PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Post-traumatic stress, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study
AUTHORS	Farren, Jessica; Jalmbrant, Maria; Ameye, Lieveke; Joash, Karen; Mitchell-Jones, Nicola; Tapp, Sophie; Timmerman, Dirk; Bourne, Tom

VERSION 1 - REVIEW

REVIEWER	Gökhan Açmaz Kayseri Education and Training Hospital of Medicine
REVIEW RETURNED	29-Mar-2016

GENERAL COMMENTS	This paper can be accepted and published in your journal.

REVIEWER	Charleen S Y Cheung Department of Obstetrics and Gynaecology The University of Hong Kong / Queen Mary Hospital Hong Kong SAR
REVIEW RETURNED	04-Apr-2016

GENERAL COMMENTS	Important topic that worths more exploration. 1. Methods / Design / first paragraph - would appreciate if authors could elaborate on the pilot they were referring to, especially on the implication on sample size calculation. 2. The controls are supposed to show the baseline stress/anxiety/depression levels. Have the authors considered to include 3 months / 9 months data for the control group? any change would eliminate the scores from acute effect from early pregnancy complication. 3. The group with viable pregnancy has lower percentage of existing children and higher percentage of previous miscarriage. How would the authors interpret this? 4. There seems a high proportion of participants with past psychiatric diagnosis in this study. In a study evaluating PTSD / anxiety and depression symptoms, would authors consider putting past / present psychiatric diagnosis as one of the exclusion criteria? 5. Any idea whether those with viable pregnancies had re-attendance to EPAU? Ongoing miscarriage symptoms (even for threatened miscarriage) may pose increase in anxiety scores.

	6. For those who score to have moderate/severe depressive symptoms, had they been referred for psychological or psychiatric assessment? Any of them being diagnosed formally diagnosed to have psychiatric disorder? 7. Though beyond the scope of this study, authors can consider looking into the difference in depression, stress or anxiety levels between women put on expectant / medical / surgical management options in a larger sample. Thank you.

REVIEWER	Martin Cernvall Uppsala University, Uppsala, Sweden
REVIEW RETURNED	22-Apr-2016

GENERAL COMMENTS	Thank you for the opportunity to review the manuscript entitled Post-traumatic stress disorder, anxiety and depression following misscarriage or ectopic pregnancy: a prospective cohort study (BMJOPEN-2016-011864). The purpose of this paper was to investigate the levels of PTSD, anxiety and depression in women following miscarriage or ectopic pregnancy compared to a control group, and to investigate whether levels were different between those with miscarriage and those with ectopic pregnancy. Major points Overall this is an important study and the overall aim is clearly described and the methods chosen have the potential to provide data for the aims. However, the conclusions that can be drawn from the study are severely hampered by the limitations of the study such as the high drop-out rate, in particularly in the control group. Although these limitations are addressed and discussed I am hesitant towards recommending these results to be published. Maybe one possibility would be to omit the first aim, the comparison with the control group, and to focus a paper only on the second aim, the comparison between those with miscarriage and those with ectopic pregnancy? Also, the drop-out rate up to three months is also substantial (more than 50% if you compare to the number of participants included in the study) so I would suggest the authors to seriously consider dropping this assessment-point as well. Since the investigators have used self-report questionnaires when assessing symptoms of PTSD I suggest that they are very careful not to phrase themselves in ways suggesting an actual diagnosis of PTSD, which would require an actual clinical assessment. On some place the authors are sensitive to this, and also acknowledge this issue in the discussion, but in other places they are not, e.g., in the title and in the abstract. I would suggest that the authors perhaps include a word such as “probable” when referring to a diagnosis of PTSD. In the Methods-section there is no information on approval from an appropriate ethics committee. I also have some minor points that perhaps can of value for the authors going forward.

