PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Women's experiences in relation to stillbirth and risk factors for long-term post-traumatic stress symptoms: a retrospective study
AUTHORS	Gravensteen, Ida Kathrine; Helgadóttir, Linda; Jacobsen, Eva-Marie; Rådestad, Ingela; Sandset, Per Morten; Ekeberg, Oivind

VERSION 1 - REVIEW

REVIEWER	Susan Ayers Professor of Maternal and Child Health School of Health Sciences City University London UK
REVIEW RETURNED	27-Jun-2013

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript, which reports a survey of 101 women who had a stillbirth between 5 and 18 years prior to the survey. The authors have previously reported quality of life and depression in this sample, compared to a control sample, which found no differences in QoL or depression. The current paper reports additional data for the stillbirth women only. These are: information on women's experiences of stillbirth, their appraisals of care during stillbirth, and factors associated with post-traumatic stress symptoms (PTSS). Overall, the paper clearly addresses these aims and is well written. In my opinion the information on women's experiences of stillbirth and factors associated with PTSS is more informative than women's evaluations of care which is likely to have changed substantially over the last 18 years. The information on PTSS adds to the literature on whether spending time with the stillborn infant leads to positive or adverse effects. This is somewhat controversial with some studies finding adverse effects (e.g. Hughes et al., 2002; Turton et al., 2001; 2009) and others finding positive effects (e.g. Cacciatore et al., 2008; Rắdestad et al., 1996; Surkan et al., 2008). The results of this paper are consistent with the latter research suggesting time with the baby is associated with positive outcomes. I have a few comments and suggestions for the authors as follows: **Points that need addressing:** 1. The design of the study has a number of limitations which need to be clearly acknowledged and conclusions balanced accordingly. Limitations include the retrospective design and range of time since stillbirth (5 to 18 years) which may have resulted in poor recall. This is evident in Table 2 where up to 18% of women say they 'do not remember' some aspects of the birth. Time since birth is also one of the most consistent predictors of mental health following stillbirth so the relationship

	between time since birth and outcomes needs to be reported. Similarly, the effect of younger age on PTSD could be due to shorter time since stillbirth. Time since stillbirth should therefore be controlled for in all multivariate analyses. 2. The response rate was low at 31% and missing data mean the results are based on 57 to 101 women. The sample is therefore self-selected and unlikely to be representative. Women with PTSS symptoms of avoidance, for example, are less likely to take part in such research. In surveys of this type it is also very common to have a large proportion of white European women from high socioeconomic groups. One way to address this is to examine whether the women who took part differed significantly from women who did not respond. 3. In my view the part of the paper examining factors associated with PTSS is potentially the most interesting. However, it can be significantly strengthened in a number of ways. The measure used (IES) does not measure full diagnostic criteria or even all the symptoms of PTSD. It is therefore a measure of a traumatic stress response, but not of clinical disorder. This study cannot therefore establish prevalence or predictors of disorder. By artificially dichotomising the IES into symptoms greater or less than a score of 20 the authors implicitly use a model of ‘disorder’ and in doing so lose variance so statistical power is reduced. In my view, a better approach conceptually and statistically would be to use multiple regression on the continuous IES scores. 4. A related point is the measure of PTSS, which is critical and needs to be clarified. It is not clear whether the IES was completed about symptoms in relation to the stillbirth or any stressful/traumatic event. The time frame in which it was completed also isn’t specified – is it symptoms at the time of completion, or symptoms in the month after stillbirth? **Points to be considered:** 5. As a cross-sectional survey it is not possible to make causal inferences so the authors need to ensure they refer to ‘associations’ between factors, rather than using causal language such as ‘predict’. Similarly, it is probably best to avoid the term ‘prevalence’ (see point 3). 6. Were women included if they had multiple births during which one baby was stillborn and the other survived? It is possible that the impact on these women differs from those whose only baby died. 7. I am a bit confused by the fact that your previous report from this sample on QoL and depression includes a control group but this paper doesn’t. Is there any reason for that? A control group would make this a stronger design in terms of whether levels of PTSD symptoms are greater than those observed in a normal population. If you didn’t collect this information you could refer to mean IES scores in community samples to see if your sample score more highly than normal. 8. Page 7. On what basis were possible predictors selected? 9. Page 7. You state that variables were included in the multivariate model if they were associated with IES >20 with p <0.2 – I’m not sure why you chose this p-value when the convention is p<.05? 10. Page 10. You describe some qualitative comments that women made. How this information was gathered is not clear from the

