for SSRIs</td>
<td>Reference cohort of 150780 women with no SSRI prescriptions</td>
<td>Increased risk of congenital malformations after exposure to SSRIs Among offspring of SSRI users, 1.4% had cardiovascular malformation (1% in controls)</td>
<td>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</td>
</tr>
</tbody>
</table>

BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

a. Adapted from Centre for Reviews and Dissemination guidelines: 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.
Individually, exclusion of studies by Bakker or Reis & Kallen (RR = 1.11, CI 0.94–1.31) made the pooled 95% CI 0.98–1.64), Louik (RR = 1.52, 95% CI 0.98–2.34) studies. The result non-significant.

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

Alwan control remained significant after excluding the studies by the difference between paroxetine and the unexposed
differences, 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 al9 and Louik et al18 (RR = 1.38, 95% CI 1.02–1.86). Individually, exclusion of studies by Bakker et al13 (RR = 1.27, 95% CI 0.98–1.64), Louik et al18 (RR = 1.28, 95% CI 0.98–1.66) or Reis & Kallen17 (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.2 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.24 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

Table: Risk of cardiovascular malformations with paroxetine group

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Paroxetine Events</th>
<th>Total</th>
<th>Unexposed controls Events</th>
<th>Total</th>
<th>Weight, %</th>
<th>Risk ratio M-H, random, 95% CI</th>
<th>Risk ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alwan et al9</td>
<td>32</td>
<td>70</td>
<td>4268</td>
<td>9622</td>
<td>23.7</td>
<td>1.03 (0.80, 1.33)</td>
<td>1.03 (0.80, 1.33)</td>
</tr>
<tr>
<td>Bakker et al13</td>
<td>10</td>
<td>16</td>
<td>678</td>
<td>1277</td>
<td>16.6</td>
<td>1.18 (0.80, 1.73)</td>
<td>1.18 (0.80, 1.73)</td>
</tr>
<tr>
<td>Berard et al8</td>
<td>10</td>
<td>552</td>
<td>24</td>
<td>1403</td>
<td>6.9</td>
<td>1.06 (0.51, 2.20)</td>
<td>1.06 (0.51, 2.20)</td>
</tr>
<tr>
<td>Davis et al14</td>
<td>6</td>
<td>182</td>
<td>1594</td>
<td>49654</td>
<td>6.1</td>
<td>1.03 (0.47, 2.26)</td>
<td>1.03 (0.47, 2.26)</td>
</tr>
<tr>
<td>Diav-Citrin et al15</td>
<td>7</td>
<td>348</td>
<td>8</td>
<td>1359</td>
<td>4.0</td>
<td>3.42 (1.25, 9.36)</td>
<td>3.42 (1.25, 9.36)</td>
</tr>
<tr>
<td>Einarson et al16</td>
<td>9</td>
<td>1174</td>
<td>8</td>
<td>1174</td>
<td>4.4</td>
<td>1.13 (0.44, 2.91)</td>
<td>1.13 (0.44, 2.91)</td>
</tr>
<tr>
<td>Louik et al18</td>
<td>25</td>
<td>96</td>
<td>3601</td>
<td>15709</td>
<td>18.9</td>
<td>1.14 (0.81, 1.59)</td>
<td>1.14 (0.81, 1.59)</td>
</tr>
<tr>
<td>Malm et al19</td>
<td>1</td>
<td>149</td>
<td>18</td>
<td>1771</td>
<td>1.1</td>
<td>0.66 (0.09, 4.91)</td>
<td>0.66 (0.09, 4.91)</td>
</tr>
<tr>
<td>Reis &amp; Kallen17</td>
<td>24</td>
<td>1208</td>
<td>11 910</td>
<td>1236053</td>
<td>16.0</td>
<td>2.06 (1.39, 3.07)</td>
<td>2.06 (1.39, 3.07)</td>
</tr>
<tr>
<td>Vial et al21</td>
<td>2</td>
<td>500</td>
<td>2</td>
<td>500</td>
<td>1.2</td>
<td>1.00 (0.14, 7.07)</td>
<td>1.00 (0.14, 7.07)</td>
</tr>
<tr>
<td>Wogelius et al6</td>
<td>1</td>
<td>219</td>
<td>1508</td>
<td>150780</td>
<td>1.2</td>
<td>0.46 (0.06, 3.23)</td>
<td>0.46 (0.06, 3.23)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>4514</td>
<td></td>
<td>1469302</td>
<td>100.0</td>
<td>1.25</td>
<td>(1.01, 1.54)</td>
<td>(1.01, 1.54)</td>
</tr>
<tr>
<td>Total events</td>
<td>127</td>
<td></td>
<td>23619</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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 al26 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 al26 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,3,26 which advise avoiding paroxetine use in early pregnancy.

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References