05-Mar-2018

Dear Dr. Williams

Manuscript ID BMJ.2018.043336 entitled "Risks of ovarian, breast and corpus uteri cancer in women treated with assisted reproductive technology; 2.2 million person years of observation in Great Britain"

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.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

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), Jon Deeks Doug Altman (Statistics advisor), Sophie Cook, John Fletcher, Elizabeth Loder, George Rőggla, Tiago Villanueva, Wim Weber.

Decision: Put points

Detailed comments from the meeting:

We thought your study addresses an interesting and potentially important research question.

We had the following questions:

There's a recent and very large systematic review you might want to cite:

JBRA Assist Reprod. 2017 Jun 1;21(2):115-119. doi: 10.5935/1518-0557.20170026.

Do women offered assisted reproduction technologies have a higher incidence of gynecologic cancer? A systematic review and meta-analysis.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5473704/

You use "old fashioned" statistical methods comparing observed rates with national rates to compute standardised incidence ratios. One of the reviewers thinks this is inappropriate and Cox models should be used. We don't think that it would make much of a difference to the findings – maybe change the magnitude of the relationships a little, but not much.

You make no adjustments for confounding – so difficult to draw causality conclusions, but you are careful in not making them, just describing the observed risk relationships.

The absolute risk is not explained well. Errors in the confidence interval calculation and not reported widely.

Tables could be better organised.

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:
Dear Mr. Weber,
dear editors,

Thank you for giving me the opportunity to comment on the study „Risk of ovarian , breast and corpus uteri cancer in women treated with assisted reproductive technology; 2.2 million person years of observation in Great Britain" by Williams et al.. The authors aimed to investigate the risk of corpus uteri, breast, and ovarian cancer among women who underwent assisted reproductive technology. Compared to the standard population it was found that risk was increased for breast cancer in-situ and invasive, and borderline ovarian cancer.

This a well-written and interesting study with an impressive sample size that might give new insights for this relevant research question. Nevertheless, there are some residual concerns:

Major
1. The authors observed an increased risk in ovarian cancer; however this significant results did not remain after restricting the cohort where infertility was due male factor only. As the authors also discuss, (biological) reasons that might be associated with the female infertility itself (e.g. endometriosis), might play a big role as potential confounder. Given the fact that for ovarian cancer risk also no clear dose-response with number of cycles was observed, this might underline this observation. For the analyses on invasive and borderline ovarian tumors, the authors should also report results for sensitivity analyses restricting to the cohort to male factor as reason for infertility.

2. Besides confounding due to intrinsic (biological) reasons of infertility, also others confounders such as socio-economic status, co-morbidities or co-medication would have been of interest to control for confounding. This might be preferably analyzed using a conventional cohort/nested case-control design where women who underwent assisted reproductive technology are e.g. age- or frequency-matched to

comparable controls. Corresponding multivariable regression analyses could be used to control for further confounders here. However, I assume that such potential data was not available for analysis?

3. The authors should explain a bit more in detail what they mean with „Sensitivity analyses excluded the first 12 months of follow-up". Does that mean that they restricted the cohort of women who underwent assisted reproduction to the ones who were cancer free at least for the first 12 months after the first cycle?

Minor
4. Page 6: „Overall 7% of women undergoing assisted reproduction, 1991-2010, were not included in this study, representing a loss of less than 1% of person-years follow-up". Why were they not included? Due to missing values for important variables or because they refrained to give their consent?

5. Statistical analysis, first sentence, page 7: „Person-years at risk were calculated from date of first treatment…". Maybe change „Person-years….." to „Follow-up was calculated from…" to make it more consistent throughout the manuscript.

Additional Questions:
Please enter your name: Janick Weberpals

Job Title: Doctoral Student

Institution: German Cancer Research Center (DKFZ)

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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HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: No conflicts of interest.

Reviewer: 2

Recommendation:

Comments:
Originality - does the work add enough to what is already in the
published literature? If so, what does it add? If not, please cite relevant
references.

