Reviewer's report

Title: New insights into mechanisms behind miscarriage

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Reviewer: Robert Silver

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This is a review article describing accepted and putative causes of recurrent pregnancy loss. The subject is of some interest to readers of the journal (as written it may be better suited for a specialty journal) and the information has some clinical utility. Questions and suggestions for improving this manuscript include:

1. The article tries to both review what is known about causes of recurrent and sporadic pregnancy loss and highlight novel information. The problem is that the review of what is known is uneven with detail given on some topics while other topics are excluded. The paper should either be limited to new information or should include a comprehensive review of what is known. (Compulsory revision)

2. Although generally accepted, the nomenclature used to describe pregnancy loss is not terribly clinically useful. It is worth pointing this out to the reader. An article in Obstetrics and Gynecology highlighted these issues and suggested alternative nomenclature (Obstet Gynecol 2011;118:1402-8). (Discretionary revision)

3. It is not clear that two-thirds of all conceptions are lost. This is generally accepted to be about 30%. A reference for this statement should be provided. (Compulsory revision).

4. How is it known that biochemical losses are due to aneuploidy? No one has ever been able to assess karyotype or perform examination of these losses. (Compulsory revision).

5. The authors state that antiphospholipid antibodies may be a marker for, rather than a cause of pregnancy loss. This is true. However, there are considerable data from murine models indicating that these antibodies can be pathogenic. (Discretionary revision)

6. Antiphospholipid syndrome is now thought to be as much if not more due to autoimmunity rather than thrombosis. There are abundant data regarding complement activation as a primary cause of pregnancy loss in these women. This section should be developed if the authors wish to maintain a comprehensive review. (Compulsory revision).

7. Heparin, low molecular weight heparin and aspirin all have immunosuppressive effects. Given the considerable data (both positive and negative) regarding their use, they deserve more discussion under the immunotherapy section of the paper. (Discretionary revision).
8. If the authors want to do a complete overview of the subject it is hard to leave out uterine malformations. Arguably, this is one of only three generally accepted causes of recurrent pregnancy loss. Similarly, if thyroid abnormalities are to be discussed it is hard to leave out diabetes, luteal phase defect and PCOS. Although none of these is clearly a cause of pregnancy loss (subclinical disease) they are about the same as thyroid abnormalities. Again, the paper should either be comprehensive or limited to novel things. Including some things but not others in an overview weakens the paper. (Compulsory revision).

9. Given the data presented regarding failure of embryo selection, the authors should speculate about the potential benefit of IVF in those cases. They do not have enough proof to recommend the practice but a discussion would be of interest. (Discretionary revision).

10. Enhancement of the section on gene polymorphisms would be of interest. It is likely that many cases of pregnancy loss are due to genetic abnormalities that are not diagnosed by traditional testing (e.g. karyotype). There are novel data regarding microarray. In addition, there are numerous candidate genes associated with a small increase in the risk of pregnancy loss. The RR of pregnancy loss attributed to most of these polymorphisms including the ones included in the paper is modest and not clinically useful, which should be highlighted. (Compulsory revision).

11. Additional tables / figures would enhance the paper. For example a table summarizing potential causes of pregnancy loss, appropriate work-up for pregnancy loss, potential treatments for pregnancy loss and important areas for further research would all be of interest and utility to the reader. (Compulsory revision).

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No competing interests.