	Introduction It would be nice if ectopic pregnancy could be briefly explained in a sentence. Methods In terms of the statistical techniques used I can recommend the authors to consider using generalized estimating equations to study change over time with a binary variable. This approach would allow to take into account the dependency across observations when using repeated measurements. Results The Results-section could be structured for better readability. Ideally, the two paragraphs “Levels of Post-traumatic stress” and “Levels of anxiety and depression” could ideally be structured the same way. On page 12 the response rates at one and three months are described. I would argue that it would be more correct to base the denominator of the response rate on what the authors have labeled as their “study population”, that is 186. Furthermore, the repsonse rate at three months is described as 44/68 (65%). However, would it not be more accurate to use the initial number of participants as the denominator? In figure 1 the group of participants are referred to as the “study population” and I suggest that they rephrase this to “study sample” since this is far from a population-based study. In the results section and elsewhere the authors use the word “incidence” and I would suggest that they instead use the word “prevalence”. In this study the authors report on prevalences of different types of distress with data collected from a sample of women. I assume that the authors are interested in statistical inference, that is the true prevalence in the population, and I would therefore suggest that the authors calculate and add proper confidence intervals to the proportions presented in the results-section and tables. As with Table 3 it would be nice if Table 2 also included a column with the control-group. In table 4, the two EPL groups are compared in terms of the mean PDS score, would it not be nice if the same comparison was made between the EPL-group and the control group? Discussion I generally think that the Disucssion is balanced and that the authors address the important limitations of the study, however the high drop-out rate might be a bit too high and can result in biased estimates which warrants extreme caution when drawing conclusions. Furthermore, the control group is much smaller than the exposed group, and the implications for this are not adressed. On page 16 the authors suggest that the present results suggest

	that the study procedures are feasible and that they can be up-scaled to a larger study. They high drop-out rate would suggest that the procedure was not feasible and this is recognized by the authors who state that they will add two reminders to the procedure. A question arises: are the authors certain that two e-mail reminders will fix the problems with retention in a larger study?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Gökhan Açmaz

Institution and Country: Kayseri Education and Training Hospital of Medicine

Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below
This paper can be accepted and published in your journal.

Response: Many thanks for your positive review

Reviewer: 2

Reviewer Name Charleen S Y Cheung

Institution and Country: Department of Obstetrics and Gynaecology, The University of Hong Kong / Queen Mary Hospital, Hong Kong SAR

Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below
Important topic that worths more exploration.

1. Methods / Design / first paragraph - would appreciate if authors could elaborate on the pilot they were referring to, especially on the implication on sample size calculation.

Response: Thank you. We have adjusted the choice of wording on p7 to make this clearer: all data included represents the whole of the pilot study. We have discussed the hypothesis enabling the sample size calculation for the main larger study at the end of the paper.

2. The controls are supposed to show the baseline stress/anxiety/depression levels. Have the authors considered to include 3 months / 9 months data for the control group? any change would eliminate the scores from acute effect from early pregnancy complication.

Response: Thank you for this point. We have considered this. However, our concern was that the pregnant control group would be affected by physical and psychological factors relating to the ongoing pregnancy or birth of a child, such that they could not represent useful comparators in the longer term.

3. The group with viable pregnancy has lower percentage of existing children and higher percentage of previous miscarriage. How would the authors interpret this?

Response: This is likely the result of the process of recruitment, which took place in the early pregnancy unit for both the control group and the group with losses. Women tend to attend this unit either because they are experiencing symptoms (bleeding or pain), or because of previous history of miscarriage. Thus, those women with healthy pregnancies are more likely to have a history of miscarriage in order to be attending this unit.

An additional hypothesis would be that women with a history of miscarriage were more likely to be invested in the study, and thus more likely to respond, thus inflating the rates of previous miscarriage in the group who responded. We do not have data on past pregnancy outcome in non-respondents to assess for this. A study such as this is likely to have a responder bias, as we have mentioned in the discussion. In this case, we feel the bias is likely to reduce rather than exaggerate the effect size.

4. There seems a high proportion of participants with past psychiatric diagnosis in this study. In a study evaluating PTSD / anxiety and depression symptoms, would authors consider putting past / present psychiatric diagnosis as one of the exclusion criteria?

Response: Overall, 28.1% of respondents reported a past psychiatric diagnosis, and 2.2% a current diagnosis. Whilst this may seem high, mental health difficulties are commonplace and it has been estimated that as many as 25% of people in the UK will experience some form of mental health problems each year (1). We felt it was important to reflect this large patient group in our conclusions. We also felt that such an exclusion would be difficult to standardize and accurately enforce, due to variations in the diagnosis rather than incidence of mental health problems.

Moreover, having a previous history of mental health problems may make individuals more vulnerable to relapses when faced with stressful life events such as EPLs: this is a hypothesis we wish to test with larger numbers.

5. Any idea whether those with viable pregnancies had re-attendance to EPAU? Ongoing miscarriage symptoms (even for threatened miscarriage) may pose increase in anxiety scores.

Response: We do have this data: of those who were ultimately diagnosed with a viable pregnancy, 28% required more than one scan for diagnosis. 74% were discharged on the day of diagnosis, and not seen again in the early pregnancy unit.

In view of the limited size of the control group, we have not used this for subanalysis at the moment, but we thank the reviewer for this interesting point, and would plan to do so in the future with larger numbers.

