LETTER TO THE EDITOR

Paroxetine use during pregnancy and the risk of cardiac defects

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Dear Editor,

We would like to thank Dr Bracken for his comments [1] on our meta-analysis, titled 'The risk of major cardiac malformations associated with paroxetine use during the first trimester of pregnancy: a systematic review and meta-analysis' recently published in the *British Journal of Clinical Pharmacology*. [2] Our meta-analysis results are consistent with previously published meta-analyses [3, 4] including that by Wurst *et al.* [3] which was funded by the maker of paroxetine. An observational study is not designed to address causality but associations, which we did with this meta-analysis. Additional criteria should be considered when assessing causality between paroxetine and birth defects, as was done previously by Bérard [5].

Although we agree that independence of data is important to avoiding potential bias in epidemiological studies, we disagree that this will necessarily lead to false results. Indeed, in recent years, advances in statistical analyses and programming have led researchers in the field of perinatal epidemiology to analyse dependent data (for example, multiple pregnancies per woman), and thus increase sample size and statistical power. We disagree that considerable overlap exists between studies from Denmark or Scandinavia. Although some overlap was reported in studies included in our meta-analysis, it is incorrect to assume that studies emerging from the same geographical area have the same underlying data [6]. Indeed, different database linkages, inclusion/exclusion criteria or calendar years considered could all result in different study cohorts [6], with minimal overlap, as was recognized in the Scandinavian and US studies in our meta-analysis. This is also postulated in the International Committee of Medical Journal Editors recommendations [7]. We further disagree that authors have included the entire country population in their study, for the same reasons listed above. Although overlapping data could be present, they would have a minimal effect on the point estimate and width of the confidence interval [6, 8]. If, however, updates on the same underlying cohort are performed, only the most recent peer-reviewed update should be considered [6], as was done for the

Swedish Birth Register studies in our meta-analysis [2]. Finally, it is not clear how one can recalculate the estimates and confidence intervals without having the exact percentage of data overall, as well as personal data between studies.

Confounding by indication and other study characteristics have been considered in our meta-analysis. Indeed, we performed stratified analyses on study characteristics such as study design, inclusion/exclusion criteria and adjustment for maternal depression by statistical analysis or design. In all instances, increased risk was repeatedly shown, indicating that these characteristics did not substantially affect the study results. Although the study by Jimenez-Solem and colleagues [9] had a paused group, this group nevertheless included a proportion of antidepressant users, which could potentially explain the fact that the estimates in first trimester users and the paused group were similar. As for the study by Huybrechts *et al.* [10] over-adjustment could potentially explain the results, given that adjustments on over 200 covariates were performed; adjusting on covariates that are not confounders or risk factors for malformations will lead to biased estimates [11, 12].

Given all these points, we believe that our meta-analysis is consistent with a causal relationship between paroxetine use in pregnancy and cardiac defects. This also has biological plausibility, given that the inhibition of serotonin reuptake at the appropriate time during organogenesis has the potential to result in cardiac defects or any other defects; this has further been shown by Bracken and Holford [13] with amitriptyline (a tricyclic antidepressant with a similar mechanism of action to paroxetine and other selective serotonin reuptake inhibitors). Finally, given the lifelong impact of birth defects, the safety of antidepressants during pregnancy should never be assumed when the null hypothesis is not rejected.

Competing interests

AB is a consultant for plaintiffs in litigations on paroxetine and birth defects. All other co-authors have no conflicts of interest.

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