	method section. 11. Table 2. Your n is very variable – why? I assume ‘narcosis’ should be ‘narcotics’ 12. Table 3. The number of women who did not wish to hold their baby is stated as 13 and 16 in the text and table respectively. 13. Table 5. Many of these variables are continuous (e.g. gestational age; time since birth) and have been artificially dichotomised. You lose statistical power by doing this and the cut-offs used are questionable in places – for example why would 10 years since stillbirth be the critical cut-off in terms of whether women have PTSS or not? 14. Page 20. Other papers have looked at multivariate predictors of PTSD following stillbirth e.g. Crawley, Lomax & Ayers (2013) **References** Cacciatore, J., Rådestad, I., & Fr_øen, J. F. (2008). Effect of contact with stillborn babies on maternal anxiety and depression. Birth: Issues in Perinatal Care, 35, 313–320. Crawley, R., Lomax, S., & Ayers, S. (2013). Recovering from stillbirth: the effects of making and sharing memories on maternal mental health. *Journal of Reproductive and Infant Psychology,* 31(2), 195-207. Hughes, P., Turton, P., Hopper, E., & Evans, C. D. H. (2002). Assessment of guidelines for good practice in psychosocial care of mothers after stillbirth: A cohort study. Lancet, 360, 114–118. Rådestad, I., Steineck, G., Nordin, C., & Sjögren, B. (1996). Psychological complications after stillbirth – Influence of memories and immediate management: Population based study. British Medical Journal, 312, 1505–1508. Surkan, P. J., Rådestad, I., Cnattingius, S., Steineck, G., & Dickman, P. W. (2008). Events after stillbirth in relation to maternal depressive symptoms: A brief report. Birth: Issues in Perinatal Care, 35, 153–157. Turton, P., Evans, C., & Hughes, P. (2009). Long-term psychosocial sequelae of stillbirth: Phase II of a nested case-control cohort study. Archives of Women’s Mental Health, 12, 35–41. Turton, P., Hughes, P., Evans, C. D. H., & Fainman, D. (2001). Incidence, correlates and predictors of posttraumatic stress disorder in the pregnancy after stillbirth. British Journal of Psychiatry, 178, 556–560.

REVIEWER	Dr Elizabeth Ford Research Fellow in Primary Care Epidemiology Brighton and Sussex Medical School UK I declare I have no competing interests
REVIEW RETURNED	12-Jul-2013

THE STUDY	The general level of English is good but there are a few errors: intro p4 line 9 sequels should be sequelae methods p6 line 18 duplex - i don't understand why you don't just use "twin" results p10 line 44 change "meant" to "felt" table 3 p13 line 42 AND p14 line 12 change "allegations" to

	"statements" or "claims" Table 3 line 46 change "jaded" to "tired" or "exhausted", define narcosis, change "analgesics" to "pain relief" discussion p19 line 42 change "rather" to "reasonably" p20 line 35 change "as have been" to "to those" Additionally move all citations in brackets to before the comma or full stop as it seems strange to have them after (effectively in the next sentence).
GENERAL COMMENTS	Thank you for the opportunity to review your manuscript which was interesting and makes an important contribution to our understanding of mental health after stillbirth. I have a few suggested revisions in addition to the language points made above. 1) page 11 table 2 please define more clearly what is meant by analgesics (which particular ones) and narcosis. "Pain relief" may be a more accessible term. 2) p15 lines 6-11 confirm that these are current IES scores relating to current symptoms 3) I just wonder if you treated IES scores as a continuous variable you would have more power? Given that scores of 20 or above don't actually related to an established clinical diagnosis, I wondered if you got similar results looking at scores as a continuous outcome (possible with transformation due to skew). If results are similar then changing to this type of analysis is at the authors' discretion. Discussion. Could you speculate more on the association of PTSS with prior abortion? For example women who have had abortion for a prior fetal anomaly might be particularly vulnerable to a subsequent stillbirth. Limitations: page 20. This section is not adequate. You cannot assert (line 39) that "a higher response rate would presumably not have changed our main conclusions" - please discuss that the selection bias may result in an underestimation of symptoms as those most traumatised may choose not to take part. There is likely to be literature on this for general cases of PTSD which it would be good to reference. Similarly you cannot assert women have a good memory of events without reference to literature on this. Please expand this section acknowledging the weaknesses of the design (which are to be expected when researching this topic)

