Dear Dr. Charlton

Manuscript ID BMJ.2015.028891 entitled "Maternal use of oral contraceptives and risk of birth defects"

Thank you for sending us your paper, manuscript # XXX entitled "YYY". We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise your paper as explained below in the report from the manuscript meeting. We are provisionally offering acceptance but will make the final decision when we see the revised version. The report from the manuscript meeting, the comments from the reviewers and general requirements for submission are available at the end of this letter.

We are looking forward to reading the revised manuscript and, we hope, making a final acceptance decision.

https://mc.manuscriptcentral.com/bmj?URL_MASK=167910a929e3470aa60e33b6115b76c6

Yours sincerely

Georg Roeggla
groggla@bmj.com,

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.

Manuscript meeting 15.10.2015

Elizabeth Loder (chair), Jon Deeks (stats), Kristina Fister, Georg Roggla, Wim Weber, Jose Merino, Tiago Villanueva, Rebecca Burch, Rubin Minhas

Decision: Provisional acceptance

The committee was interested in the topic of your research. The following concerns were mentioned:

• Please report the novel aspects of your paper in comparison to previous papers in more detail. You state your findings are consistent with the majority of previous studies that found women who use OCs during early pregnancy have no increased risk for most types of major congenital malformations.
• Oral contraceptives is a big umbrella term for formulations with very different hormonal profile and dosages (1st, 2nd generation progestagens, combined, non-combined). Does this influence your findings?
• Should you adjust for possible comorbidities?
• Can folate use influence the outcome?
• Classic Scandinavian drug safety epidemiology.
• Of course you don't know whether or not OC were actually used, but this is as good as you can get. Whilst the overall question of "any birth defect" is answered quite conclusively, the confidence intervals on individual birth defects are still quite wide, (e.g. Hypoplastic left heart syndrome) so if there are particular defects which are biologically more plausible, this may not have ruled them out. But you know all this and have explained it well.
• We question how you link your research to the previous case control study findings – you claim that your findings do not corroborate the previous findings.
• The previous case control study had greater statistical power than this cohort – this study is possibly is less prone to bias.

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. Please also respond to the additional comments by the committee. 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 the external peer reviewers**

REFEREE COMMENTS

Reviewer: 1

Recommendation:

Comments:
This is a clearly executed manuscript in an important area of research. I suggest the following revisions:
The authors mention imputing missing values using the mode. The number and percentage of all missing values should be shown in Table 1. It is critical to know the proportion of missing values for each variable. The authors should also provide more information regarding which women were considered to have used oral contraceptives. Did they

include women on progestin only pills or morning after pills? Were women who used other hormones for contraception such as the Mirena IUD, the hormonal patch or hormonal ring, excluded from the analysis?
On page 5 please clarify what is meant by calendar year. Does this mean year of birth? As this a cohort study the power to assess relationships for specific birth defects is more limited than the statistical power in a recent analyses of the National Birth Defects Prevention Study (a case control study) that was led by this reviewer, i.e. Waller et al.. For gastroschisis, our study had 447 cases of which 40 were exposed to OCs during pregnancy for an adjusted OR of 1.82 for exposure during pregnancy compared with the current analyses which included 138 cases of gastroschisis of which 3 were exposed during pregnancy and an adjusted OR of 0.84 (0.26 -2.68). It seems important to point out that this analyses had more limited statistical power to detect an increased risk of gastroschisis and hypoplastic left heart syndrome among women exposed to OCs than Waller et al. For hypoplastic left heart syndrome my paper included 186 cases of which 16 were exposed during pregnancy for an adjusted OR of 2.33. In comparison, the current analyses includes 93 cases of HLHS of which 3 were exposed during pregnancy for an adjusted OR of 2.47. Although in the current analyses the elevated OR of 2.47 for HLHS was not significant it also seems important to note that both studies found an elevated OR > 2.0 for HLHS. Due to the lower statistical power in this study it is not surprising that the OR of 2.47 did not achieve statistical significance. In table 3, the word gastroschisis is misspelled.
The current analyses used a different method of exposure ascertainment compared with previous studies which used maternal interview and yet results were reasonably similar to previous studies. I think the currently analyses makes an important contribution to the literature.
signed, Dr. Dorothy Kim Waller

Additional Questions:
Please enter your name: Dorothy Kim Waller

Job Title: Associate Professor of Epidemiology

Institution: School of Public Health, UT 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

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: None to declare

Reviewer: 2

Recommendation:

Comments:
9Sept2015

General comments
This manuscript presents a Danish record linkage cohort study of oral contraceptive use and risk for major birth defects. It is well written overall, the study approach is sound and incorporates modern methods, and the topic is of considerable public health importance. The authors conclude that maternal OC use shortly before or during pregnancy does not increase the risk for major birth defects, subgroups of defects, nor specific defects that have been suggested in previous research. They note that this should reassure patients and physicians. These conclusions seem quite reasonable given the presented data. Furthermore, while "negative" findings, it is important that results such as these are published so that we can reassure ourselves and the public about commonly-used medications that do NOT appear to convey risks when used during pregnancy.

Specific comments
No major shortcomings were identified, but improvements could be made to clarify some of the methods and results, as noted below.
1. Abstract: Please spell out "oral contraceptives" at first use vs. OC abbreviation.
2. Methods/ Oral Contraceptive Exposure: Please clarify the definition of "never users". The Methods say "those who never filled an OC prescription since the introduction of the prescription register" and "The National Prescription Register contains information… since 1995". However, the Table footnotes say "who have never once filled an OC prescription since the study period began in 1997" (2 year difference)?
3. Results/ 1st sentence: I suggest adding the prevalence on birth defects in this sample, 2.5% (22,013/880,694).
4. Results/ 2nd sentence: Among the 21% "never users", have you examined the distribution by year of live birth? It would be interesting to note what proportion of these were in the early study years and thus more likely to be misclassified as "never" given the window started in either 1995 or 1997.

5. Results/ 5th paragraph, line 37: Please correct typo: “less ‘than’ 1.15”.
6. Discussion/ 4th paragraph: Considering the previous comments re: “never users”, the results among this group might need some additional caveats in the Discussion. Rather than being a “highly select group”, it’s quite possible that they’re just a mixed group, with some being true never users and some being misclassified given the study methods.
7. Discussion/ 5th paragraph, limitations: Can you provide literature to support that the prescription register data is “likely more accurate” than self-reported data? As you mention in the following sentence, you do not know if the women actually took the filled prescription.
8. Table 1: Given the missing percentages provided in Table S2, please state (perhaps via footnote) whether these Table 1 numbers include imputed values or whether the missings were excluded.
9. ALL Tables: Please see previous comment about clarifying the footnote re: “never users”.
10. Table 4/ Sensitivity Analyses: Were there not enough numbers to perform either sensitivity analysis for the secondary outcomes (i.e., birth defect subgroups)? The results for smaller subgroups and specific defects would be more meaningful than lumping all major defects together.

Thanks,
Cheryl S. Broussard, PhD

Additional Questions:
Please enter your name: Cheryl S. Broussard

Job Title: Epidemiologist

Institution: CDC

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

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Information for submitting a revision

Deadline: Your revised manuscript should be returned within one month.

How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s). As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation ‘Revised Manuscript Marked copy’. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

3. Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).

4. Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

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8. Data sharing statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research)

9. Funding statement and statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements).

10. Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).

11. Please ensure the paper complies with The BMJ's style, as detailed below:

a. Title: this should include the study design eg "systematic review and meta-analysis."

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

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END

Date Sent: 15-Oct-2015