6. For those who score to have moderate/severe depressive symptoms, had they been referred for psychological or psychiatric assessment? Any of them being diagnosed formally diagnosed to have psychiatric disorder?

Response: Women have all received treatment as usual, which includes being signposted to their GPs or patient support groups during their clinical consultations, and again as part of the recruitment to this study. In line with our ethics approval, only if a patient's free-text response led to a potential concern about a risk to themselves was the patient formally contacted, along with their GPs, to recommend a formal assessment.

While other women may have later been assessed and referred by other organisations, we were not

able to ascertain this information, in accordance with our study protocol.

In the future study, we plan to correlate study responses with a formal assessment for a randomly selected sample of women.

7. Though beyond the scope of this study, authors can consider looking into the difference in depression, stress or anxiety levels between women put on expectant / medical / surgical management options in a larger sample.

Response: The authors thank the reviewer for this helpful comment. We are prospectively collecting the data on management approach (including failure of first line management) and plan to look at this as part of the larger study.

In order to assess causality, this would need to be done as a randomized controlled study. Trials such as MIST show us that randomizing miscarriage management is severely hampered by patient preference, so we would need to carefully assess the feasibility of this before embarking(2).

Reviewer: 3

Reviewer Name: Martin Cernvall

Institution and Country: Uppsala University, Uppsala, Sweden

Please state any competing interests or state 'None declared':
None declared.

Please leave your comments for the authors below
Thank you for the opportunity to review the manuscript entitled Post-traumatic stress disorder, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study (BMJOPEN-2016-011864). The purpose of this paper was to investigate the levels of PTSD, anxiety and depression in women following miscarriage or ectopic pregnancy compared to a control group, and to investigate whether levels were different between those with miscarriage and those with ectopic pregnancy.

Major points

1. Overall this is an important study and the overall aim is clearly described and the methods chosen have the potential to provide data for the aims. However, the conclusions that can be drawn from the study are severely hampered by the limitations of the study such as the high drop-out rate, in particularly in the control group. Although these limitations are addressed and discussed I am hesitant towards recommending these results to be published. Maybe one possibility would be to omit the first aim, the comparison with the control group, and to focus a paper only on the second aim, the comparison between those with miscarriage and those with ectopic pregnancy? Also, the drop-out rate up to three months is also substantial (more than 50% if you compare to the number of participants included in the study) so I would suggest the authors to seriously consider dropping this assessment-point as well.

Response: Thank you for this point, which we have carefully considered. The drop out rate (39.5% to the first questionnaire) is considerable, as we have explored in our discussion.

However, in comparison to similar studies, we have been able to see clear reasons why our response rate is lower. For example, Engelhard's study relied on advertisements placed in magazines, which will inevitably select a motivated group likely to be associated with a higher response rate(3). In Cumming's study, only 40.3% of those approached for the study returned their consent form, compared to 94.0% in our own(4). This reflects the fact that Cumming required women to sign and return a consent form by post after the initial approach, where as we allowed women to consent on the day of approach (and confirmed later by email – which required response to be removed). The default position of those disinterested or not wishing to be involved was thus to ignore the emails – both confirming their involvement, and then later containing the link to the questionnaire. The authors feel that one of the strengths of the study is the consecutive recruitment of women from the early pregnancy unit, and the high rate of consent to participate, but this is inevitably reflected in a higher apparent drop-out.

We have also searched for comparison elsewhere in the literature. Although we were unable to find anything specifically related to medical journals, a 2008 behavioural sciences paper calculated a mean response rate of 52.7% (SD 21.2) over a large sample of survey studies(5).

As a result of this pilot study, we have changed the methodology to allow reminder emails. Thus far, the response rate has improved slightly to 67% at one month for those with losses. In the larger study, we will look at whether the non-respondents have different baseline characteristics from those who respond e.g. in terms of parity.

With respect to the three-month time point, given that only those participants who had filled in the first questionnaire received this second questionnaire, we do feel that this is a better denominator (rather than the overall number of women with losses). We discuss this further in response to another of your comments later.

Overall, while substantial, we feel that the drop-out rates at both time points are a reasonable and worthwhile reflection of our methodology. We do not feel it detracts from the importance of the pilot study in recognizing that psychological morbidity exists, and the need for a larger study, the determined sample size of which accounts for the response rate.