Yes – this is the largest study of this kind and is in a clinically relevant area. The findings impact on a large number of people (over 1 million IVF cycles performed globally last year) and address an area of knowledge that engenders great anxiety amongst patients and causes concern to providers of services

* Importance of work to general readers - does this work matter to
clinicians, patients, teachers, or policymakers? Is a general
journal the right place for it?
Yes – with 3% of UK births following IVF there is general relevance to the clinical community

* Scientific reliability
Research Question - clearly defined and appropriately answered?
Yes – a well defined and adequately powered linkage study between one of the largest ART databases World wide (that of the HFEA) and national cancer registry data

Overall design of study - adequate ?
Yes

Participants studied - adequately described and their conditions
defined?
As far as is possible with this methodology. The subgroup analyses depend on the accuracy of clinical diagnoses of causes of infertility. Approaches to diagnosis have relaxed over the duration of the study as the inexorable advance of IVF as a solution to all causes of infertility has reduced the clinical need for investigative rigour. For example, laparoscopy is performed far less frequently than in the early part of the century so diagnosis of endometriosis (an important factor linked to diagnosis of ovarian cancer in this study) is made less often and on the basis of soft clinical signs than previously. This point is not adequately addressed in the discussion.

Methods - adequately described? Complies with relevant reporting
standard - Eg CONSORT for randomised trials ? Ethical ?
Yes – well described
The early part of the study was not covered by individual patient consent but the data were anonymised and usage approved by HFEA. This database has been used in several previous published studies and has been deemed ethical by reputable journals.
Ref 3 describes an effect of oral clomifene only – not injectable FSH as is used in >90% of IVF cycles. This should be mentioned.

Results - answer the research question? Credible? Well presented?
Yes – well described. Highly detailed data tables are not easy to interpret but comprehensive
Comparison data are only available in 5 year age bands. Patient data are presented per year. Could the authors be more clear about how they corrected for this potential mismatch?
Are data available for pregnancy as well as livebirth. Was the protective effect of livebirth also observed for other pregnancies.

Interpretation and conclusions - warranted by and sufficiently
derived from/focused on the data? Message clear?
Yes although I would have appreciated information to describe the magnitude of the effect of risk of ovarian cancer. This paper will raise anxiety amongst patients in the "at risk" categories, and amongst clinicians. We are only provided with statements of relative, not absolute risk. The discussion should try to contextualise the positive findings. The current version is similar to papers linking oral contraceptives to risk of venous thrombosis or the WHI study publications, which over empathised the risk of harm by presenting only relative risks.
Why might a twin pregnancy be more protective against uterine cancer?

References - up to date and relevant? Any glaring omissions?
The authors should update ref 24 – viz ICMART report from 2016

Abstract/summary/key messages/What this paper adds - reflect
accurately what the paper says?

Succinct and well presented

Additional Questions:
Please enter your name: William Leigh Ledger

Job Title: Professor

Institution: University of New South Wales

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

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Reviewer: 3

Recommendation:

Comments:
This report is an authoritative analysis of the cancer risk in women following exposure to the medications and procedures undertaken using assisting reproduction. It is well written, clear in its aims and acknowledges its weaknesses. The linked access to mandatory notification of the procedures and the cancer registry has provided a unique opportunity for assessment of the potential risks. The authors consist of authorities in the relevant disciplines, notably epidemiology and the experience of employing similar research discipline of epidemiology for cancer screening and risk ,now applied to fertility interventions and possible risk of cancer.
The reassuring observations reported here will be welcomed by clinicians and patients alike.
It would be useful to know if the authors plan to analyse the risk of malignancy in women who act as oocyte? Egg "donors" who have been recruited due to their normal reproductive health as there is a increasing demand for oocytes from fertile young women.

