The safety of quinolones—A meta-analysis of pregnancy outcomes

Benjamin Bar-Oza, Myla E. Moretti, Radinka Boskovica, Lisa O’Brien, Gideon Korena

1. Introduction

Quinolones are a group of antimicrobial agents which act by inhibiting bacterial DNA synthesis [1]. They are known to cross the human placenta [2] and could potentially have adverse effects on the developing fetus, although this has not been shown in humans. In reproductive studies reported by the manufacturer, no evidence of teratogenicity was found in mice, rats, rabbits or monkeys, even in very high doses. In contrast, these agents are reported to cause degeneration of developing cartilage tissue in neonatal mice [3] and in juvenile dogs [4,5] and therefore fluoroquinolones have typically not been recommended for use during pregnancy. Studies in human children have not been able to show evidence of cartilage toxicity however [6].

The use of quinolones has increased in the last decade with a significant shift to use the fluorinated quinolones [7–9]. Given that more than half of pregnancies are unplanned, a large number of women may potentially be exposed to these drugs during the first trimester of pregnancy.

Several small to medium scale studies found no association between the use of quinolones and an increased rate of congenital anomalies [10–18].

The objective of the present study was to systematically review and compare using meta-analytical techniques, whether first trimester exposure to quinolones is associated with increased risks for major malformations, stillbirths, preterm births or low birth weight.

2. Materials and methods

Medline, Embase, Scopus, Biological Abstracts and Proquest Thesis Dissertation databases were searched using the following keywords pregnancy outcome, abnormalities-drug induced, congenital anomalies, fluoroquinolones, quinolones, nalidixic acid, oxolinic acid, ciprofloxacin, norfloxacin, ofloxacin, enoxacin, feroxacin, levofloxacin, lomefloxacin, pefloxacin, gatifloxacin, grepafloxacin, sparfloxacin, gemifloxacin, moxifloxacin and trovafloxacin.

Key resources in teratology, ReproTox, Shepard’s Catalog of Teratogenic Agents, TERIS, ReproRisk, Drugs in Pregnancy and Lactation and Maternal-Fetal Toxicology were also searched for relevant publications. Articles were retrieved if they reported on human data. Reviews, case reports and retrospective case series were excluded from the formal meta-analysis. Subsequently,
reference lists from retrieved articles and books were examined for citations that may not have been captured using the prior search methods.

Two reviewers independently reviewed the retrieved citations for inclusion eligibility. A third reviewer was included in cases of dispute and to resolve discrepancies between reviewers choices. Once the list of studies to be included was determined, both reviewers independently extracted data from the publications into two-by-two tables. Studies were included in the meta-analysis if they reported pregnancy outcomes following first trimester exposure to one of the quinolone antibiotics and if they included outcomes for an unexposed control or comparison group. Both cohort and case control studies were included. The primary outcome measure was the rates of major malformations. Secondary outcomes included rates of stillbirths, preterm deliveries and low birth weight.

Data were pooled and combined into a summary odds ratio using a Mantel–Haenszel random effects model. The data were analyzed using Cochrane's Review Manager version 4.2. Publication bias was examined visually using a funnel plot. In the event that a study presented only a single group, with no control population, it was not included in the summary odds ratio. However, using the method proposed by Einarson [19] we also performed a single group analysis, calculating a pooled summary incidence rate which included all studies summarized in the meta-analytical procedure as well as a large prospective cohort that did not provide a comparator group and thus could not be included in the summary odds ratio. Reviewers assessed the quality of the articles and abstracts using a 27-item checklist based on work by Downs and Black [20]. The quality score was expressed as a percentage of the applicable items presented in the article. Scores above 50% were considered acceptable for inclusion into the meta-analysis. A chi-square test for heterogeneity was also used to assess combinability.

3. Results

Five studies met the inclusion criteria for analysis [10,11,16–18] (Table 1). Studies rejected from the analysis included: reviews [21], studies without a control group [22–25], and studies which were publications of duplicate data already captured among the included studies [12,14,26]. Two studies, one large scale study published by the European Network of Teratology Information

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Year of publication</th>
<th>Journal</th>
<th>Number of exposed/number of non-exposed</th>
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<td>International Journal of Gynecology &amp; Obstetrics</td>
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<td>Antimicrobial Agents and Chemotherapy</td>
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</table>

**Table 1**

Studies included in meta-analysis and single group analysis.

![Fig. 1. Summation of studies reporting the rate of major malformations.](image1)

![Fig. 2. Summation of studies reporting the rate of still births.](image2)
Services (ENTIS) [15], and a small cohort collected by the manufacturer [22], did not include control groups and so they were included only in the single group analysis of an overall incidence rate for major malformations.

The summary odds ratios (OR) for all the included studies was 1.05 (95% CI 0.90–1.22) for major malformations (Fig. 1), 2.6 (95% CI 0.36–18.67) for stillbirths (Fig. 2), 1.15 (95% CI 0.69–1.91) for preterm births (Fig. 3), and 0.73 (95% CI 0.30–1.79) for low birth weight (Fig. 4). All of these OR were non-significant.

The chi-square tests for heterogeneity for the different endpoints were not significant (p = 0.54–0.82), suggesting that the studies were combinable. The analysis was repeated to include only fluoroquinolones as those are the agents most predominantly in use today. Specifically, the Czeizel et al. study [11] was removed as they reported only on a non-fluorinated agent, nalidixic acid. The resulting OR remained non-significant (1.11, 95% CI 0.57–2.15) and was not heterogeneous.

When considering only the exposed groups, thereby including two additional publications which did not have control groups, and excluding the case control study, the summary incidence rate for major malformations following maternal exposure to quinolones in pregnancy was 3.49% (95% CI 2.20–4.79). The rate of stillbirths was 0.19% (95% CI 0.12–0.51), prematurity was 4.83% (95% CI 3.27–6.39), and low birth weight 1.52% (95% CI 0.60–2.43).

4. Comments

The quinolone antibiotics offer significant advantages for some infections, in particular those such as urinary tract infections which may not be sensitive to other agents. In pregnancy urinary tract infections have been associated with adverse pregnancy outcomes such impaired infant development and mental retardation [27]. In a recent study we have shown that women exposed to quinolones during the first trimester tend to terminate pregnancy due to perception and fears of malformations, more often than other callers to teratogen counseling services. Our analysis presented here is reassuring for the those women who may require quinolone therapy during pregnancy and for their clinicians who are faced with decisions regarding treatment choices.

By summarizing and pooling data from five studies, the overall summarized OR suggests that quinolone antibiotics are not a risk for major malformations following first trimester exposure in human pregnancies. The analysis was repeated to include only fluoroquinolones as those are the agents most predominantly in use today, and the resulting OR remained non-significant for major malformations. Moreover, these patients were not at an increased risk for delivering stillbirths, premature or low birth weight babies. Though the number of first trimester-exposed pregnancies included in this meta-analysis was 984 for all the quinolones and 318 for fluoroquinolones, the findings are strengthened by the fact that the confidence intervals were very narrow. To further support these reassuring findings, the summary incidence rate of a major malformation, which included all exposed groups including those studies without a control group, was 3.49% (95% CI 2.20–4.79), well within the rates expected in the general population.

The study is somewhat limited by the fact that because of the data available in the published studies, we were not able to conduct analyses by particular drug or particular malformation. We were not able to evaluate the particular critical period of major malformations because in general only the exposure during the first trimester was published.

In summary, the fears of teratogenicity commonly ascribed to quinolones are not justified by systematic analysis of all existing data.

References