2. Since the investigators have used self-report questionnaires when assessing symptoms of PTSD I suggest that they are very careful not to phrase themselves in ways suggesting an actual diagnosis of PTSD, which would require an actual clinical assessment. On some place the authors are sensitive to this, and also acknowledge this issue in the discussion, but in other places they are not, e.g., in the title and in the abstract. I would suggest that the authors perhaps include a word such as "probable" when referring to a diagnosis of PTSD.

Response: Many thanks for this comment. We have now amended the text, including the title, to be more consistent in our acknowledgement of this limitation.

3. In the Methods-section there is no information on approval from an appropriate ethics committee.

Response: Many thanks; we have now added this to the text.

4. I also have some minor points that perhaps can of value for the authors going forward.

Introduction
It would be nice if ectopic pregnancy could be briefly explained in a sentence.

Response: Many thanks - this has been done.

5. Methods

In terms of the statistical techniques used I can recommend the authors to consider using generalized estimating equations to study change over time with a binary variable. This approach would allow to take into account the dependency across observations when using repeated measurements.

Response: In order to correct for the baseline characteristics when assessing evolution over time, we are planning to use GEE modeling, as suggested, in the main study. For this pilot study, as the statistical power is low, we did not perform modeling.

6. Results

The Results-section could be structured for better readability. Ideally, the two paragraphs “Levels of Post-traumatic stress” and “Levels of anxiety and depression” could ideally be structured the same way.

Response: Many thanks - this has been changed accordingly.

7. On page 12 the response rates at one and three months are described. I would argue that it would be more correct to base the denominator of the response rate on what the authors have labeled as their “study population”, that is 186. Furthermore, the response rate at three months is described as 44/68 (65%). However, would it not be more accurate to use the initial number of participants as the denominator?

Response: We have consistently used the number of women actually invited to participate in each questionnaire as the denominator – and thus removed those who withdrew participation prior to receiving the email, as well as those who did not supply a valid email address.

As we have discussed above, in view of the fact that non-respondents to part 1 were not invited to participate in part 2, we do not feel such a denominator would be reflective. This methodology has been amended going forward: in the main study currently in progress, all women with consent and a valid email address are invited to take part in part 2. Thus far, 11% of those who did not complete part 1, have completed part 2. This supports our rationale for using only those who are invited to participate as the denominator, as it shows we could expect a significantly higher numerator if the whole study population had been targeted.

8. In figure 1 the group of participants are referred to as the “study population” and I suggest that they rephrase this to “study sample” since this is far from a population-based study.

Response: Many thanks for pointing this out: this has been changed.

9. In the results section and elsewhere the authors use the word “incidence” and I would suggest that they instead use the word “prevalence”.

Response: Thank you, this has been changed.

10. In this study the authors report on prevalences of different types of distress with data collected from a sample of women. I assume that the authors are interested in statistical inference, that is the true prevalence in the population, and I would therefore suggest that the authors calculate and add

proper confidence intervals to the proportions presented in the results-section and tables.

Response: The 95% confidence intervals have been added to tables 1, 2 and 3. They have also been added to the text of the results section, though the authors wonder if this adversely affects the readability, and would be happy to remove them from this section if the reviewer or editor sees fit.

Please note that in this pilot study the statistical power for statistical inference is clearly quite low.

11. As with Table 3 it would be nice if Table 2 also included a column with the control-group.

In table 4, the two EPL groups are compared in terms of the mean PDS score, would it not be nice if the same comparison was made between the EPL-group and the control group?

Response: (to both the above comments) Many thanks. There are inherent difficulties in recruiting a control group for a diagnosis that relies on a trauma exposure. As would be expected, only a minority of our control group identified a potential trauma: five reported a bereavement, three relationship problems, and one both. In only five cases did they confirm that they had felt helpless or terrified, and in only four was any impairment identified. None of these four cases met criteria in terms of severity score for moderate PTSD.

Overall, because of the heterogeneity of the 'trauma' exposure (with both identified sources of trauma subject to debate as to whether they would indeed classify as trauma by new criteria(6)), and the low incidence of trauma exposure in the group as a whole, with no cases suggestive of PTSD, we did not feel an overall severity score was a valid comparison. With a larger control group in our main study, we hope to be able make a comparison between EPL and other specified types of trauma exposure.

We have added a column to table 4, as you have suggested, to allow comparison with the control group and the subgroups of EPL. By doing this, we have been able to delete table 3 (and thus table 4 has become table 3!).

12. Discussion

I generally think that the Discussion is balanced and that the authors address the important limitations of the study, however the high drop-out rate might be a bit too high and can result in biased estimates which warrants extreme caution when drawing conclusions.

Furthermore, the control group is much smaller than the exposed group, and the implications for this are not addressed.

