Reviewer’s report

Title: UTERINE AND PLACENTAL BLOOD FLOW INDEXES AND ANTINUCLEAR AUTOANTIBODIES IN UNEXPLAINED RECURRENT PREGNANCY LOSS: SHOULD THEY BE INVESTIGATED IN PREGNANCY AS CORRELATED POTENTIAL FACTORS ? A RETROSPECTIVE STUDY

Version: 0 Date: 10 Sep 2019

Reviewer: Jean Christophe Gris

Reviewer's report:

This is a retrospective study which claimed aim is to analyse, in pregnant women, the impact of positive antinuclear auto-antibodies (ANA), but also of low-molecular weight heparin (LMWH) treatment, on various indices derived from ultrasonic explorations performed in order to evaluate the uterine and placental vascularisation. The clinical targeted population is composed of women with unexplained miscarriages, compared with women with at least 2 normal pregnancies at term, apparently matched on age and body mass index values. The underlying clinical question being on the association between ANA and abnormalities in placental perfusion which may favour miscarriages; also on any impact of LMWH treatment in that setting.

My main concerns are the following:

1- the number of women included in that study is very low. And ever more that low when considering the subgroups, categorised according to the presence/absence of positive ANA and the presence/absence of LMWH treatment during pregnancy. These subgroups being submitted to comparisons in order to clarify the purpose. It is impossible to hope for clear answers in such a situation, due to strongly limited statistical powers.

2- LMWH treatment was given to women in the first part of the study, then not given in the second and last part of the study, without any blind, randomised allocation. This introduces a strong bias in the results, nobody can be sure that treated and non-treated women are really similar.

3- Comparisons between groups are performed using parametric statistic tests. The recurrent miscarriage group contains, as a whole, 20 women, i.e. far from 30, and related subgroups between 10 and 16 women. It is thus strongly necessary to describe results using not mean and SD (!!!) values but median and range values, which will better match with the chosen representation of the data based on box and whiskers plots, and to perform comparisons using only non-parametric test, i.e. the Mann-Whitney test to compare 2 groups, and the Kruskall-Wallis test to compare more than 2 groups.

4- The way the data were analysed, mainly through multiple focused comparisons, is archaic and cannot allow convincing. The possible interaction between ANA status and LMWH status in each woman opens the door to generate significant confounding factors leading to false, artificial apparent
results. It cannot identify real risk factors of abnormal uterine/placenta vascularisation really independent from the other studied ones. A multivariate logistic regression analysis is needed: is positivity for ANA a real risk factor of an abnormal uterine/placenta vascularisation index independently from LMWH treatment, age, BMI,...?

5- The paper is very difficult to read due to the accumulation of abbreviations.

6- The authors should give the state of the art between the ultrasonic explorations they used and their derivated parameters they studied on the risk of miscarriage. They should also tell us if early, embryonic-type miscarriages, before 10 weeks, can be studied in the same way than fetel deaths, from the 10th week.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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