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Susan Ayers

Points that need addressing
1. The design of the study has a number of limitations which need to be clearly acknowledged and conclusions balanced accordingly. Limitations include the retrospective design and range of time since stillbirth (5 to 18 years) which may have resulted in poor recall. This is evident in Table 2 where up to 18% of women say they ‘do not remember’ some aspects of the birth. Time since birth is also one of the most consistent predictors of mental health following stillbirth so the relationship between time since birth and outcomes needs to be reported. Similarly, the effect of younger age on PTSD could be due to shorter time since stillbirth. Time since stillbirth should therefore be controlled for in all multivariate analyses.

Reply: We agree that the retrospective design and long follow up time poses significant limitations. It is correct that for some of the descriptive variables the women report that they “do not remember”, however the numbers are not as high as 18% as some categories were joined together in the tables. We have tried to highlight this more clearly by separating the ”do not remember” and ”not sure”

categories from other categories in Table 2.
In our revision we have expanded the limitations section and made some changes to the conclusions according to the reviewer's suggestion (page 21-23).
The relationship between PTSS and time since stillbirth has been reported in the bivariate analyses and found not to be significant (p= >0.2) whether it is dichotomized at median or used as a continuous variable (table 5). This is the reason why we did not include this variable in the final model according to our statistical procedure plan (page 8). When including time since stillbirth in the final model the variable is not significant (p=0.149), whereas young age remains highly significant (p=0.001). We have added these results on page 20-21.

2. The response rate was low at 31% and missing data mean the results are based on 57 to 101 women. The sample is therefore self-selected and unlikely to be representative. Women with PTSS symptoms of avoidance, for example, are less likely to take part in such research. In surveys of this type it is also very common to have a large proportion of white European women from high socioeconomic groups. One way to address this is to examine whether the women who took part differed significantly from women who did not respond.

Reply: We agree that the low response rate is a critical limitation. The reason why the number differs from 57 to 101 is because some questions are only relevant for subgroups of women. For instance the women were instructed to answer questions about holding the baby if they had already answered yes to having held it. Yet, there are some variables with missing values and we have tried to highlight this in the tables in the revised manuscript.
As written in the original manuscript (page 7, 9, 21), we have aimed to limit the risk of selection bias by performing analyses on available clinical and socio-demographic variables for responders and non-responders and this resulted in no significant differences.
We have revised the limitations section according to the reviewer's suggestion (page 21).

3. In my view the part of the paper examining factors associated with PTSS is potentially the most interesting. However, it can be significantly strengthened in a number of ways. The measure used (IES) does not measure full diagnostic criteria or even all the symptoms of PTSD. It is therefore a measure of a traumatic stress response, but not of clinical disorder. This study cannot therefore establish prevalence or predictors of disorder. By artificially dichotomising the IES into symptoms greater or less than a score of 20 the authors implicitly use a model of 'disorder' and in doing so lose variance so statistical power is reduced. In my view, a better approach conceptually and statistically would be to use multiple regression on the continuous IES scores.

