**Moving beyond uterotonics for the treatment of postpartum haemorrhage: lessons from the WOMAN Study**

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In May this year, the long-awaited results of the WOMAN study into the benefits of tranexamic acid (TXA) for the treatment of postpartum haemorrhage (PPH) were published (WOMAN Study Collaborators 2017). The study is one of the largest ever randomised trials (RCTs) in maternal health, and certainly the biggest related to PPH care. Just over 20,000 women with PPH in 193 hospitals in 21 countries around the world were randomised to receive 1g of intravenous TXA or matching placebo. The primary outcome was death from PPH, and this was reduced from 1.9% to 1.5% in those who received the TXA – a risk reduction of 0.81 (95% confidence interval 0.65-1.00). The effect was more pronounced in those who received the drug within 3 hours of giving birth where there was a 31% reduction in death (from 1.7% to 1.2%). The risk of laparotomy for bleeding was reduced even further by nearly 40%. Importantly, TXA appeared to benefit those with both atonic and traumatic bleeds, and was unrelated to mode of birth. There were no significant differences in any other outcomes. This is not surprising, given that multiple therapies (including uterotonics, tamponade, manual removal of placenta, hysterectomy and blood transfusion) are often used concurrently at the time of a PPH, and would have been given before the TXA (or placebo) had a chance to work. These other therapies therefore, although classed as ‘outcome measures’, could just as well be seen to be ‘baseline data’ and are consequently evenly distributed between the study arms. The one exception is ‘laparotomy for bleeding’ where the procedure tends to be carried out later for ongoing trickling, and for this there was a clear benefit for TXA (unless its administration was delayed for >3 hours). This largely fits with TXA having an important (but not immediate) effect, largely on the ‘tricklers’ who continue to have ongoing blood loss for some hours after birth.

Even if this is true, it is surprising that there was no effect seen on transfusion. Although transfusions are often given acutely at the time of the bleed (where we would expect no effect) many also occur in the days following (where we might expect to see a TXA effect). It does appear that the TXA had no major effect on blood volume lost. So why did the women die? One explanation is that the deaths were largely as a result of the additional laparotomies for ongoing trickling – the potent mix of an already anaemic, shocked woman retuning to theatre a few hours after birth or CS proving too much for some overstretched health services. Further analyses are awaited.

Reassuringly, there were no differences between the groups in rates of complications including thromboembolism, although data on this was only formally collected up to the time of hospital discharge.

With such a huge database of women with PPH, there is much to unpick from these results and the authors are to be congratulated on their commitment to making the data freely available online for others to mine. We are therefore likely to see many secondary analyses of this data. Of particular interest would be setting-specific outcomes, especially related to thrombotic outcomes. In richer settings, sedentary lifestyles, obesity and age all increase the risk of thromboembolism whilst high quality health care reduces the risk of death from PPH. The risk-benefit balance therefore shifts, giving rise to more concerns about the use of pro-coagulants in postnatal women. Fortunately, however, these settings also have robust health care systems, which mean that the research team would be able to collect most cases of thromboembolism that occurred between hospital discharge and day 42. This contrasts with poorer settings where many women could have died postnatally from thromboembolism but not been reported to the research team as serious adverse events. It is encouraging that, in this double-blind study, there are no concerning signals of harm: if anything, the numbers of venous thromboembolic events were lower in those given TXA. However, further setting-specific analyses are awaited and will help to determine how best to use the treatment.

So, if we accept that TXA is beneficial, then to whom should we give it? Some might argue that giving it as prophylaxis will maximise the potential benefits, reducing mean postnatal blood loss and the need for iron therapy for many women. However, it would also expose a vast number of healthy women having normal, uncomplicated births to a drug that could still increase thromboembolism. In the WOMAN study, it was given to any women with blood loss over 500mls for vaginal births or 1000mls for CS. This puts it as one of the first-line PPH treatments, given to just 5% of the population shortly after the onset of heavy bleeding and it would seem appropriate to continue this plan. Clinicians should resist ‘mission creep’ and not be tempted to extend its indication into use for all caesareans or for prophylaxis, or to increase the dose to achieve a greater effect without further evidence of safety.

