Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis
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Authors' objectives
To review all controlled studies of antihistamine use in early pregnancy, using a meta-analysis to quantify the relative risk of major malformations associated with their use.

Searching
MEDLINE was searched from 1960 to 1991 using the following keywords: 'pregnancy', 'antihistamine', 'antinauseant', 'antiemetic', 'cough/cold', 'morning sickness', 'hyperemesis gravidarum', 'nausea', 'vomiting', 'hypersensitivity', 'allergy', 'adverse fetal outcome', 'malformation', 'congenital abnormalities', 'birth defect', and 'teratogen'.

Study selection
Study designs of evaluations included in the review
Controlled studies were eligible for inclusion. Details of the specific study designs were not presented, but the included studies seem to be case-control, retrospective or prospective observational studies.

Specific interventions included in the review
Antihistamines: any compound with histamine-H1-receptor antagonist action as its principal intended effect.

Participants included in the review
Women in the first trimester of pregnancy were included.

Outcomes assessed in the review
The risk of major malformations associated with antihistamine use in early pregnancy was assessed.

How were decisions on the relevance of primary studies made?
The articles were independently assessed by two reviewers according to the 'Methods' section. The authors' names and institutions were removed to prevent selection bias.

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

Data extraction
The authors did not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The pooled odds ratio was calculated using the Mantel-Haenszel method.

How were differences between studies investigated?
Heterogeneity across studies was assessed using the Mantel-Haenszel chi-squared test.

Results of the review
Twenty-four studies (over 200,000 women in total) were included.
The summary odds ratio for major malformations in the offspring of women exposed to antihistamines during the first trimester was 0.76 (95% confidence interval: 0.6, 0.94). The heterogeneity across studies was statistically significant (p<0.01).

Authors' conclusions
H1-blockers used mainly for morning sickness during the first trimester do not increase the teratogenic risk in humans and may, in fact, be associated with a protective effect. Further research is needed to verify the possibility that by preventing vomiting, antihistamines may ensure better metabolic conditions to the foetus and thus may reduce some birth defects. Alternatively, it is possible that pregnancies characterised by vomiting are associated with better outcome due to other reasons, such as hormonal status or placental function. Women suffering from morning sickness, which is not controlled by non-pharmacological methods, can safely use antihistamines.

CRD commentary
The literature search was limited to only one database (MEDLINE) and, therefore, it is likely that many relevant studies may have been missed. The validity of the included studies was not assessed, even though observational studies are vulnerable to many possible biases. The potential for publication bias needs to be considered. In general, the authors' conclusions seem appropriate and balanced.

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