Response: Many thanks: we have now addressed this in the discussion. Although the control group was significantly smaller than the EPL group in this study, it was of a similar size to the ectopic pregnancy group, enabling a fair comparison between control and ectopic pregnancy patients. Clearly we will pay close attention to the recruitment of the control patients in the main study.

13. On page 16 the authors suggest that the present results suggest that the study procedures are feasible and that they can be up-scaled to a larger study. They high drop-out rate would suggest that the procedure was not feasible and this is recognized by the authors who state that they will add two reminders to the procedure. A question arises: are the authors certain that two e-mail reminders will fix the problems with retention in a larger study?

Response: As we have discussed above, this has thus far improved the response rate to 67% (compared to 61%) at the first questionnaire. As explored, in view of our recruitment method, we would not expect to increase this further.

References

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2. Trinder J, Brocklehurst P, Porter R, et al. Management of miscarriage: expectant, medical, or surgical? Results of randomised controlled trial (miscarriage treatment (MIST) trial). BMJ 2006;332(7552):1235-40.
3. Engelhard IM, van den Hout MA, Arntz A. Posttraumatic stress disorder after pregnancy loss. Gen Hosp Psychiatry 2001;23(2):62-6.
4. Cumming GP, Klein S, Bolsover D, et al. The emotional burden of miscarriage for women and their partners: trajectories of anxiety and depression over 13 months. BJOG 2007;114(9):1138-45.
5. Baruch Y HC. Survey response rate levels and trends in organizational research. Human Relations 2008;6(8):1139-60.
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VERSION 2 – REVIEW

REVIEWER	Martin Cernvall Uppsala University, Sweden
REVIEW RETURNED	07-Jul-2016

GENERAL COMMENTS	Thank you for the opportunity to review a revised version of this manuscript. The authors have adressed all of the points that I raised, and I think they argue well on points where they disagree with my suggestions. I find the revisions satisfactory. However, I am somewhat struggling with the fact that this is framed as a pilot-study but the authors make rather strong recomendations for how health care for these women can be improved based on their results.Perhaps the authors should be more cautions given that this is a pilot-study, and akcnowledge this clearly in their conclusions? I also have some minor suggestions: In the introduction the author´s are still discussing PTSD and I would suggetst that the rephrase themselves to "symptoms of PTSD" or symptoms of posttraumatic stress". Furhtermore, on page 5 it is stated that "...25% reported symptoms of PTSD" howevere it is unclear if this suggest clinical levels? Perhaps this could be clarified. Methods It would be nice if the authors reported the internal consistency (Cronbachs alpha) for their instruments with their samples. Results I suggest that the authors present their CIs in [brackets] instead for clarity (in text and tables)

VERSION 2 – AUTHOR RESPONSE

Reviewer name: Martin Cernvall

Institution and Country: Uppsala University, Sweden

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
Thank you for the opportunity to review a revised version of this manuscript. The authors have adressed all of the points that I raised, and I think they argue well on points where they disagree with my suggestions. I find the revisions satisfactory. However, I am somewhat struggling with the fact that this is framed as a pilot-study but the authors make rather strong recommendations for how health care for these women can be improved based on their results.Perhaps the authors should be more cautions given that this is a pilot-study, and akcnowledge this clearly in their conclusions?

Response: Thank you. We have now acknowledged again the fact that this is a pilot study in the final paragraph of the conclusion, and softened the recommendations as follows:
“Our findings are relevant to healthcare professionals who deal with early pregnancy loss. Exposure to EPL on a daily basis may lead clinicians to normalize the experience and overlook the possible profound psychological sequelae. The data presented is in the context of a pilot study, however if our findings are supported by further large prospective studies, we believe that consideration should be given to screening all women who have suffered an EPL for PTSD. There is also a need to assess how to predict those women who are most at risk of serious psychological morbidity, in order to better direct limited resources, and to facilitate early intervention and appropriate treatment.”

I also have some minor suggestions:
In the introduction the author´s are still discussing PTSD and I would suggest that the rephrase themselves to "symptoms of PTSD" or symptoms of posttraumatic stress". Furthermore, on page 5 it is stated that "...25% reported symptoms of PTSD" howevere it is unclear if this suggest clinical levels? Perhaps this could be clarified.

Response: This has been amended and clarified as suggested.

Methods
It would be nice if the authors reported the internal consistency (Cronbachs alpha) for their instruments with their samples.

Response: Thank you for this suggestion. This has now been included.

Results
I suggest that the authors present their CIs in [brackets] instead for clarity (in text and tables)

Response: Thank you. This has been amended.