BMJ - Decision on Manuscript ID BMJ.2016.031600

Body: 16-Apr-2016

Dear Dr. Kyrgiou

Manuscript ID BMJ.2016.031600 entitled "The risk of preterm birth after treatment for cervical pre-invasive and early invasive disease increases with increasing cone depth: a systematic review and meta-analysis."

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.

Kristina Fišter
kfister@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=1e339fd7d77b44fb8fbfc49fd54eadb3

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: Elizabeth Loder (chair), Gary Collins (statistician), editors - Wim Weber, Georg Roeggla, Tiago Villanueva, Rubin Minhas, Kristina Fišter.

Decision: Put points

Detailed comments from the meeting:

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 these additional comments by the committee:

* The search is over 1 year old – December 2014, perhaps it's worth considering an update. Also, has the paper been elsewhere before it came to us? As per the ICMJE recommendations, we encourage all authors to share with us any correspondence from previous submissions to other journals.

* Apart from the summary of scores nothing else is done with this assessment - there are detailed tables in the appendix – it would be useful if you discussed this more.

* Assessment of heterogeneity seems limited and glossed over, in the Methods you say 'If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported' – how did you examine this? (i.e., did you carry out meta-regression); we felt this wasn't explored as well as it could have been.

* The title should not declare the findings. Perhaps use the term "adverse obstetrical outcomes"

* There are 69 studies but for many of the outcomes only a few contribute information. Furthermore the results of individual studies all seem to be in the same direction so the summary results only improve precision.

* The first paragraph of the introduction is very UK-centric. Is this paragraph absolutely needed? If so, could it put the topic in a more international perspective?

* Excluding the 49 studies with no untreated reference population seems like throwing away information. If this were a network meta-analysis could those have been included?

* Bottom of p 5 "We excludes studies..." Shouldn't the conjunction be OR instead of AND?

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:
This meta-analysis addresses effect of treatment of CIN on obstetric outcomes, especially on preterm birth. This subject has been discussed a lot. This meta-analysis is the first that compares different comparison groups and clearly shows that although women with CIN have a higher baseline risk of prematurity, cervical treatments and particularly large cone size increases this risk even more. Increased risk that is associated with multiple treatments and large cone volumes is presented at the first time in this meta-analysis. Meta-analysis is very well written, statistics is excellent. It is actually very hard to find something that could be improved.
This study is also important to general readers, because patients are also aware of this risk and often seek for advice. Authors will disseminate the results to the lay audience.
Specific questions:
* Scientific reliability
Research Question - clearly defined and appropriately answered? Yes

Overall design of study - adequate ? Yes

Participants studied - adequately described and their conditions defined? Yes

Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ? Yes

Results - answer the research question? Credible? Well presented? Yes.

Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear? Yes

References - up to date and relevant? Yes, very comprehensive literature search.

Abstract/summary/key messages/ What this paper adds – reflect accurately what the paper says? Yes. I suggest to add something about cone size in the key messages.

If the paper is a randomised controlled trial we will have asked the authors to provide the protocol and a CONSORT checklist. Other research designs should have the relevant checklist (PRISMA, STARD etc). These are available by clicking on "Download associated files".

Some minor comments:
1. Title: It could be modified a bit. Now it contains term “cervical preinvasive and early invasive disease”. Current WHO classification has abandoned term “microinvasive cervical cancer” and therefore it is not recommended anymore. Authors use this term also on p 5, line 27.
2. Abstaract, p2, line 50. Quite often term “very preterm birth” is used instead of “severe prematurity” on gestational weeks below 34/32.
3. Absract, p 3, line 3. The increased risk with increasing cone depth could be presented in more condensed in the Abstract.
4. M&M, p5, line 35-36. I do not understand term “aka” in front of procedures.
5. M&M. P8, line 46. Patient involvement. This is very important topic, but is this the right place for this?
6. Study limitations. Cone depth measurement is not precise; therefore results regarding this measurement should be interpreted with caution. This should be discussed in the study limitations section.

