The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis

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CRD summary
This review concluded that proton pump inhibitor use during early pregnancy was not associated with an increased risk for major congenital birth defects, spontaneous abortions and preterm delivery. In light of uncertainty over generalisability and parts of the review process, plus the potential influence of one large study, the reliability of the authors’ conclusions is unclear.

Authors' objectives
To determine the foetal safety of proton pump inhibitors (PPIs) during early pregnancy.

Searching
MEDLINE, EMBASE, International Pharmaceutical Abstracts, EBM Reviews and CINAHL were searched without language restrictions from inception to July 2008; search terms were reported. Reference lists of relevant articles were searched to identify additional articles.

Study selection
Studies that assessed exposure to proton pump inhibitors during at least the first trimester of pregnancy in comparison with a group that had not been exposed to proton pump inhibitors were eligible for inclusion; selected studies specifically examined the rate of congenital malformations after maternal exposure to proton pump inhibitors. Eligible proton pump inhibitors comprised: omeprazole; pantoprazole; rabeprazole; lansoprazole; and esomeprazole. The most frequently used was omeprazole. Included studies comprised both retrospective and prospective cohorts. Eligible studies described foetal outcomes, including congenital malformations, spontaneous abortions and premature delivery.

Two reviewers independently selected studies for inclusion; disagreements were resolved through consensus.

Assessment of study quality
Study quality was assessed using the Downs-Black scale based on: reporting; external and internal validity; bias; confounding; and power. The maximum possible score was 32, which was converted to a percentage.

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

Data extraction
Data were extracted as odds ratios (OR) for predefined dichotomous outcomes. It appeared that the author of one study was contacted for additional information.

The authors stated neither how the data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
The pooled ORs and 95% confidence intervals (CIs) were combined for the natural logarithm of the OR using a random-effect model. Heterogeneity was assessed using the Q and I² statistics. A secondary analysis that included only omeprazole was conducted. Publication bias was assessed using a funnel plot.

Results of the review
A total of seven studies were included in the review. Of the 134,940 patients, 1,530 were exposed to proton pump inhibitors and 133,410 were not exposed to proton pump inhibitors. The study quality score (percentage) ranged from 66% to 72%. Publication bias was absent.
Proton pump inhibitors were not considered to be associated with an increased risk for major congenital birth defects (OR 1.12, 95% CI 0.86 to 1.45; seven studies), spontaneous abortions (OR 1.29, 95% CI 0.84 to 1.97; two studies) or preterm delivery (OR 1.13, 95% CI 0.96 to 1.33; five studies). The use of omeprazole was not associated with an increased risk for congenital malformations (OR 1.17, 95% CI 0.90 to 1.53; six studies). There was no evidence of statistical heterogeneity.

Authors' conclusions
Proton pump inhibitors were not associated with an increased risk for major congenital birth defects, spontaneous abortions or preterm delivery, which suggested that proton pump inhibitors can be used safely in pregnancy.

CRD commentary
The review question was clear and was supported by specific inclusion criteria. Limited study details were reported. The authors searched five relevant databases without language restrictions, which reduced the chances of language bias. It did not appear that unpublished studies were sought, although one unpublished study was included in the review; some studies may have been missed. Publication bias was assessed and no evidence of it was found. The authors reported that they used methods designed to reduce bias and error in the selection of studies, but it was unclear whether this extended to the extraction of data and study quality. An appropriate assessment of study quality was reported. Only overall results were reported, which made it more difficult for the reader to form their own interpretation of the evidence; studies were considered to be of fair quality. It was appropriate to pool the trials in a meta-analysis, but there was a large difference in the number of patients in the exposed group compared with the non-exposed group, plus the weighting of the results was centred around one study; this may have introduced bias. Statistical heterogeneity was assessed and found to be absent, although both clinical and methodological heterogeneity may have been present. The authors' conclusions reflected the results of the review, which contained data on a substantial number of individuals. In light of uncertainty over parts of the review process, generalisability of the findings and the potential influence of one large study, the reliability of the authors' conclusions is unclear.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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Other publications of related interest
This additional published commentary may be of interest.
Bharucha AE. Review: PPI use in pregnancy was not associated with increased congenital malformations, spontaneous abortion, or preterm delivery. Annals of Internal Medicine 2009; 151(5): JCS-14.

Indexing Status
Subject indexing assigned by NLM

MeSH
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.