CRD summary
This generally well-conducted review of non-randomised studies concluded that first trimester exposure to paroxetine did not appear to be associated with increased rates of cardiac malformations. This conclusion reflects the results of this review of reasonable quality studies that included a large number of women and is likely to be reliable.

Authors' objectives
To determine whether first trimester exposure to paroxetine is associated with an increased rate of cardiac defects.

Searching
MEDLINE, EMBASE, REPROTOX, Scopus and Biological Abstracts were searched from January 1985 to November 2007. No language restrictions were reported. Search terms were reported. References of retrieved articles, proceedings of professional societies in relevant fields and Internet sites were searched.

Study selection
Case control and cohort studies that reported on the risk of cardiac malformations following in utero exposure to paroxetine during the first trimester of pregnancy (0 to 14 weeks gestation) and included a control group of pregnant women without paroxetine exposure were eligible for inclusion in the review. Populations from which study and control cases were drawn were required to be comparable for case control studies. Only live births were in included in assessment of outcomes.

Both case control and cohort studies were included in the review. Control groups were women exposed to antidepressants other than paroxetine and three studies used women exposed to medications known to be non-teratogenic. Studies were conducted in USA, Canada and Europe.

Two reviewers independently assessed studies for inclusion. A third reviewer adjudicated unresolved disagreements.

Assessment of study quality
The studies were assessed for validity by two reviewers using the Downs and Black checklist and a quality score was calculated as a percentage of applicable items. Disagreements were resolved by a third reviewer.

Data extraction
Data were extracted into 2x2 tables by two reviewers. A third reviewer resolved disagreements.

Methods of synthesis
Data from case control studies were combined in a random-effects meta-analysis weighted using both between and within study variance. A pooled odds ratio (OR) with 95% confidence intervals (CI) was calculated. Data from cohort studies was combined to calculate a pooled rate difference with standard error for the number of infants born with cardiac malformation in the exposed and non-exposed groups. Statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ tests. Publication bias was assessed using the Begg and Mazumdar test; funnel plot analysis was planned but too few studies were included for it to be possible.

Results of the review
Nine studies were included in the review (total n not reported): six were cohort studies and three were case-control studies. Quality scores ranged from 70% to 93%.

Cohort studies: The rate of cardiac malformations in the exposed groups (n=3,428) was 1.14% compared to 1.09% in the control groups (n=62,981). The weighted average difference in rates was 0.3% (95% CI -0.1% to 0.7%) and nonsignificant (p=0.19). There was sufficient statistical power to detect significance at a rate as low as 1.26%; the authors stated that the rate in the general population had been reported as having a 95% CI of 0.7 to 1.19.
Case control studies: There was no statistically significant difference between the cases and the controls in rates of cardiac malformations (OR 1.18, 95% CI 0.88 to 1.59; n>30,000). The authors calculated that an additional 170,351 patients would be required to achieve statistical significance.

There was no evidence of significant statistical heterogeneity in either the cohort or the case control studies.

There was no evidence of publication bias.

**Authors' conclusions**

First trimester exposure to paroxetine did not appear to be associated with increased rates of cardiac malformations.

**CRD commentary**
The review question and the inclusion criteria were clear. The authors searched a number of relevant databases and other sources, which reduced the chances that relevant studies were omitted. No restrictions on language or publication status were reported. Publication bias was assessed and no evidence for it was found. The authors reported that they used rigorous methodology at all stages of the review process and conducted a validity assessment appropriate to the non-randomised studies include in the review. The included studies were assessed as being of reasonable quality and included a large number of women. Further information on included studies was limited. Appropriate methods were used for the statistical synthesis and assessment of heterogeneity. The authors’ conclusions reflect the results of the review and appear likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that the conclusions of the review should be reassuring to prescribing physicians and women who required paroxetine therapy during pregnancy. They further stated that risks and benefits associated with anti-depressant use during pregnancy should always be assessed on a case by case basis.

**Research:** The authors did not state any implications for further research.

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No funding related to paroxetine or any other serotonin specific reuptake inhibitor was declared. Financial relationships with a number of pharmaceutical manufacturers were declared.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.