Additional Questions:
Please enter your name: Maija Jakobsson

Job Title: MD, PhD, Senior Consultant

Institution: Helsinki Univeristy Hospital, Finland

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:
There have been a number of systematic reviews on this topic. Preterm labour and adverse Obstetric outcomes remain an important issue for colposcopists and women needing treatment of CIN. Perhaps in some areas of healthcare, the argument has been accepted e.g. primary care and public health.
The methodology is appropriate and clear and adheres to STROBE.
The authors clearly set out the rational for this updated meta-analysis and the ongoing uncertainty in treating women and providing accurate information on the risk of preterm labour prior to treatment.
The results are clearly presented and the sub-group analysis useful for colposcopists/clinicians. A clearer clinically relevant message on identification of high risk groups or minimising risk would be useful for the target audience.
For example is the key message that the meta-analysis results are reassuring in that RR is only slightly raised by treatment effect over and above having cervical disease and we can reassure the majority of women who will need only a single type 1 excision? Or should the reader be concerned about planning depth and volume of excision more carefully to minimise risk of future cancer and PTL? A key message on high risk groups and discussion on implications for clinical practice. I would be interested to know what advice clinicians should be giving to patients on their increased risk compared to the normal population and the size of the effect above this for single excision.

Minor comments:
Pg 6 line 48. Should be length of labour
Pg 17 line 20. Is there evidence to support statement that treatments have become less aggressive following increasing risk of preterm labour rather than the move to fertility preserving techniques? The Strander study referenced relates to move from hysterectomy to conserving cervix not reducing amount of cervical tissue removed/destroyed on cervical conserving techniques. The risk lf residual or recurrent CIN is also important in this context since these women are the ones at high risk from repeat excisions.
Pg 18 lines 1-19. The message on risk of PTL and appropriate selection of high risk group for surveillance and intervention is confusing and I was not clear if there was any benefit or risk of disbenefits or not. It just require an additional line that the RR for women with a single type 1 treatment is not sufficiently increased to warrant antenatal monitoring of cervical length or currently offered interventions such as cervical cerclage. I do not know if the authors feel there data supports this.
Pg 18. Line 38. It would be helpful to use a more specific term than 'young'.
Pg 18. Line 46. It would be helpful to be more specific than 'acceptable parameters'. Is this <10/12 mm?

M E Cruickshank

Additional Questions:
Please enter your name: M E Cruickshank

Job Title: Professor of Gynaecology/Honorary Consultant

Institution: University of Aberdeen

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 3

Recommendation:

Comments:
Maria Kyrgiou and her collaborators have once again performed a large systematic review and metaanlysis in the field of associations between treatment for cervical precancer and pregnancy outcome. This is basically a needed update of their own metaanalysis in the BMJ 2008 and an important expansion and update of an Australian metaanlysis from 2011.

The methodology of the work is as far as I can judge immaculate. I find no relevant articles that are not included. The discussion is clear and concise and their conclusions are partly novel, as they state.

I have one major concern, however. A very common, and quite difficult clinical situation for colposcopists is to assess, and inform a younger woman about the risk for future preterm birth as an effect of a standard treatment of a fully visible lesion (Transformation zone type 1). The length of an excision would probably only have to be 8 mm. This metaanalysis does not give an answer to the question if there is a risk to treat. The crucial analysis of cone length stratified for different comparison groups is unfortunately not done. The clinical relevant comparison group in this, and most cases, are untreated women with HPV infection and cervical lesions. Perhaps there are not sufficient data for this subgroup analysis, but I would expect this at least be commented upon as a limitation.

Moreover: Data on the smallest, and most common i today's clinical practice, excisions have narrow confidence intervals, half of the studies are very small and the studies are heterogenous. This should call for specific caution in interpretation of the data on this group.

Thus the first conclusion in the main findings (Page 14, line 51) and other parts of the manuscript should be rephrased as the authors have not shown that the risk for performing a small excision (<10mm) on a women with a cervical lesion should increase her risk for preterm birth and adverse sequele – as compared to abstaining from treatment.

Minor points
There are no discussion of how acquisition of data on cone length can vary and the implications for the results. E.g. formalin fixed vs. fresh mesurement.

The double figures for cone length (e.g. ≤ 10/12 mm), volume (>3/4 cc) and pregnancy length (e.g. <32/34 w) should be explained in the text and the tables.

The terms depth and length for cone material are used alternatively in the manuscript.

cc and mm (not mm3) are both used for volume.

In table 3 the both the signs ≤ and ≥ are used, not explaining to what category the exact figure belong (e.g. 10 mm)

Pages 56 – 58 are forest plots. The difference between the analysis in page 56 and 57 is not clear to me.