Additional Questions:
Please enter your name: J G Grudzinskas

Job Title: Consultant(hon) Gynaecology

Institution: St George's University NHS Foundation Trust

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: 4

Recommendation:

Comments:
Allan Jensen, Group Leader, PhD
Danish Cancer Society Research Center

The manuscript analyse the risk of corpus uteri, breast and ovarian cancer (invasive and borderline tumours) following assisted reproduction in a nationwide historic cohort in Great Britain between 1991 and 2010. The manuscript thus covers an important topic for which there is a growing amount of published literature but where the results are not overwhelmingly conclusive. The authors find no increased risk of breast cancer overall or for invasive breast cancer only but find an increased risk for in-situ breast cancer. The risk of corpus uteri cancer was not increased, whereas an increased risk of ovarian cancer (both invasive and borderline ovarian tumors) was observed. The major strength of this study is the large size of the cohort (the largest to date). Other strengths of the study includes the relatively long-term follow-up, the ability of researchers to link to information on cancer diagnoses and vital status and a small loss to follow-up. Overall, the paper therefore has some value as a contribution to the already published literature covering this important area.

However, to my opinion, this study has one important limitation and I do not think the manuscript may be ready for publication in its present form.

My main concern about this study is the analytic approach used which, to my mind, is not fully optimal. The analytic approach used is a so-called 'SIR'-analysis, where the observed number of cancer cases in the exposed population is compared to the expected number of cancer cases in the general population. Such a comparison takes age and calendar time into account but does not has the ability to consider other important confounders (i.e. parity, causes of infertility, endometriosis, oral contraceptives, etc.) Therefore, the calculated relative risks (SIRs) will most likely be confounded (most likely resulting in an overestimation of the risk estimates) and therefore difficult to interpret. On page 14, lines 38-45, the authors states that their study has '…sufficient size to stratify by potential confounding factors and

thereby investigate characteristics of associations.'. This is correct, but it does not eliminate the problems with missing proper adjustment for confounding variables. Another problem with the analytic approach is that the risk estimates might be slightly underestimated, as the background comparison population also includes the exposed women. Lastly, the authors have made no attempt to censor for different kinds of gynecological surgery (in the exposed women) and have therefore overestimated the number of person-years at risk in the analysis.

All in all, the results from this analytic approach is not easy to interpret and I suggest that the authors use a different analytic approach and select a comparison group, i.e. a group of unexposed women with individual-level confounder-, censoring- and outcome information from the background population of Great Britain. Then a survival model (e.g. a cox regression model) can be applied and a more proper handling of confounders and censoring variables can be achieved which means that the true association between the various exposure variables and the outcomes can be obtained with higher validity.

Thus, if the authors have the ability to change the analytic approach and satisfactory address the other minor comments below, the manuscript may be suitable for a re-submission to BMJ

Title: I suggest that the number of (exposed) women could be mentioned instead of the number of PY, as I think the former is more informative.

Introduction:

Page 5, lines 16-32: I am not convinced that the references mentioned are sufficient. E.g., only one study is mentioned when referring to earlier studies on fertility drugs and ovarian cancer risk. Please make a more thorough description of the earlier publications in this research area.

Methods:

Page 7, lines 19: Have you also excluded non-melanoma skin cancer before follow-up? Please specify. I do not think that it necessary to exclude women with this cancer type.

Results:

The risk of breast cancer is split up in in-situ and invasive breast cancers and correspondingly, ovarian tumors are split up in invasive and borderline tumors. I suggest that the authors also look at the association with the different histological subtypes of respectively breast- and ovarian cancer as it is well-known that the aetiology of the different histotypes may differ, and it could therefore be interesting to see if that is also the case for the association with ART/infertility. Also, if the information is available, uterine cancers could also be split up in type 1 and type 2 endometrial cancers.

IVF vs. ICSI: The exposure variable seems to be ART only. As ICSI is a more invasive method than IVF, and it can be hypothesised that it may affect cancer risk to a higher degree than IVF. If the authors have differentiated information on IVF and ICSI, I strongly suggest that these should be analysed as separate exposures. If this information is not available, it could be mentioned as a limitation.

Additional Questions:
Please enter your name: Allan Jensen

Job Title: Group Leader, PhD

Institution: Danish Cancer Society Research Center

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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