What more is there to be learnt from the published results? The collection of data from 20,000 women with PPH provides a fascinating insight into the population of women with PPH worldwide. The fact that uterine atony was the main cause in only 64% of cases reminds us that the commonly reported atony rate of 85% comes from data on vaginal births and is not reflective of all PPHs. Similarly, that 30% of recruits were from women who’d had a CS and the high frequency of placenta praevia / accreta as a cause (nearly 10%) reminds us of the increasing importance of PPH from surgical causes.

The study also tells us a lot about current practice for PPH treatment. Despite only 64% of women having atony as the main cause, and all having received oxytocin prophylaxis, 99% of women still received oxytocin as a treatment, 63% received misoprostol and 43% ergometrine. The use of repeated doses of uterotonic for these women, whilst widely practiced, is of dubious benefit. There is very little hard evidence in this area as recruitment and informed consent of women having a PPH is so difficult. And one of the very few robust studies comparing uterotonic treatments for PPH is widely ignored. Widmer et al conducted a double-blind randomised trial of misoprostol versus placebo in 1422 women receiving oxytocin treatment for atonic PPH (Widmer et al 2010). The primary outcome of additional blood loss of 500mls was seen in 14% of the misoprostol group and 14% of the control group. Side-effects however were much more common in the misoprostol group with 65% experiencing shivering and 43% with fever. The authors concluded that misoprostol should not be used (by whatever route) in addition to standard injectable uterotonics. And yet, despite this good quality evidence, its use has become widespread for PPH treatment even where oxytocin is widely available. Far from helping, it is only likely to give the woman uncomfortable side effects and delay the use of definitive treatment.

The WOMAN Trial sets new standards for PPH studies. The use of rapid intrapartum consent methods, the inclusion of all women with PPH (not just vaginal births) and the use of robust outcomes show how PPH research should be done. But it is also to be hoped that the WOMAN study represents the start of a new era of PPH treatment. It has been common to focus on the use of uterotonics for PPH treatment and exhaust their use before turning to physical or haematological interventions. This was based on the understanding that the vast majority of PPHs were atonic. But whilst this is true in the case of the uncomplicated vaginal births recruited to clinical trials, we now recognise that PPH is a far more complex disease than that. In a study of 181 women with massive PPH over a year in the UK (Green et al 2016), only 3% were uncomplicated vaginal births and, as expected, the majority of these 3% had atonic PPHs. However, 69% occurred following a CS, and 23% were due to placenta accreta or praevia: overall atony accounted for only 40% of cases. It is therefore misleading to believe that PPH is unpredictable and largely due to atony. We know who gets these really big bleeds – it is the big abruptions, the major placenta praevias, and the second stage emergency CSs. And the impact of uteronic therapy in these is minimal. To prevent and treat major haemorrhage is far more complicated – it takes surgical skill, well organised, responsive emergency care, blood products, and high quality clinical care with cardiovascular and haematological support. And the WOMAN study is part of that new focus. In richer settings, TXA can now take its place alongside other innovations like the bedside assessment of clotting with freeze-dried fibrinogen where needed and arterial embolization. As part of bleeding control the non-pneumatic anti-shock garment (NASG) can limit blood loss, buying time to organize the emergency response, and intrauterine tamponade can provide an immediate cessation of bleeding. In settings with far less money for health care, the focus must be on increasing the availability of blood, PPH first aid (using aortic and bimanual compression and the NASG) and improving the quality of emergency services, transfusion and clinical care. Tranexamic acid is cheap and easy to administer and should become part of every doctor’s and midwives’ emergency maternity kit. The next important question will be whether oral administration can be as effective, as this will be an important development to increase its reach into rural areas.

**References**

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