Reply: As cited in our original manuscript we have multiple references on using IES as a dichotomised variable with a cut-off of 20 (page 7). Previous studies from our hospital and one of the present authors (ØE) have used the IES dichotomised at a score of 20 (1-2). In those studies, as in the present, we have also used linear regression analyses, and the results were not significantly different (see comment point 3 to reviewer Elizabeth Ford). As the distribution of IES is skewed, it would be necessary to log transform the distribution to use linear regression and this would in our view make the interpretation more complex. We have discussed this point with our statistical advisor professor L Sandvik, who is one of the co-authors of the two papers referred to. We are aware that the IES cannot be used to diagnose PTSD as we have pointed out in the discussion (page 20). The same holds for scales that measure hyperarousal in addition to intrusion and avoidance, e.g. the IES-R. The IES and IES-R, however, correlate highly, and high scores on both scales indicate a level of symptoms that may indicate PTSD or a clinical case level (optimal sensitivity and specificity), even though not being a diagnostic tool. Accordingly, we prefer to use the logistic regression analyses as in the original manuscript unless the editor insists otherwise.

References:
1. Tøien K, Myhren H, Bredal IS, Skogstad L, Sandvik L, Ekeberg O. Psychological distress after severe trauma: a prospective 1-year follow-up study of a trauma intensive care unit population. J Trauma 2010; 69: 1552-9
2. Skogstad L, Tøien K, Hem E, Ranhoff AH, Sandvik L, Ekeberg O. Psychological distress after physical injury: A one-year follow-up study of conscious hospitalised patients. Injury 2012 Oct 23. doi:pii: S0020-1383(12)00451-2. 10.1016/j.injury.2012.10.001. [Epub ahead of print]

4. A related point is the measure of PTSS, which is critical and needs to be clarified. It is not clear whether the IES was completed about symptoms in relation to the stillbirth or any stressful/traumatic event. The time frame in which it was completed also isn't specified – is it symptoms at the time of completion, or symptoms in the month after stillbirth?

Reply: PTSS is measured at follow up, accordingly 5-18 years after stillbirth and the participants were instructed to answer the IES questions using their prior stillbirth as the reference traumatic event. We have tried to clarify this in the revised manuscript according to the reviewer's suggestion (page 6).

Points to be considered:
5. As a cross-sectional survey it is not possible to make causal inferences so the authors need to ensure they refer to 'associations' between factors, rather than using causal language such as 'predict'. Similarly, it is probably best to avoid the term 'prevalence' (see point 3).

Reply: We are aware that we have to be careful to use the term "predictors" in a cross-sectional or retrospective study. Thank you for addressing this. According to our statistical advisor professor Sandvik this is a retrospective cohort study, and we do think it is suitable to use the term "risk factors" as most of the independent variables refer to facts that were present before the measure of the dependent variable, although measured in retrospect. Accordingly, we have changed the term "predictors" to "risk factors" and "associations". We have removed the term "prevalence" from the revised manuscript.

6. Were women included if they had multiple births during which one baby was stillborn and the other survived? It is possible that the impact on these women differs from those whose only baby died.

Reply: Women with singleton or twin pregnancies were included in the study as described in the methods section (page 6). Only four women had a twin birth at the time of stillbirth and in three of those cases one twin survived. We would argue that this number is so small that excluding these three women would not change our conclusions. We have examined the three women where only one baby died and found that their mean and median score on PTSS symptoms was actually slightly, but not significantly higher than for the rest of the population. We suggest not to include this in the manuscript as the numbers are too few to make any conclusions about this.

7. I am a bit confused by the fact that your previous report from this sample on QoL and depression includes a control group but this paper doesn't. Is there any reason for that? A control group would make this a stronger design in terms of whether levels of PTSD symptoms are greater than those observed in a normal population. If you didn't collect this information you could refer to mean IES scores in community samples to see if your sample score more highly than normal.

