Is metronidazole teratogenic: a meta-analysis
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Authors' objectives
To assess whether the use of metronidazole during pregnancy is associated with a higher risk of congenital malformations, using a meta-analysis.

Searching
MEDLINE was searched from January 1966 to December 1996, and IDIS from January 1985 to December 1996, using the search terms provided. Additional studies were identified by examining the reference lists of all the reviewed articles and retrieved primary studies. An enquiry was also submitted to the Spanish Collaborative Study of Congenital Malformations (ECEMC) for further data.

Study selection
Study designs of evaluations included in the review
Observational epidemiological studies, including cohort and case-control studies, were included in the review. All of the studies used a comparison group of unexposed women (control group), and the numbers of malformations found in both the control and the metronidazole groups were recorded.

Specific interventions included in the review
Metronidazole. All metronidazole treatments administered during the first trimester of pregnancy, whatever the dose or indication, were included in the review.

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

Outcomes assessed in the review
The numbers of congenital malformations were assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed.

Data extraction
The authors do 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 studies were combined in a meta-analysis using the Mantel-Haenszel method, in order to combine information from multiple 2x2 tables. An odds ratio (OR) with 95% confidence intervals (CIs) was calculated for each study, and an overall summary OR for all of the studies was provided.

How were differences between studies investigated?
The Breslow-Day test (see Other Publications of Related Interest) was performed to verify the absence of any
heterogeneity between the studies included in the meta-analysis.

Results of the review
One unpublished study (case-control) and four published studies (all cohort studies), with a total of 199,451 participants (2,524 exposed and 196,927 non-exposed), were included in the review. The unpublished case-control study featured data collected by the ECEMC concerning the number of metronidazole-associated malformations found out of a total of 111,3796 live births in Spain between April 1976 and December 1993. Details were also provided of seven studies (all case-series studies) that were excluded from the analysis, as they did not use an unexposed control group.

No statistically-significant heterogeneity was identified between the five studies ((chi-squared 4.72, p=0.32) that allowed the data to be pooled using a meta-analysis. The risk of congenital malformations associated with the use of metronidazole varied between the studies: the ORs ranged from 0.92 (95% CI: 0.71, 1.19) to 2.15 (95% CI: 0.75, 6.13). However, only one of the studies (with 31 exposed women) identified a two-fold increase in the risk of congenital malformations, and this result was not statistically significant (OR 2.15, 95% CI: 0.75, 6.13). Overall, the summary OR for the five studies was 1.08 (95% CI: 0.90, 1.29). The results did not vary significantly when the data from the case-control study were removed from the analysis (summary OR 1.05, 95% CI: 0.87, 1.27; heterogeneity test, chi-squared 3.74, p=0.29).

Authors’ conclusions
This meta-analysis did not find any relationship between metronidazole exposure during the first trimester of pregnancy and birth defects.

CRD commentary
In general, this was a clearly presented and well-designed review that provided a detailed account of the reviewers’ attempts to identify relevant literature, their inclusion criteria and how the studies were combined. The review, however, failed to provide details of how decisions were made on the relevancy and validity of the articles, and how the data were extracted from the studies. There was also a discrepancy between the numbers of study participants listed in table 1 (n=199,451) and the total number of participants quoted in the discussion (n=201,562). Overall, the authors’ conclusions appear valid given the data presented.

Implications of the review for practice and research
The authors did not state any implications for practice or further research. However, it would appear from this review, and another similar review identified by the authors, that there is no significantly increased risk of congenital malformations from the use of metronidazole in the first trimester of pregnancy.

Bibliographic details

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Other publications of related interest

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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.