The safety of quinolones: a meta-analysis of pregnancy outcomes
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CRD summary
This review evaluated the risks of malformations, stillbirths, pre-term births or low birth weight in babies with maternal exposure to first trimester quinolone treatment, concluding that the drug was not associated with adverse outcomes for exposed babies. Given the potential for bias, these conclusions are not likely to be reliable and should be interpreted with a significant degree of caution.

Authors' objectives
To determine if first-trimester exposure in pregnant women to quinolones is associated with increased risks of malformations, stillbirths, pre-term births or low birth weight.

Searching
MEDLINE, EMBASE, Scopus, Biological Abstracts and ProQuest Thesis Dissertations were searched. Search terms, but not dates, were reported. In addition, REPROTOX, Shepard's Catalog of Teratogenic Agents, TERIS, REPRORISK, Drugs in Pregnancy, and Lactation and Maternal-Fetal Toxicology were searched for relevant publications. Reference lists from retrieved articles and books were also scanned for additional relevant studies. It was unclear if there were any language restrictions.

Study selection
Clinical studies, including cohort and case-control studies, that compared pregnancy outcomes in babies following first trimester exposure to quinolones with outcomes for babies who were not exposed to quinolone treatment, were eligible for inclusion. Studies in which the quality scores were less than 50%, and reviews, case reports and retrospective case series were excluded from the meta-analysis. The rate of major malformations was the primary outcome measure. Secondary outcome measures were rates of stillbirths, pre-term delivery and low birth weight.

The included studies were published between 1994 and 2005, and were comprised of cohort studies and one case control study.

Two reviewers independently assessed the studies for inclusion in the review; any disagreements were resolved by a third reviewer.

Assessment of study quality
The reviewers assessed methodological quality using a 27-item checklist by Downs and Black. For each study, a score was awarded, based on the percentage of applicable items fulfilled. Scores above 50% were considered acceptable for inclusion in the meta-analysis.

The authors did not state how the quality assessment was performed or how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted the number of events for each outcome using two-by-two tables. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated.

Methods of synthesis
Comparative studies were grouped according to outcome and pooled odds ratios with 95% confidence intervals calculated using a Mantel-Haenszel random-effects model. A pooled incidence rate was also calculated, for both comparative and non-comparative studies, using a single group analysis based on the methods of Einarson. Statistical heterogeneity was calculated using the χ² test. Publication bias was assessed by visual examination of a funnel plot.
Results of the review
Five studies (n=213,059 infants) were included in the meta-analysis, including one case-control study and four cohort studies. Data from a further two single-arm cohort studies (n=449 infants) were included with the data from the five other studies for the single group analysis to determine an overall incidence rate for major malformations. The quality scores assigned to each study were not reported.

There were no statistically significant differences observed between the group exposed to quinolone treatment and the control group of non-exposed babies for major malformations, stillbirths, pre-term births, or the risk of low birth weight. There was no evidence of significant statistical heterogeneity for any of the analyses.

The incidence rates for the groups exposed to quinolones were: 3.49% (95% CI 2.20 to 4.79) for major malformations; 0.19% (95% CI 0.12 to 0.51) for stillbirths; 4.83% (95% CI 3.27 to 6.39) for premature birth; and 1.52% (95% CI 0.60 to 2.43) for low birth weight.

The results of the assessment of publication bias were not reported.

Authors’ conclusions
The use of quinolone therapy during the first trimester of pregnancy was not associated with increased risks of major malformations, stillbirths, pre-term births and low birth weights. In addition, the summary incidence rates of adverse outcomes were within the rates of events expected in the general population.

CRD commentary
The review addressed a clear question and had clearly stated inclusion criteria with respect to participants, treatment and outcomes and study design. Although the authors appeared to have searched for both published and unpublished studies, only published studies were included in the review, which suggested that there was a risk of publication bias. The results of the authors’ assessment of publication bias were not reported. The risk of language bias was unclear, as the authors did not report if any language restrictions were applied.

There were some discrepancies in the inclusion criteria pertaining to eligible study designs and the studies actually included in the review, in that a further analysis was undertaken using a prospective cohort for which no comparator or control group was provided. Pooling uncontrolled and controlled study designs may not have been appropriate, which made this analysis subject to a substantial risk of bias. Although the authors only included studies meeting a specified level of quality, the findings from cohort and case-control studies were associated with a number of potential biases. In addition, there was insufficient information about the studies pertaining to types of participants and medications received. The authors reported that they assessed the quality of the individual studies, but the findings of this assessment were not reported, suggesting that substantial caution is required when interpreting the results of this review.

The authors’ conclusions are unlikely to be reliable and caution is required when interpreting them given the potential for bias.

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

Research: The authors did not state particular implications for research, although they noted that analyses by particular drugs or malformations were not undertaken, and that they could not evaluate the critical period of major malformations because only the exposures during the first trimester were published, and included in the review.

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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.