This is a major work within the field. It deserves to be published and it is suitable for the BMJ audience. I suggest the authors get an opportunity to revise the manuscript

Björn Strander

Additional Questions:
Please enter your name: Björn Strander

Job Title: Consultant, PhD

Institution: Sahlgrenska Academy, Gothenburg, Sweden

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 4

Recommendation:

Comments:
Dear Editors and authors

This is a very interesting meta-analysis from a team that has been studying the issue of premature birth and its relation to excision/ablation of cervix for many years. Of course there is no randomised study included in this meta-analysis and there is not going to be one in the future so the meta-analysis of observational studies are the best data that can be provided to lead clinicians in this very interesting and debatable issue.
The risk of preterm birth and reproductive morbidity after treatment for CIN has gone back and forth and then back again. I feel that many clinicians found hard to follow the literature in the last few years and find it even harder to properly counsel patients when seen in the colposcopy clinics about the associated risk.
A few examples of papers leading to this conflict come to my thoughts: Sadler (JAMA 2004), Noehr (Obs Gyn 2009), Ortoft (BJOG 2010), Albrechtsen (BMJ 2008) supporting substantial increase in risk after treatment from population-based studies and Castanon (BMJ 2012) suggesting that this association may not be actually true (although the authors did recall these conclusions in the latest paper (BMJ 2014).
The manuscript is well presented and I must say it is the most comprehensive meta-analysis I have seen in the literature. All the important factors affecting outcomes have been included in the analysis. All the relevant obstetric outcomes are thoroughly assessed, singleton and multiple birth, single and multiple cones, nulliparous and parous women etc.
I have the following comments to make

1)It would be interesting to see the subgroup analysis on the risk of preterm birth for different cone depth groups only for studies that have as a comparison group women with CIN but no treatment. The number of studies is likely to be small but I do think it would be useful to see the results for this subgroup comparison.

2)Can the authors discuss the limitations of the previously published recent small meta-analyses.

3) What does 10/12mm or 34/32weeks mean? This is not clear to me. Also if a cone biopsy had a depth of 10mm this was categorised as ≤10/12 or ≥10/12?
In the last line of second paragraph of preterm birth I assume it should be <6cc instead of <6mm
In addition, as before it is not clear for me how this categorisation works. For instance the comparison of ≥15/17 with ≤17/15 is quite confusing and it needs more clarification in the methods. Are these the groups used in the initial studies included in the analysis? In which category a 16mm deep cone belongs in?

4) Figure 2 and Figure 3 are exactly the same and depicting the same issue which is premature birth depending on the depth of the cone. I think the authors made a mistake and instead of presenting a figure of prematurity depending on the mode of treatment they submitted the same figure twice. The only thing that differs is the year. At the first figure is on descending and on figure 2 on random order. This needs to be corrected.
Also the total number of women presented in Figure 3 is different than the one presented in table 3 and the one written in the manuscript. For example the total number of women included in the first category of Figure 3 (A) should be 550929 and not 546824.

5) The authors used the Newcastle score to assess quality of retrospectve cohort studies but did not exclude any studies according to this score. They also included 2 studies with a score of 6. Why was this scoring system used (a lot of difficulties with this scoring system noted in the literature as different reviewers were scoring the same manuscripts differently, JCE Sep 2013) if it was not used to exclude studies? Did they have in mind a pre-defined score that would prompt them to exclude studies?

6) What is the difference between prematurity and spontaneous prematurity?

7)In results: you mention 4 prospective reports, but you reference 5

8) Page 15, Line 5: As expected….: I think I would rephrase that sentence to improve the language.

9) Table 3: Versus and not verses.
Suplem Table 1: the score (9) is missing from van Rooijen 1999
Methods 4t paragraph: the word spontaneous in between 2 ; doesn't make sense

10) It will be interesting to see a comparison of treated women with a cerclage compared to untreated population in relation to prematurity?

11) How was the volume of the cone specified?

I think this paper is clearly needed and I think it would be very well fitted in a journal like the BMJ with wide readership. This meta-analysis 10 years after the first paper published in the Lancet by the first author will bring new insight on the existing evidence base with absolute risk that can also be used when counselling patients. I have no doubt that this is the most comprehensive meta-analysis I have seen and I think the results will be invaluable to clinicians.

In summary, I think this is a very important and well conducted meta-analysis in this field and it will be very well fitted in a journal like the BMJ with wide readership. It provides comprehensive evidence base in this field and particularly on the risk of preterm birth stratified by the cone size. I think it should be accepted for publication.

Additional Questions:
Please enter your name: Dr. Ioannis Biliatis

Job Title: Subspecialty fellow in Gynaecological Oncology

Institution: Royal Marsden Hospital, London

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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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).

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

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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.

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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: 16-Apr-2016