LETTER TO THE EDITOR

Reply to 'Comment on "Use of antibiotics during pregnancy and the risk of major congenital malformations: a population based cohort study" by Muanda et al.'

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We thank Acar *et al.* [1] for their comments on our study titled 'Use of antibiotics during pregnancy and the risk of major congenital malformations: A population based cohort study'. Though we fully agree with Acar *et al.* that we could not completely rule out a chance finding as clearly stated in our study, there are important considerations that should be taken into account when interpreting our findings. First, most of our results were consistent with previous published studies on the risk of major congenital malformations following in utero exposure to antibiotics especially for penicillin, macrolides, quinolones, doxycycline, nitrofurantoin and metronidazole as reported in our study [2]. Therefore, such replications of findings are more likely hypothesis-testing research rather than exploratory approach as stated by Acar *et al.*

Second, biological plausibility has been reported for each association seen in our study which strengthen our findings [2].

Third, adjustment for multiple testing can provide misleading results especially in presence of rare outcomes such as the case in our study. Indeed, by reducing the type I error (α), multiple test adjustments may increase the type II error (i.e. the probability of not rejecting the null hypothesis when the alternative is true) for those associations that are not null [3, 4]. Therefore, the increase of the type II error (β) will decrease the ability of a study to detect a real difference between groups (power = $1 - \beta$).

The American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification which was developed by the American Society of Health-System Pharmacists (ASHP) was used to classify antibiotics as stated in our manuscript [2]. The AHFS classification allows the grouping of drugs with

similar pharmacologic, therapeutic and/or chemical characteristics in a four-tier hierarchy [5].

Finally, no increased risk of major congenital malformations following in utero exposure to fluoroquinolone class has been reported in eight studies as stated in our manuscript [2]. Though, those previous studies, including published meta-analyses, were limited by several methodological flaws (low power, recall and indication bias) as pointed out in our paper, their findings were overall similar to ours [2]. Of the eight studies reported in our manuscript, only two studies were able to assess the risk of birth defect associated with the use of individual fluoroquinolone [6, 7]. The first study looked at the risk of major congenital malformations following in utero exposure to individual fluoroquinolone, and their findings were similar to ours as stated in our manuscript [2, 7]. Unlike us, they could not examine the risk of organ specific malformations [2, 7]. The second study investigated the risk of major congenital malformations and organ specific malformations associated with the use of ciprofloxacin, and their findings were consistent with ours [2, 6]. Unlike us again, they did not assess the risk of major congenital malformations associated with other fluoroquinolone such as levofloxacin, ofloxacin, norfloxacin and moxifloxacin [2, 6]. Contrary to the statement by Acar *et al.*, we were able to look at the risk of major congenital malformations overall as well as the risk of eight specific organ system anomalies following gestational exposure to 17 individual antibiotics including the five most used fluoroquinolones (ciprofloxacin, norfloxacin, moxifloxacin, ofloxacin, levofloxacin) [2]. Of interest, we have also recently reported that fluoroquinolone use in early pregnancy was increasing the risk of spontaneous abortion (a class effect) [8].

Therefore, the decrease of livebirth rate following an in utero exposure to fluoroquinolone noted by Acar *et al.* in the preliminary results of their unpublished meta-analysis may be explained by the increased risk of spontaneous abortion associated with the use of this antibiotic class. Put together, our findings on the fetal safety of fluoroquinolones highlight the current U.S. Food and Drug Administration (FDA) and Health Canada concerns regarding safety issues associated with the use of fluoroquinolone.

Competing Interests

There are no competing interests to declare.

References

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