Reply: As the IES questions refer to emotions relating to a traumatic event the questions were not relevant to our control group. Our controls were selected based on having had a live born baby in the same time period as the cases and not by means of having experienced a comparable traumatic event. We agree that this is a challenge and we have discussed in the manuscript if the IES score may be somewhat overestimated as Qol, which is measured by a generic scale, does not differ

significantly between cases and controls (page 20).
To our knowledge there are no comparable IES data from the general population, as the questions in the scale are only relevant to those having experienced a traumatic event.
The mean IES score in our study was the same as in a sample of hospitalised trauma patients at one year follow-up (15.8, 95% CI 13.5-18.1) (Skogstad L, Tøien K, Hem E, Ranhoff AH, Sandvik L, Ekeberg O. Psychological distress after physical injury: A one-year follow-up study of conscious hospitalised patients. Injury 2012 Oct 23. doi:pii: S0020-1383(12)00451-2. 10.1016/j.injury.2012.10.001. [Epub ahead of print]). The present distribution was more skewed (median IES 10.0), but this reflects that there are some women who have considerable distress many years after the stillbirth. We think this information may require too much space to be added in the revised manuscript, but we leave it for the editor to decide.

8. Page 7. On what basis were possible predictors selected?

Reply: The majority of the predictors were selected in part based on what has been found by previous studies on stillbirth and mental health, many of which are cited in the introduction, as well as some studies on post traumatic stress. In addition we have added some plausible predictors and possible confounders based on clinical experience. We specify in the discussion section that some of our significant findings in the final regression model should be interpreted with caution they are not yet confirmed by other studies (page 21).
Established predictors/confounders: Age at index, civil status, country of birth, occupational status, income, education, parity at index, gestational age at index, time since the stillbirth, live birth after stillbirth, having held the baby, the amount of time spent with the baby, follow-up interventions
Plausible predictors/confounders: subsequent partnership break-up, spontaneous abortion, induced abortion prior to stillbirth, awareness of the baby's death before the birth, autopsy, arranged memorial.

9. Page 7. You state that variables were included in the multivariate model if they were associated with IES >20 with p <0.2 – I'm not sure why you chose this p-value when the convention is p<.05?

Reply: According to our statistical advisor professor Sandvik, there are different traditions when including independent variables from bivariate analyses into a multivariable model. Using p<0.2 as cut-off is not uncommon. In the multivariable model we included variables that were bivariately associated with IES with a p-value < .20 to be sure not to miss significant variables due to statistical suppression.

10. Page 10. You describe some qualitative comments that women made. How this information was gathered is not clear from the method section.

Reply: We have described this more clearly in the revised manuscript (page 6)

11. Table 2. Your n is very variable – why? I assume 'narcosis' should be 'narcotics'

Reply: See comment to point 2. This is for the most part because some questions are only relevant for subgroups of women, e.g. those who have seen/held their baby or those who suspected that something was wrong with the baby before death in utero was diagnosed. In addition, there are some missing data that we have tried to highlight more clearly in the revised tables. The term "narcosis" has been changed to "general anaesthesia" in the revised manuscript.

12. Table 3. The number of women who did not wish to hold their baby is stated as 13 and 16 in the text and table respectively.

Reply: Thank you. The number 13 has been corrected to 16 in the revised version. Sorry for the misprint.

13. Table 5. Many of these variables are continuous (e.g. gestational age; time since birth) and have been artificially dichotomised. You lose statistical power by doing this and the cut-offs used are questionable in places – for example why would 10 years since stillbirth be the critical cut-off in terms of whether women have PTSS or not?

Reply: Some of the variables have been dichotomised because there was a noticeable cut-off when we plotted the variable against PTSS (eg: from age 27 the PTSS is dropping). The rest of the variables were dichotomised at median in collaboration with our statistical advisor, Professor Leiv Sandvik, to make all predictors dichotomous.
However, as we agree that this may be unnecessary we have changed gestational age and time since stillbirth into continuous variables in the revision (Table 5)

14. Page 20. Other papers have looked at multivariate predictors of PTSD following stillbirth e.g. Crawley, Lomax & Ayers (2013)

Reply: Thank you for informing us about this paper. As the study was published just two weeks before our submission and is not available through PubMed and Ovid we have unfortunately missed this publication. We have now referred to the study in the introduction (page 4) and discussion (page 21) in the revised manuscript.

