PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quantitative assessment of pregnancy outcome following recurrent miscarriage clinic care: a prospective cohort study
AUTHORS	Shields, Rebecca; Khan, Omar; Lim Choi Keung, Sarah; Hawkes, Amelia; Barry, Aisling; Devall, Adam; Quinn, Stephen; Keay, Stephen; Arvanitis, Professor Theodoros; Bick, Debra; Quenby, Siobhan

VERSION 1 – REVIEW

REVIEWER	Eisenberg, Michael Baylor College of Medicine
REVIEW RETURNED	14-Jun-2021

GENERAL COMMENTS	The authors have described an initial analysis and experience with the creation of a cohort of couples experiencing recurrent miscarriage. The authors report recruitment, retention and follow up of those couples. As the authors point out, there is a paucity of data on the subject. Collecting paternal data is also novel and important. Several specific points warrant mention. 1. The authors note many variables of data which have been collected but only discuss a few. The association of reproductive outcomes among these couples for other maternal variables would be important. 2. An analysis of paternal variables and the association with future pregnancy/live birth would be important. 3. Is there data on any longitudinal changes couples made when facing recurrent pregnancy loss such as smoking cessation or weight loss?

REVIEWER	Farren, Jessica Tommy's National Early Miscarriage Research Centre, Queen Charlotte's and Chelsea Hospital
REVIEW RETURNED	25-Jun-2021

GENERAL COMMENTS	Thank you for giving me the opportunity to review this paper The authors should be congratulated on a well written and interesting paper, as well as involvement in the development of a repository which will hopefully hold the key to changing miscarriage care in the future! Some small potential improvements:

	Page 2, line 23 – how many pts were approached/seen during this time Page 2, line 41-46 – The conculsions refer to results that are not in the results section (subfertility and repeated miscarriage). I also think the conclusion about BMI and smokingshould ideally be fitted in here. Also - conclusions refer to the study enabling clinics to compare 'management strategies' and yet there is no discussion of management strategies in the rest of the paper. Perhaps 'In future, the respository' in place of 'study findings' would make more sense? Page 3, line 33 – "Preconception care is inadequate": do we have evidence that better preconception care can modify risk factors? Otherwise may be better to say there may be an opportunity to modify risk factors with pre-conception care – or just leave out this sentence all together. Page 4, line 6 – would take out 'of' – '12 weeks gestation' Page 4, line 11 – "euploidic foetal" should read "euploid fetal" – I would suggest consistently spelling "fetal" in a paper for a British journal Page 4, line 16-23 – I'm not sure this paragraph adds anything to this paper: I think the point about standardised outcomes should be made, but the rest of the discussion about information giving/areas for improvement is not considered in the rest of the paper. It implies that the repository has feedback from patients – which it does not, I don't think? Page 4, line 50 – rather than 'this should' consider 'the objective/aim is' Page 5, line 28 – "Miscarriage care followed the ESHRE guildelines" – is this correct? Or was pre-existing miscarriage care unaltered by involvement? Imperial, for example, use the TEG. Page 5, line 37 – I wonder whether you can cover here what the eligibility criteria for referral are for GPs (perhaps in supplementary material somewhere) Page 7, line 8 –Much of this section on improving data collection I feel doesn't fit in methods and should be in the results/conclusion instead. For example, in the methods you could describe the sequential changes that were made to the text messages, and in the results how this changed participation, and in the conclusion the fact that you will continue to make amendments? Response rates should be in results I think. Page 7, line 37 – a flowchart would be really helpful here. There is no final number of participants that had completed 2 years follow-up. It would also be helpful to have a better sense of what the 'active cohort' is from this flowchart Page 8, Table 1 – I'm a little confused as to where those who have had healthy pregnancies and have completed the two year follow-up go? Are they included with the continuing cohort? Could you also give ranges for the ages?

