Author's response to reviews

Title: New insights into mechanisms behind miscarriage

Authors:

Elisabeth C Larsen (elisabeth.clare.larsen@regionh.dk)
Ole B Christiansen (ole.bjarne.christiansen@regionh.dk)
Astrid M Kolte (astrid.marie.kolte@regionh.dk)
Nick Macklon (n.s.macklon@southampton.ac.uk)

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Author's response to reviews: see over
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Regarding: 1613693543932612

New insights into mechanisms behind miscarriage

Dear Claire Barnard

Thank you very much for provisionally accepting our manuscript. We have addressed the comments and concerns raised by the reviewers, and revised the manuscript accordingly. All changes are highlighted in the revised manuscript. Below, please find a point-by-point outline as regards the comments.

On behalf of all the co-authors,

Yours sincerely

Nick Macklon
Professor of Obstetrics and Gynaecology. Academic Unit of Human Development and Health. University of Southampton.
Director, Complete Fertility Centre Southampton, Princess Anne Hospital. Cowford Road. Southampton SO16 5YA.
United Kingdom
Reviewer 1 - Answers to comments

1. In the current review regarding both sporadic and recurrent miscarriage we have described both known causes as well as discussing recently identified possible mechanisms. Within this scope, a comprehensive description of every putative cause is not possible, and we have therefore aimed to focus on those established causes on which a broad consensus exists, and which are likely to be of most interest to the readership of this journal. However, we agree that more attention to specific areas is merited, and we have now added a short section addressing uterine malformations and extended the section describing endocrine disturbances. In the Introduction we have stated that the review describes well-known mechanisms as well as novel information. (Please see Page 4 – Introduction)

2. We agree that the nomenclature used to describe pregnancy loss can be of limited clinical utility. We have pointed this out in the revised version of the paper and included the reference suggested (Obstet Gynecol 2011; 118: 1402-8). (Please see Page 4 – Introduction)

3. When we state that two-thirds of all conceptions are lost we include losses occurring in the 3rd and 4th week of gestation, i.e. the time leading up to an implantation. The section describing “Epidemiology” (section 2) has been rephrased and we have also reorganised Section 2 and 3 to give the reader a better understanding of the statistics referred to. In order to provide further clarification, we have added a summary figure (Please see Page 5 – Epidemiology of sporadic and recurrent miscarriage and Figure 1).

4. The reviewer is indeed correct in highlighting that the association between biochemical losses and aneuploidy is theoretical rather than proven and we have rephrased the relevant sentence accordingly (Please see Page 6 – Mechanisms and reasons for physiological early pregnancy loss)

5. We have described a study using murine models showing that antiphospholipid antibodies can be pathogenic. (Please see Page 8 – Immunological and immunogenetic causes)

6. We have added a short section describing that antiphospholipid antibodies may induce complement activation (Please see Page 9 – Immunological and immunogenetic causes).

7. In the immunotherapy section we have addressed the question as regards the immunosuppressive effects of low molecular weight heparin (Please see Page 10 Immunological and immunogenetic causes)

8. We have included uterine malformations (Please see Page 8) and extended the section describing endocrine disturbances (Please see Page 11 and 12)

9. We concur with the reviewers point and have now addressed the possible role of improving embryo selection by PGD in this context (See Page 14)

10. The section on gene polymorphisms has been enhanced as suggested (Please see Page 16 HCG-gene polymorphisms and epigenetic causes.)

11. We agree that an additional table and figure, along the lines suggested by the reviewer would enhance the paper. We have added a summary table, which gives an overview of miscarriage-associated factors and their possible causal role for miscarriage/recurrent miscarriage, possible treatments and proposals for future research, and a figure, which clarifies the discussion relating to the fate of human concepti.
Reviewer 3 – Answers to comments

We thank the reviewer for their constructive comments and have corrected the typing and spelling errors identified on page 5 and 6.