Reviewer's report

Title: Anti-fibrinolytic agents in bleeding during pregnancy, delivery and puerperium: A systematic review

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Reviewer: Lelia Duley

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Comments

1. Is the question posed by the authors well defined?

This review has too broad a scope, and would benefit from a more clearly defined question. The title and paper refer to treatment during ‘pregnancy, delivery and the puerperium’ and the text refers to ‘obstetric haemorrhage’. But the background and discussion cover only postpartum haemorrhage. There is no mention of antepartum haemorrhage, other than as a risk factor for postpartum haemorrhage, nor of intrapartum haemorrhage. Hence this review seems to be primarily about postpartum haemorrhage; which should be reflected in the title and text. This would also make clinical sense, as the strategies for treatment of antepartum and intrapartum haemorrhage are rather different to postpartum haemorrhage. Also, if administration before birth is included there needs to be discussion of the possible impact on the baby.

Some bleeding is normal during the birth, and it is not clear whether this review includes anti-fibrinolytic drugs for prevention and/or treatment of postpartum haemorrhage. In the background there should be discussion of prevention of postpartum haemorrhage, as well as treatment. There is clear evidence that prophylactic uterotonic drugs reduce the risk of postpartum haemorrhage by 50-60% (Cochrane review – Cotter 2001). Presumably the hypothesis of this review is that anti-fibrinolytic drugs be used in addition to prophylactic uterotonics, not as an alternative. But this should be clearly stated.

Page 4 para 3, there is no reference for the definitions listed. The definition of PPH is usually #500 ml, and cut offs are not usually based on mode of delivery - severe PPH is #1000 ml.

2. Are the methods appropriate and well described?

The reporting of methods and results should follow Quorom. The search strategy does not include any terms to identify participants – such as pregnancy, or postpartum. Methods state the main quality assessment was concealment of allocation. However, the criteria for excluding studies due to inadequate study design are not stated. In results, sequence generation is presented, but as this has not been covered in methods it is again unclear what the cut off for inclusion was. Gobel 2007 is quasi random with no concealment of allocation, hence there
is potential for bias.

Outcomes should include PPH and severe PPH, rather than ‘amount of blood loss’. If ‘amount’ means mean and SD this should be stated. The problem with using mean is that these data are inevitably skewed. The outcomes listed seem rather dominated by rare adverse events. It would also be useful to include measures such as need for other drug treatment, length of third stage, duration of stay in hospital, and side effects of treatment. Some indication of time frame would also be useful, for example for mortality and postpartum Hb. Other outcomes of interest to women include fatigue and breastfeeding.

In figure 1, the large SD for Gai 2004 and Yang 2001 suggest these data are skewed, and hence using a mean may not be meaningful.

3. Are the data sound?

Yes, but more detail about the interventions would be useful for clinical interpretation. For example, when was the treatment given. It is unclear whether the intervention was being given in these studies as prophylaxis of PPH, or treatment. Gai 2004 lists Apgar score and birthweight as outcomes, which implies the intervention was given before the birth. Rather than ‘no treatment’ a better term is ‘no tranexamic acid’.

The characteristics of the studies should be presented as one table, not as one table per study. This table should have each study as a row, making interpretation by readers easier.

PPH as a dichotomous outcome was reported in these trials, these data should be reported.

It seems surprising that in the 4000+ citations there were no potentially eligible excluded studies.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

Reporting should follow Quorom. I have not checked the full list, but the main omission is I think the lack of a flow chart indicating how the reviewers reduced 4242 records to 3 included studies.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

The discussion appropriately highlights the lack of data, and the problems such as poor study design and lack of follow up. However, I think that before concluding that further trials are needed there should be some discussion of whether a mean reduction of 92 ml could translate into a clinically worthwhile reduction in PPH. In view of the potential for bias, the skewed data, and the lack of data on more clinically substantive outcomes, a more cautious conclusion about further trials might be warranted. This topic merits further investigation, but I am not sure this would be sufficient support yet for a large RCT.
It would be useful to have a paragraph outlining the design of future RCTs – participants, interventions and outcomes (including duration of follow up). Is it a trial of prevention or treatment that is being suggested?

6. Are limitations of the work clearly stated?

Yes, but see above.

Also, the background highlights the importance of PPH in low and middle income countries. It would therefore seem appropriate to mention cost and availability of these drugs in low and middle income countries – and that cost effectiveness needs to be evaluated as well as effectiveness.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Yes.

8. Do the title and abstract accurately convey what has been found?

No, see above.

9. Is the writing acceptable?

Yes. Subheadings in the methods and results would be helpful.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests