Subject: BMJ - Decision on Manuscript ID BMJ.2016.037083

Body: 17-Feb-2017

Dear Dr. Rai

Manuscript ID BMJ.2016.037083 entitled "Antidepressants during pregnancy and offspring autism: population-based cohort study"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

dr. Wim Weber
European editor, The BMJ
wweber@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: José Merino (Chair), Gary Collins (Statistics advisor), Kristina Fišter, John Fletcher, Elizabeth Loder, Rubin Minhas, Amy Price, Tiago Villanueva, Wim Weber, Daoxin Yin.

Decision: Put points

Detailed comments from the meeting:

We thought your study addresses an important and interesting research question. We had the following queries:

We wondered if the severity of depression varies between the groups and can be properly accounted for, despite propensity analysis (there is no adjustment for severity). Some covariates vary considerably (i.e. smoking) and may not reflect true rates of that risk factor.

The focus on the sibling analysis drops off the headlines as the result is negative - it shouldn't disappear.

Is the negative control really a negative control? We would have thought that using the a group comprising mothers taking some other medication (e.g. hypnotics or treatments for irritable bowel disease) would be more appropriate.

We can’t see how the size of the cohort used after matching in the propensity score analysis, nor can we see how well the matching was; there is no table of matched characteristics with standardized differences.

There was some missing data (e.g., BMI), how was this handled in any of the analyses, more importantly what else was missing and how much?

You might want to cite this recent systematic review: Reprod Toxicol. 2016 Dec;66:31-43. doi: 10.1016/j.reprotox.2016.09.013. Epub 2016 Sep 22.
Prenatal selective serotonin reuptake inhibitor use and the risk of autism spectrum disorder in children: A systematic review and meta-analysis.
https://www.ncbi.nlm.nih.gov/pubmed/27667009

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
The article explores a relatively new topic in the field of Perinatal Psychiatry: the hypothesized association between in utero exposure to SSRIs and an increased risk of ASDs in children.

The work is very interesting, and may contribute to improve the clinical approach to expectant mothers who need antidepressant treatment. Gynecologists, pediatricians, and psychiatrists may be especially interested in reading this article.

Research question is clearly defined and appropriately answered and the overall design of study is adequate.

Participants studied are adequately described and their conditions clearly defined.

Results are balanced and well presented.

Interpretation and conclusions mirror sufficiently data reported by the authors.

References
I would suggest a brief discussion about results emerging from this study and those reported in the review by Gentile, 2015 (Prenatal antidepressant exposure and the risk of Autism Spectrum Disorders in children. Are we looking at the falls of Gods?" Journal of Affective Disorders. 182:132-7

Abstract, summary, and key messages reflect accurately what the authors report in their article.

Best regards
Salvatore Gentile

Additional Questions:
Please enter your name: Salvatore Gentile

Job Title: MD, Ph.D

Institution: ASL SALERNO (Italy) Dept Mental Health

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
This is an interesting and well-designed study investigating the association between antidepressant use during pregnancy and risk of autism in the offspring. Several analytic methods were used to address confounding by indication, an issue which has been a limitation in past studies on this topic. Results consistently indicate a small but significant increased risk independent of the underlying indication for the antidepressant use. Some suggestions for improving the manuscript follow:

1. Intro - clarify what is meant by 'updated total population cohort'

2. Methods

a. Patient involvement - delete sentence starting with 'We will disseminate...'
b. Medication use during pregnancy - last line on pg4 and first on pg5 is not clear.
c. Depression and other psychiatric disorders in parents - specify which 'other diagnoses of psychiatric disorders' were included, and during which time periods these diagnoses were considered, e.g., during pregnancy? anytime before delivery of study child? anytime including after delivery of study child? Only diagnoses made prior to the birth of the study child should be included.
d. Analysis 1 - how was the comparison group defined? Both psychiatric disorder but no antidepressant use during pregnancy? or psychiatric disorder anytime but no antidepressant use during pregnancy? What proportion of mothers who used antidepressants had a psychiatric diagnosis?
e. Analysis 2 - it is not clear which children were included in this analysis. The numbers in the supplement are very low (204 ASD cases, 68 exposed) compared to the total shown at the bottom of Figure 1 (489 ASD cases, 136 exposed).

3. Results - last sentence in this section is incomplete

4. Discussion
a. Second sentence typo "particularly autism with intellectual disability". Should read "particularly autism without intellectual disability"
b. pg 10 - lines 48-49 - this sentence doesn't follow the rest of the paragraph, which seems to be saying that confounding is possible but not that likely, at least not that likely to completely account for the results.
c. very last sentence of manuscript is not clear. Important to investigate possible biologic mechanisms underlying the observed association with prenatal antidepressant exposure? alternative autism prevention strategies - alternative to what?

Tables:
TAble 1 - how are women categorized into 'Maternal depression dx before birth by dx type' categories? Are they mutually exclusive?
Table 3 - add N exposed cases

Additional Questions:
Please enter your name: Lisa Croen

Job Title: Senior Research Scientist

Institution: Kaiser Permanente, Division of Research

Reimbursement for attending a symposium?: No

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Reviewer: 3

Recommendation:

Comments:
In this manuscript, the authors used population-based registers for Stockholm county, Sweden for children 4-17 years of age during 2001-11, to examine the association between maternal antidepressant use or maternal psychiatric disorders during pregnancy, and diagnosis of autism spectrum disorder (ASD) with or without intellectual disability (ID). The study is presented well, and provides some useful results that contribute to the international literature. What follow are some comments that may serve to strengthen the manuscript:

It would be helpful to make an explicit statement of study hypothesis at the end of the introduction, perhaps following p 3, line 55.

In describing the methods, was there any trend in ASD prevalence over the study period? Exclusion of children under age 4 is reasonable, but by birth cohort did the prevalence change over time, and did the pattern of age at first diagnosis change over time (this reviewer would hypothesis that median age occurred earlier in 2011 than in 2001).

Unless required by the journal, the paragraph on patient involvement, p 4, could be removed, or summarized in a sentence attached to the end of the previous paragraph.

Ascertainment of ASD and ID are potential issues for this study. It appears (p 5, lines 18-36) that all data were obtained from ICD and DSM codes in the several registers used as input data sources. The text notes that validation studies were done (lines 32-36), but can the authors verify that a case diagnosed in 2004-6 has similar clinical features to those diagnosed in 2010-11?

In describing diagnosis of depression and other psychiatric disorders, these were apparently solely from ICD codes. Did the authors also supplement these with DSM diagnostic codes? Is it possible some cases not publicly funded were missed since they are not in the SAPCR?

In the description of the analysis, p 6, was age at diagnosis controlled in the analysis?

The results from analysis 4 (p 7) are for only two years of birth cohort, and these children were only ages 4-5 at the conclusion of the study. Thus, these results should be interpreted with extreme care. The paper could be more straightforward if this analysis were removed.

Based on results in first para of results on p 8, the prevalence of ASD was 2.1% among nonexposed pregnancies. This is considerably higher than what is reported in many other prevalence studies. It deserves some comment, as if the prevalence overall is higher the study findings may be less generalizable to other settings.

The last few sentences in the results need some work (p 9, lines 11-15). What is the specific point of focusing on differences in point estimates with overlapping CIs? Was a statistical test done to determine whether the estimates differ significantly? And the last sentence ends 'including . . .', seems something was left off.

The previous study used some of this study for a case-control

design and was also published in BMJ (p 10, line 8). The discussion should more clearly outline how the present study provides stronger evidence, and whether its findings provide clarity to the prior results.

The second full para on p 10 begins by mentioning that this study has strengths and limitations, however, no limitations are explicitly addressed. There most definitely are limitations and these should be fully discussed here.

The discussion concludes by suggesting the attributable fraction for antidepressants is small, likely 2% at most. This might be interpreted in the context of other studies seeking to determine the relative contributions of identified risk factors, for example Schieve LA et al, Ann Epidemiol 2014;24:260-266.

Minor:
p 3 line 32 - consider 'autism-like' rather than 'autism like'
p 5 line 47 - this might be an American v British English difference, but in the US we would use 'publicly' rather than 'publically'
p 5 the paragraph headed 'Ascertainment of autism' should to titled 'Ascertainment of autism and intellectual disability
p 8 line 29 consider space between % and CI

Additional Questions:
Please enter your name: Russell S. Kirby

Job Title: Distinguished University Professor and Marrell Endowed Chair

Institution: University of South Florida

Reimbursement for attending a symposium?: No

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Other than that, I have no competing interests to disclose.