Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies

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CRD summary
This review evaluated the effects of newer antidepressants in the first trimester of pregnancy on major malformations. The authors concluded that newer antidepressants are not associated with an increase in the risk of major malformations. The review presented insufficient information about the individual studies to confirm the robustness of these conclusions.

Authors' objectives
To evaluate the effects of newer antidepressants given in the first trimester of pregnancy on major malformations in neonates.

Searching
MEDLINE, EMBASE and REPROTOX were searched from 1966 (stated as 1996 in review abstract) to present using the reported search terms. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Prospective cohort studies were eligible for inclusion.

Specific interventions included in the review
Studies that compared exposure to newer antidepressants with no exposure were eligible for inclusion. The newer antidepressants of interest included currently available selective serotonin re-uptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), serotonin-norepinephrine re-uptake inhibitors (venlafaxine), dual-action drugs (nefazodone, trazodone and mirtazapine) and selective noradrenaline re-uptake inhibitors (reboxetine and bupropion). Studies evaluating tricyclics and related drugs, monoamine oxidase inhibitors, botanicals and related compounds were excluded. The studies included in the review evaluated fluoxetine (10 to 80 mg/day, mean 25.8 and 26.8 in two other studies), fluvoxamine (10 to 60 mg/day), paroxetine (10 to 60 mg/day), sertraline (25 to 250 mg/day), venlafaxine (37.5 to 300 mg/day), and nefazodone, trazodone and bupropion (doses of these not reported). Most of the studies were conducted in Canada or the USA.

Participants included in the review
Studies of pregnant women who were exposed to the specified drugs in the first trimester of pregnancy were eligible for inclusion. Studies of women who were exposed to known teratogens or foetotoxic agents were excluded.

Outcomes assessed in the review
Studies that assessed major structural or functional malformations (including those requiring surgical correction) were eligible for inclusion. Malformations reported in the individual studies were listed according to exposure status. These included malformations in various body systems such as the heart, liver, brain, intestine and genital tract. Only outcomes for live births were considered.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies and resolved any disagreements through consensus.

Assessment of study quality
The studies were assessed using a checklist of 29 items (no details provided) based on work described by Feinstein,
Lichtenstein and Elwood. Studies scored 1 if the item was present and 0 if the item was absent. The quality score was expressed as a percentage of items present in the article.

The authors did not state how the validity assessment was performed.

**Data extraction**

Two reviewers independently extracted the data and resolved any disagreements through consensus. For each study, the number of participants with the outcome of interest was extracted for each treatment group and the relative risk (RR) calculated, along with its 95% confidence interval (CI).

**Methods of synthesis**

How were the studies combined?
The pooled RR with 95% CI was calculated using a random-effects model. Publication bias was assessed visually using a funnel plot and tested statistically using the methods proposed by Begg and Mazumdar. The authors calculated the power of the meta-analysis to detect an RR of 2.5 with an alpha of 5% and baseline malformation rates of 2% and 1%.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Where possible, pooled RRs with 95% CIs were calculated for each drug separately.

**Results of the review**

Seven prospective cohort studies (n=1,774) were included.

The meta-analysis showed no association between exposure to any of the newer antidepressants and major malformations (RR 1.01, 95% CI: 0.57, 1.80). No statistically significant heterogeneity was detected (p=0.92). There was no evidence of publication bias from either the funnel plot or the Begg and Mazumdar test (p=0.45). The authors calculated that the meta-analysis had 90% power of detecting an RR of 2.5% when assuming a baseline malformation rate of 2%, and 80% power when assuming a baseline rate of 1%.

No association between any of the individual drugs evaluated and malformations was demonstrated. These drugs were bupropion (1 study, n=99), fluoxetine (3 studies, n=300), nefazodone/trazodone (1 study, n=147) and venlafaxine (1 study, n=125). The highest RR was obtained for venlafaxine (RR 2.19, 95% CI: 0.20, 23.88).

**Authors' conclusions**

Newer antidepressants are not associated with an increase in the risk of major malformations.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Three relevant databases were searched without language restrictions, thus reducing the possibility of language bias. Appropriate methods were used to examine the possibility of publication bias and no evidence of this was found. Methods were used to minimise reviewer errors and bias in the study selection and data extraction processes, but it was unclear whether similar steps were taken in the validity assessment. Validity was assessed, but no details of either the items assessed or the results of the assessment were reported; in particular, definitions used in individual studies for the outcome of interest (i.e. major malformations) were not reported, nor were methods used to detect malformations. This means that it is not possible for the reader to judge the quality of the included studies for themselves or to assess differences between the studies.

Statistical heterogeneity was assessed but there was insufficient information to assess the clinical comparability of the studies. The review authors did point out that most (five of the seven) included studies were produced by the Motherisk Program in Toronto and that participants may not be representative of the general population. There appeared to be
insufficient information about the individual studies to confirm the robustness of these conclusions. Given the limitations highlighted, the authors' conclusions should be interpreted with some degree of caution.

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

Practice: The authors stated that since depression is a serious illness, pregnant women should not be expected to stop antidepressants and should not necessarily be switched to another antidepressant.

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

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