Reviewer's report

Title: Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial

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Reviewer: Johanna van der Bom

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Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial by Aawar et al.

The manuscript describes the protocol for a randomised controlled trial comparing the effect of fibrinogen concentrate versus placebo on number of allogenic blood products transfused after the study medication among women with low fibrinogen levels – assessed by Fibtem A5 < 16 mm which is about 3 g/l.

1. Will the study design adequately test the hypothesis?

The authors formulate the aim “The aim of the study is to investigate whether infusion of fibrinogen concentrate, based on the Fibtem A5 test, during a moderately severe PPH reduces the total number of allogenic blood products transfused after study medication until discharge compared to placebo”.

I could not find a clear hypothesis. From the text I deduced that the study will test the following hypothesis “the infusion of fibrinogen concentrate with a target Fibtem A5 level of at least 23 mm among women suffering ongoing PPH and a Fibtem A5 below 16 mm reduces the total number of allogenic blood products transfused after study medication until discharge compared to placebo.”

There are some limitations of the current design that will affect the findings and inferences. Most of these limitations are also recognised and discussed by the authors.

a) Blinding is only achieved until after the decision to give the first 4 units of FFP. The actual outcome will occur after this moment and this unblinding can/will lead to a different transfusion strategy for the two intervention arms. It is therefore no longer possible to infer that a possible observed difference between the intervention arms is purely the result of the intervention; it may also be the result of the clinician’s believe in an effect of the intervention. This may lead both to an over- and underestimation of the obtained estimate of effect.

b) A clinician can decide to access the results of the Fibtem and coagulation screen that is measured 15 min after randomisation even before the decision to give the first 4 FFP units. If this happens the investigators plan to exclude this woman from the primary efficacy analysis. This hampers exchangeability between intervention arms and interferes with the planned intention-to-treat analysis.

c) What do the investigators do to prevent allocation concealment? At the time of
randomisation the next consecutive study pack will be opened. Given the block size, is it possible to predict the next intervention?

d) Even if the hypothesis is adequately tested it is important to consider the following limitation of the current design. The ultimate aim of infusion of fibrinogen concentrate is of course the prevention of PPH related morbidity, such as mortality and hysterectomy. Yet, the endpoint of the study is total number of allogenic blood products. The assumption is that more allogenic blood products is related to higher morbidity. This assumption may not be met in the case of mortality or in the case of earlier hysterectomy. Thus, fewer allogenic blood products could be more severe than more allogenic blood product. Given the secondary endpoints the investigators will be able to examine the presence and eventual consequences of such survival bias.

e) With total number of allogenic blood products as primary endpoint, it is important to standardize the strategies to transfuse all allogenic blood products. In the manuscript I missed a standardized protocol for transfusion of allogenic blood products. Only in the discussion the investigators mention “the first 4 FFP units”. What are the triggers and prescribed doses of red blood cells, FFP, cryo and platelets? Are they similar in the participating clinics?

f) Is it true that according to the study protocol infusion of FFP will be postponed until after observing a Fibtem A5 under 16 mm? Does this mean that the investigators plan not to prevent, but instead to await coagulopathy. Given their experience I am convinced that they find Fibtem A5 an acceptable value for women with PPH. It would be worthwhile to discuss this in the discussion section.

2. Is the planned statistical analysis appropriate?
   Yes, the planned statistical analysis is appropriate.

   It would be interesting to find a list (and predefined categories) of baseline variables that are considered to be included in the model that adjusts for baseline imbalances.

   Are there any subgroup analyses planned?

3. Are sufficient details provided to allow replication of the work or comparison with related analyses; if not, what is missing?
   a) Standardisation of the triggers for RBC, FFP, cryo and platelet transfusion is missing.
   b) What is the definition of secondary postpartum haemorrhage?

4. Is the writing acceptable?
   Yes.