	Page 8 – line 51 – where are the women who are currently 24-42 weeks pregnant included? Page 8, line 58 – reference figure 2 here Page 9, line 27 – smoking status – there is no table or graph displaying these results, and therefore no indication of the size of the difference between smokers and no-smokers. Add numbers or a figure here. Page 10, line 15 – are couples actively discouraged from conceiving until investigations are complete? Page 10, line 45 – I'm not sure I understand the rationale for assessing ovarian reserve in those who have a BMI over 30. The results indicate BMI affects time to viable pregnancy, not time to conception. This needs to be elucidated further. Page 10, infertility section – is it worth remarking on the fact that age doesn't impact fertility in this group, conflicting with other studies – and why this might be Figure 1 – would it be good to carry on the lines for viable pregnancy for a further 20 weeks after the line for conception finishes at 2 years? I just wonder if this might give a good sense of where the group is at after 2 years conceiving. Or write this in the text somewhere perhaps. Figure 2 – I wonder if it would be possible to put the actual % cumulative conception and viable pregnancy rate at the two-year point, or perhaps put dotted lines to the y axis to enable easier comparison of these 4 graphs. Same for remaining figures. Figure 4 – displays results from people with one previous miscarriage, in spite of eligibility being 2 or more. I imagine this must be people who had a miscarriage and an ectopic or stillbirth – but given the group is so small I think it warrants further elaboration somewhere

VERSION 1 – AUTHOR RESPONSE

Comments to the Author:
The authors have described an initial analysis and experience with the creation of a cohort of couples experiencing recurrent miscarriage. The authors report recruitment, retention and follow up of those couples. As the authors point out, there is a paucity of data on the subject. Collecting paternal data is also novel and important. Several specific points warrant mention.

1. The authors note many variables of data which have been collected but only discuss a few. The association of reproductive outcomes among these couples for other maternal variables would be important.
Following publication of the Lacent series, known significant variables were concentrated on in this initial analysis. Further analysis of variable such as past medical history, caffeine intake, protein supplements and mode of conception is ongoing.

2. An analysis of paternal variables and the association with future pregnancy/live birth would be important.
Paternal age, BMI, smoking status and alcohol intake have been analysed. There is no significant association between conception and viable pregnancy with any of these variable other than male age. This has been added into the results.

3. Is there data on any longitudinal changes couples made when facing recurrent pregnancy loss such as smoking cessation or weight loss?
Unfortunately this data is not currently available. The repository is being modified to allow collection of data including weight and smoking status at early pregnancy scans which can be compared to the status at initial consultation.

Reviewer: 2
Dr. Jessica Farren, Tommy's National Early Miscarriage Research Centre
Comments to the Author:
Thank you for giving me the opportunity to review this paper

The authors should be congratulated on a well written and interesting paper, as well as involvement in the development of a repository which will hopefully hold the key to changing miscarriage care in the future!

Some small potential improvements:

Page 2, line 23 – how many pts were approached/seen during this time
857, addressed on page 2 line 12.

Page 2, line 41-46 – The conclusions refer to results that are not in the results section (subfertility and repeated miscarriage). I also think the conclusion about BMI and smoking should ideally be fitted in here. Results for BMI and smoking status have been included under the 'participant' heading, however have been repeated within the results heading now for clarity as suggested.

Also - conclusions refer to the study enabling clinics to compare 'management strategies' and yet there is no discussion of management strategies in the rest of the paper. Perhaps 'In future, the respository' in place of 'study findings' would make more sense?
'Management strategies' removed and changed to 'clinic outcome' from page 2.

Page 3, line 33 – "Preconception care is inadequate": do we have evidence that better preconception care can modify risk factors? Otherwise may be better to say there may be an opportunity to modify risk factors with pre-conception care – or just leave out this sentence all together.
Thank you, this has been removed and addressed on page 11 under 'Health Education'

Page 4, line 6 – would take out 'of' – '12 weeks gestation' Corrected
Page 4, line 11 – "euploidic foetal" should read "euploid fetal" – I would suggest consistently spelling "fetal" in a paper for a British journal. Thank you, corrected.

Page 4, line 16-23 – I'm not sure this paragraph adds anything to this paper: I think the point about standardised outcomes should be made, but the rest of the discussion about information giving/areas for improvement is not considered in the rest of the paper. It implies that the repository has feedback from patients – which it does not, I don't think?
This paragraph outlines why development of the repository is important. Comparing standardised outcomes is addressed under the heading 'Outcomes' on page 4.

Unfortunately, patients are currently not able to directly entre their data into the e-repository, however PPI groups were consulted at all stages of development and maintenance. Through the evidence generated from the e-repository the clinic aims to feed this back to those that attend the unit with the aim of improving their outcome.

Page 4, line 50 – rather than 'this should' consider 'the objective/aim is'
Changed

Page 5, line 28 – "Miscarriage care followed the ESHRE guidelines" – is this correct? Or was pre-existing miscarriage care unaltered by involvement? Imperial, for example, use the TEG.
UHCW follows ESHRE guidance. Whilst Birmingham and Imperial are working towards using the e-repository to collect outcomes in the future, at the time of analysis no outcomes had been entered in to the e-repository. Standardising care across all units maybe something to address in the future.

Page 5, line 37 – I wonder whether you can cover here what the eligibility criteria for referral are for GPs (perhaps in supplementary material somewhere)
Added as suggested.

Page 7, line 8 –Much of this section on improving data collection I feel doesn't fit in methods and should be in the results/conclusion instead. For example, in the methods you could describe the sequential changes that were made to the text messages, and in the results how this changed participation, and in the conclusion the fact that you will continue to make amendments?
Response rates should be in results I think.
Thank you for your comments. At present the process of improving the quality of the data has been left in the methods section with the aim of taking the reader through the process we went through in order to improve the quality of the data prior to analysis.

Page 7, line 37 – a flowchart would be really helpful here. There is no final number of participants that had completed 2 years follow-up. It would also be helpful to have a better sense of what the 'active cohort' is from this flowchart
As this cohort looks at cumulative outcome a minority will have completed the 2 year follow up. 198 have been in the cohort for 2 years.
A flow chart has been developed as suggested.

Page 8, Table 1 – I'm a little confused as to where those who have had healthy pregnancies and have completed the two year follow-up go? Are they included with the continuing cohort?
Could you also give ranges for the ages? The heading have been changed to help clarify the table. Those not continuing in the cohort have been removed from the table to aid clarity.

Page 8 – line 51 – where are the women who are currently 24-42 weeks pregnant included?
They are included within the 'viable pregnancy group'

Page 8, line 58 – reference figure 2 here
Referenced

Page 9, line 27 – smoking status – there is no table or graph displaying these results, and therefore no indication of the size of the difference between smokers and no-smokers. Add numbers or a figure here. This is shown in figure 5 and has now been referenced. Thank you.

Page 10, line 15 – are couples actively discouraged from conceiving until investigations are complete?

No, this is why some couples will come to the clinic already pregnant. This has been clarified on page 10 'infertility' second paragraph.

Page 10, line 45 – I'm not sure I understand the rationale for assessing ovarian reserve in those who have a BMI over 30. The results indicate BMI affects time to viable pregnancy, not time to conception. This needs to be elucidated further.
This has been removed.

Page 10, infertility section – is it worth remarking on the fact that age doesn't impact fertility in this group, conflicting with other studies – and why this might be
Age does impact on time to conception and viable pregnancy, however it alone is not statistically different between the general cohort and those within it that did not conceive.

Figure 1 – would it be good to carry on the lines for viable pregnancy for a further 20 weeks after the line for conception finishes at 2 years? I just wonder if this might give a good sense of where the group is at after 2 years conceiving. Or write this in the text somewhere perhaps.
The lines plateau or become very 'steppy' as time goes on as there is inevitable less people within the cohort. We will continue to look at the cohort and this may improve with time.

Figure 2 – I wonder if it would be possible to put the actual % cumulative conception and viable pregnancy rate at the two-year point, or perhaps put dotted lines to the y axis to enable easier comparison of these 4 graphs. Same for remaining figures.
This has been changed as suggested.

Figure 4 – displays results from people with one previous miscarriage, in spite of eligibility being 2 or more. I imagine this must be people who had a miscarriage and an ectopic or stillbirth – but given the group is so small I think it warrants further elaboration somewhere.
This was included as an aid to reassure couples who have had 1 loss, if they conceive, they will have a baby – illustrated by the fact that conception and live birth lines meet.

VERSION 2 – REVIEW

REVIEWER	Eisenberg, Michael Baylor College of Medicine
REVIEW RETURNED	21-Sep-2021

GENERAL COMMENTS	The authors have suitably revised the manuscript.

REVIEWER	Farren, Jessica Tommy's National Early Miscarriage Research Centre, Queen Charlotte's and Chelsea Hospital
REVIEW RETURNED	14-Oct-2021

GENERAL COMMENTS	A few more very minor thoughts: - Consider making it clearer included participants are just from one unit - You seem to have lost the BMI/age/number of miscarriages legends from your figures

	- (Abstract)"Analysis identified a conception rate of over 80%, with 16.6% not conceiving at least 6 29 months after joining the cohort" - this feels like repetition from the first sentence: I think it might be better these statistics were in brackets after first reported- ie. 106 (16.6%)reported no pregnancy after six months -(Abstract) You have mentioned subfertility/repeated miscarriage in the conclusion but not in the results. Ideally find a way to quantify all these relationships in the results section of the abstract? -"Having strong links, or an integrated multi-disciplinary preconception service may allow a more cohesive approach to these couples and increase their chance of having a viable pregnancy" - I would clarify who the strong links should be with Points raised previously which need further clarification "Figure 4 – displays results from people with one previous miscarriage, in spite of eligibility being 2 or more. I imagine this must be people who had a miscarriage and an ectopic or stillbirth – but given the group is so small I think it warrants further elaboration somewhere. This was included as an aid to reassure couples who have had 1 loss, if they conceive, they will have a baby – illustrated by the fact that conception and live birth lines meet" I understand this is helpful - but I'm still confused where these results came from if not from your cohort?

VERSION 2 – AUTHOR RESPONSE

Thank you for the additional comments. The response to each individual point is detailed below.

1.Consider making it clearer included participants are just from one unit

Added addition line: ‘This paper summarises data collected only from couples attending UHCW recurrent miscarriage service.’ P5 lines 4+5.

P5 lines 19+20 changed to: ‘This cohort is from a specialist recurrent miscarriage clinic in a tertiary referral centre (UHCW) within the UK’

2.You seem to have lost the BMI/age/number of miscarriages legends from your figures

The legends are written below the graph images in text.

3.(Abstract)"Analysis identified a conception rate of over 80%, with 16.6% not conceiving at least 6 29 months after joining the cohort" - this feels like repetition from the first sentence: I think it might be better these statistics were in brackets after first reported- ie. 106 (16.6%) reported no pregnancy after six months

P2 starting line 25 has been changed to: ‘639 (82%) women were followed up. 404 (83.4%) reported conception and 106 (16.6%) reported no pregnancy, at least six months following registration. Of those that conceived, 72.8% (294/404) had a viable pregnancy. Maternal smoking and BMI over 30 were significantly higher in those who did not conceive (p=0.001)’

4.(Abstract) You have mentioned subfertility/repeated miscarriage in the conclusion but not in the results. Ideally find a way to quantify all these relationships in the results section of the abstract?

P10 lines 8-10 has been added to clarify your point: ‘It is often assumed that the reason couples do not have a baby after attendance at recurrent miscarriage services is because they have miscarried again. This however is only part of the picture.’

5."Having strong links, or an integrated multi-disciplinary preconception service may allow a more cohesive approach to these couples and increase their chance of having a viable pregnancy" - I would clarify who the strong links should be with

Thank you. The sentence has been changed to: ‘Having strong links, or an integrated multi-disciplinary preconception service including miscarriage and fertility specialists along with psychologist and counsellors may allow a more cohesive approach to these couples and increase their chance of having a viable pregnancy as well as providing continuity of medical and psychological care.’ (p10 from line 43)

6.Points raised previously which need further clarification

"Figure 4 – displays results from people with one previous miscarriage, in spite of eligibility being 2 or more. I imagine this must be people who had a miscarriage and an ectopic or stillbirth – but given the group is so small I think it warrants further elaboration somewhere.

This was included as an aid to reassure couples who have had 1 loss, if they conceive, they will have a baby – illustrated by the fact that conception and live birth lines meet"

I understand this is helpful - but I'm still confused where these results came from if not from your cohort? These results do come from the cohort, initially couples who had had one second trimester loss where also invited to join. This can be removed if preferred.