Selective serotonin reuptake inhibitor exposure during early pregnancy and the risk of fetal major malformations: focus on paroxetine

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CRD summary
This review concluded that the data were too inconsistent to confirm or exclude the risk of major foetal malformations after exposure to paroxetine during early pregnancy. The review had major flaws in terms of an unreported review process and absence of study quality assessment. The extent to which the conclusion is a reliable assessment of the evidence base is unclear.

Authors' objectives
To assess the effect of prenatally administered paroxetine on the prevalence of major foetal malformations.

Searching
MEDLINE, TOXNET, EMBASE, and the Cochrane Library were searched to September 2008 for published English language articles. Search terms were reported. Reference lists were scanned to locate additional studies.

Study selection
All studies reporting the prevalence of foetal major malformations after early in utero exposure to paroxetine (alone, or in combination with other selective serotonin reuptake inhibitors) were eligible for inclusion in the review.

Some of the included controls were exposed to non-teratogenic agents or were unexposed. The majority of drugs were administered in the first trimester of pregnancy; the dosage was largely unreported. The reported outcomes were risk of teratogenicity and types of foetal malformations. Foetal malformations included cardiac anomalies, ventricular outflow tract obstruction defects, anencephaly, gastroschisis, omphalocele, eye and septal defects.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted to provide a narrative description on the direction of effect, or to report relative risks (RR), risk difference (RD), or odd ratios (OR) (adjusted where necessary), along with 95% confidence intervals (CI).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Studies were synthesised narratively and grouped according to type of study design. Studies on paroxetine alone, and in combination with other selective serotonin reuptake inhibitors were reported separately.

Results of the review
Twenty-five studies were included in the review (n=20,475 participants). Sample sizes ranged from 28 to 3,379. Eleven studies (n=8,859 participants) assessed the teratogenicity of paroxetine (seven prospective studies, three retrospective cohorts and one case-control study). Fourteen studies (n=11,616 participants) assessed the teratogenicity of selective serotonin reuptake inhibitors as a group (five prospective, four retrospective cohort and five case-control studies).

The included studies demonstrated a high degree of methodological variation, so the analyses were reported to be inconsistent and inconclusive. However, where relative risks and odds ratios were presented, several studies showed
statistically significant results, with an increased risk of major foetal malformations. Paroxetine was associated with increased risks of foetal malformations as a whole, and (in particular) with risks of cardiac anomalies, ventricular outflow tract obstruction defects, anencephaly, gastroschisis, omphalocele, and eye defects.

**Authors' conclusions**

Data were too inconsistent to confirm or exclude the teratogenicity of paroxetine in terms of major foetal malformations.

**CRD commentary**

The review question was clear, but the inclusion criteria were broad and not stated clearly enough to allow successful replication. The search strategy included some appropriate sources, but restrictions to the inclusion of published English language articles meant that relevant studies may have been missed and the associated biases introduced. There was no account of how studies were selected or data extracted, and no reported assessment of methodological quality. This represented a substantial limitation to the reliability of the review findings.

There were only scant details provided in relation to the included studies, which made it difficult to interpret the applicability of findings. Many of the reported confidence intervals were wide in relation to the statistically significant findings. Some included studies were updates of previous analyses using the same population. Only a small proportion of studies looking at selective serotonin reuptake inhibitors as a group actually assessed paroxetine.

The authors’ conclusion reflected the evidence presented, but the extent to which this is a reliable assessment of the evidence base is unclear.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that large prospective studies with a control group of untreated mothers with similar psychiatric diagnoses are needed. Experimental studies are needed to assess the physiological effects of prenatal paroxetine exposure on different maternal and foetal parameters.

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