Paroxetine and congenital malformations: meta-analysis and consideration of potential confounding factors

CRD summary
This review investigated whether first-trimester exposure to paroxetine is associated with an increased risk of congenital malformations. The authors concluded that first trimester exposure to paroxetine appears to be associated with a significant increase in the risk of cardiac malformation. However, the reliability of these conclusions is unclear as insufficient details of the included studies were provided.

Authors’ objectives
To investigate whether first-trimester exposure to paroxetine is associated with an increased risk of congenital malformations.

Searching
MEDLINE, EMBASE, REPROTOX, Scopus and Biological Abstracts were searched from 1985 to 2006; the search terms were reported. Reference lists of retrieved studies, proceedings from meetings of professional societies, textbooks and Internet websites were also checked for additional articles. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Case-control and cohort studies (prospective and retrospective) were eligible for inclusion as long as both groups were drawn from the same population. Experimental studies and case reports were excluded. The included studies were of the following designs: nested case-control, prospective controlled, population-based cohort, retrospective cohort and prospective recording-registry.

Specific interventions included in the review
Studies that examined the effects of exposure to paroxetine were eligible for inclusion. The control groups consisted of women using antidepressants other than paroxetine, or other non-teratogenic medications.

Participants included in the review
Studies of women in the first trimester of pregnancy (0 to 14 weeks' gestation) were eligible for inclusion.

Outcomes assessed in the review
Studies that reported on the number of major congenital malformations and/or the number of cardiac congenital malformations were eligible for inclusion. Outcomes were only considered for live births.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion. Any discrepancies were resolved using a third reviewer.

Assessment of study quality
The quality of the included studies was assessed using a 27-item scale based on a published checklist, with a summary quality score based on the percentage of items fulfilled. The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted data on the number of infants born with and without malformations in the
exposed and unexposed groups. Data were extracted into a 2x2 table.

**Methods of synthesis**

**How were the studies combined?**
Pooled odds ratios (ORs) were calculated using a random-effects model. Funnel plots and the Begg-Mazumdar statistic were used to evaluate publication bias.

**How were differences between studies investigated?**
Heterogeneity was assessed using the chi-squared test. A subgroup analysis based on control group medication was conducted.

**Results of the review**

Seven studies (n=17,526) were eligible for inclusion.

The quality of the included studies ranged from 60 to 93%, with 5 studies scoring at least 80%.

Significantly more children were born with major malformations (OR 1.31, 95% CI: 1.03, 1.67; 7 studies) and cardiac only malformations (OR 1.72, 95% CI: 1.22, 2.42; 6 studies) to women who were exposed to paroxetine during the first trimester than to women exposed to other antidepressants or non-teratogenic medications in the first trimester. There was no significant difference in the occurrence of major malformations when cardiac malformations were excluded (OR 1.29, 95% CI: 0.86, 1.92).

A subgroup analysis restricted to studies in which the control group consisted of women taking other antidepressants (4 studies) showed that the rate of cardiac malformations remained higher in women taking paroxetine (OR 1.70, 95% CI: 1.17, 2.46). There was no significant difference in major malformations between the groups (OR 1.30, 95% CI: 0.93, 1.8). There was no significant difference in the rates of cardiac malformation or major malformation when comparing children born to women exposed to paroxetine and those born to women taking known non-teratogenic medications (3 studies).

**Cost information**

NO.

**Authors’ conclusions**

First-trimester exposure to paroxetine appears to be associated with a significant increase in the risk of cardiac malformation.

**CRD commentary**

The study objective was well defined and the study designs, intervention and outcomes of interest were clearly stated. A comprehensive search for relevant literature was conducted and no language restrictions were applied, thus reducing the risk of language bias. The authors also formally assessed publication bias, although the results of this assessment were not discussed. The study selection and data extraction were undertaken independently by two reviewers, which reduces the potential for reviewer bias and errors. A quality assessment was carried out, although the criteria used and the results of this assessment were not reported in detail; this makes it difficult to assess the robustness of the studies.

The reporting of the included studies was limited. Heterogeneity between the studies was not discussed, which made it difficult to assess the appropriateness of the methods used for the data synthesis and the accuracy of the results. While this was generally a well-conducted systematic review, the reliability of the authors’ conclusions is unclear given the poor reporting of individual study details.
Implications of the review for practice and research

The authors did not state any implications for practice or further research.

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