Reviewer 2: Dr Elizabeth Ford

The general level of English is good but there are a few errors:
intro p4 line 9 sequels should be sequelae
methods p6 line 18 duplex - i don't understand why you don't just use "twin"
results p10 line 44 change "meant" to "felt"
table 3 p13 line 42 AND p14 line 12 change "allegations" to "statements" or "claims"
Table 3 line 46 change "jaded" to "tired" or "exhausted", define narcosis, change "analgesics" to "pain relief" discussion p19 line 42 change "rather" to "reasonably"
p20 line 35 change "as have been" to "to those". Additionally move all citations in brackets to before the comma or full stop as it seems strange to have them after (effectively in the next sentence).

Reply: Thank you for pointing out these errors. The term “jaded” has been changed to “sedated”, “narcosis” has been changed to “general anaesthesia”. The rest of the terms have been rewritten according to the reviewer’s suggestion. We agree with the reviewer that it is peculiar to cite references after comma or full stop, but this is according to the instructions to authors submitted on the BMJ webpage (http://group.bmj.com/products/journals/instructions-for-authors/formatting/): ”Reference numbers in the text must be inserted immediately after punctuation (with no word spacing)—for example,[6] not [6]. ”

1) page 11 table 2 please define more clearly what is meant by analgesics (which particular ones) and narcosis. "Pain relief" may be a more accessible term.

Reply: We have changed the term “analgesics” to “pain relief” and specified what is included by this term according to the reviewer’s suggestion (Table 2).

2) p15 lines 6-11 confirm that these are current IES scores relating to current symptoms

Reply: We have revised the text according to the reviewer’s suggestion (p 6).

3) I just wonder if you treated IES scores as a continuous variable you would have more power? Given that scores of 20 or above don't actually related to an established clinical diagnosis, I wondered if you got similar results looking at scores as a continuous outcome (possible with transformation due to skew). If results are similar then changing to this type of analysis is at the authors' discretion.

Reply: See comment, point 3 to reviewer Susan Ayers. The results are almost identical when log transforming IES and using it as a continuous variable. The only difference is that the age variable becomes just not significant (p=0.052). We would prefer to use the logistic regression method as in the original manuscript due to interpretational reasons.

Discussion. Could you speculate more on the association of PTSS with prior abortion? For example women who have had abortion for a prior fetal anomaly might be particularly vulnerable to a subsequent stillbirth.

Reply: We agree that this is an interesting finding and there could be multiple reasons for this association. One possible reason for the association could be that the mourning process after a loss of a wanted baby for some women may have induced feelings of guilt or regret over a previous decision to end a pregnancy. The majority of the women had an induced abortion in their first pregnancy and often at a young age, thus it is likely that social indication is the main cause for prior induced abortion. It would be interesting to explore, at a later time, if there is a difference in PTSS between women with different indications for an induced abortion. As the manuscript is already fairly extensive and we have no data to explain this finding we prefer not to use more space to speculate on this association unless the editor insists. We suggest that this should rather be a topic for future assessment.

Limitations: page 20. This section is not adequate. You cannot assert (line 39) that "a higher response rate would presumably not have changed our main conclusions" - please discuss that the selection bias may result in an underestimation of symptoms as those most traumatised may choose not to take part. There is likely to be literature on this for general cases of PTSD which it would be good to reference. Similarly you cannot assert women have a good memory of events without reference to literature on this. Please expand this section acknowledging the weaknesses of the design (which are to be expected when researching this topic)

Reply: We have revised the limitations section according to the reviewer's suggestion (page 21-22).

VERSION 2 – REVIEW

REVIEWER	Susana Ayers Professor of Maternal and Child Health Centre for Maternal and Child Health Research City University London London, UK
REVIEW RETURNED	19-Sep-2013

- The reviewer completed the checklist but made no further comments.

REVIEWER	Elizabeth Ford Research Fellow in Primary Care Epidemiology Brighton and Sussex Medical School UK I declare I have no competing interests
REVIEW RETURNED	21-Aug-2013

GENERAL COMMENTS	The manuscript seems acceptable for publication.