Tranexamic acid for postpartum haemorrhage: a major advance

See Articles page e222

The WOMAN trial was a massive, international, double-blind, placebo-controlled study of the effectiveness of tranexamic acid for the treatment of bleeding after childbirth. The clinical results have been eagerly anticipated and were published last year.[1] *The Lancet Global Health* has now published the results of a cost-effectiveness analysis of data from the WOMAN trial.[2] Together, these results show a clean sweep for tranexamic acid in the treatment of postpartum haemorrhage: not only does it reduce deaths from bleeding by 20% (1·9% with placebo *vs* 1·5% with tranexamic acid, risk ratio 0·81, 95% CI 0·65–1·00; p=0·045) but it is also cost-effective in countries with a high baseline risk of deaths from postpartum haemorrhage. As a consequence, WHO postpartum haemorrhage guidelines have already been updated to include tranexamic acid.[3]

However, there are some puzzling aspects to these results. First, how does an intervention reduce bleeding-related deaths and laparotomies but have no effect on any other blood-loss-related morbidity? If tranexamic acid reduced blood loss from postpartum haemorrhage in general, one would surely see an effect on the morbidity of all women in the study, not just those who had those two complications. It is true that tranexamic acid was given at the same time as many decisions were being made about their care. This approach meant that the outcomes observed were really baseline characteristics since they could not be affected by tranexamic acid. But other outcomes can only be collected at the end of the process (eg, time in hospital and quality of life at discharge), and there was no reduction in either of these. The only benefits of tranexamic acid are on death from bleeding and on laparotomy for bleeding, suggesting that there was no benefit of tranexamic acid for most women with postpartum haemorrhage.

A second question is why the maximum reduction in mortality was seen in women recruited 1–3 h after birth, even though most women were recruited in the first postnatal hour. And third, why was the number of brace sutures significantly greater in the tranexamic acid group than in the placebo group? Is this result simply a statistical blip—or could it be more?

The answer to all three questions might be found in the peculiarities of postpartum haemorrhage. There are multiple underlying causes of postpartum haemorrhage: atonic uterus is the most common cause, but retained placental tissue and genital tract trauma (either iatrogenic or caused by childbirth) are both also common. Treatments for postpartum haemorrhage generally address just one of these causes. Coagulopathy is also on the list of causes of postpartum haemorrhage, but is rarely the primary cause. This because the main mechanism for uterine haemostasis after childbirth is a uterine contraction compressing the uterine vessels rather than clotting. Thus, even in women with marked clotting disorders, 40–70% have completely normal postpartum blood loss.[4] Conversely, there is no evidence that women with a tendency for increased clotting through inherited thrombophilias are less likely than other women to have postpartum haemorrhage.[5] It would not be surprising therefore if tranexamic acid had no effect on normal postnatal blood loss. Nor would we expect the drug to have much effect on massive haemorrhage where large open vessels are pouring with blood. What we might expect to see, however, is an effect on blood loss in a subgroup of women who are bleeding vaginally or into the abdomen from smaller lacerations or trauma. In these women, the primary haemostatic mechanism is spontaneous clotting within the bleeding vessel.

The results from the WOMAN trial are entirely consistent with an effect on this subgroup of women who have postpartum haemorrhage with small but deadly spontaneous or iatrogenic lacerations to the genital tract. These lacerations tend to cause oozing and trickling, usually following caesarean section, with their clinical effects not being obvious until an hour or two after birth because of the slow rate of blood flow. The only treatment available is surgery (usually repeat laparotomy), a highly dangerous operation in already compromised women, especially in under-resourced settings with limited senior anaesthetic or surgical cover. In the WOMAN trial, most laparotomies for bleeding were done in women who had given birth by caesarean section, even though only a quarter of women

gave birth that way. The maximum effect was seen in women whose postpartum haemorrhage became evident 1–3 h after birth—the very time when oozing and trickling lacerations typically cause postpartum women to collapse on postnatal wards.

In the WOMAN trial, tranexamic acid appeared to reduce deaths irrespective of whether the cause of postpartum haemorrhage was believed to be atony or another reason. But in clinical practice, diagnosis of atony is highly subjective, especially at caesarean section or laparotomy. If there is bleeding, the surgeon will seek out the source of blood loss and treat it. If this is a generalised ooze, the surgeon will place additional sutures to that area and then close the abdomen. If there is no ooze, however, the surgeon will do one of the only other interventions possible before hysterectomy: a brace suture. Thus, a reduction in oozing results in an increase in use of brace sutures.

A final puzzle for some readers might be that, although tranexamic acid is stated to significantly reduce maternal death from bleeding, the 95% CIs include 1·00. By definition, this outcome indicates a possibility of no effect. Purists will state that the hypothesis that tranexamic acid reduces deaths from bleeding should have been rejected. There is, however, a move away from using the arbitrary cutoff of 95% for CIs, which dichotomises results into being significant or not significant. Led by the Cochrane Collaboration,[6] the aim is to look at the results of studies holistically, seeking to gain meaning from overall patterns and trends in the results rather than arbitrary cutoffs. The results of the WOMAN trial have therefore widely been accepted as showing a high probability of a clinically important reduction in death from bleeding, despite the 95% CIs reaching 1·00.

Tranexamic acid is unlikely to be effective for all causes of postpartum haemorrhage—its main benefit is probably for a subgroup of women with a deadly form of ongoing or delayed postpartum haemorrhage. But postnatal trickling and oozing is not uncommon and is often initially missed clinically.[7] These lacerations lead to a high morbidity and, until now, there has been no effective medical therapy. But now we have tranexamic acid, which, on its own, prevents over a third of all laparotomies for bleeding and a fifth of all deaths from postpartum haemorrhage. No wonder the evidence for tranexamic acid has been so enthusiastically received by clinicians and public health experts in both high-income and low-income settings. Tranexamic acid might not be the so-called magic bullet that we have all been looking for—uterotonics, emergency transport, safe surgery, and blood transfusion are all at least as important for reduction of maternal mortality—but it is a welcome addition to the armoury. And its widespread introduction will save many lives throughout the world every year.

Andrew D Weeks
Sanyu Research Unit, Department of Women's and Children's Health, University of Liverpool, Liverpool Women's Hospital, Liverpool L8 7SS, UK
aweeks@liv.ac.uk

I report non-financial support from the London School of Hygiene & Tropical Medicine to speak at a dissemination meeting related to the WOMAN trial. I also have a patent pending for the PPH Butterfly Device, a device for management of postpartum haemorrhage, to the University of Liverpool (Liverpool, UK).

1 WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389:** 2105–16.
2 Li B, Miners A, Shakur H, Roberts I. Tranexamic acid for treatment of women with post-partum haemorrhage in Nigeria and Pakistan: a cost-effectiveness analysis of data from the WOMAN trial. *Lancet Glob Health* 2018; **6:** e222–28.
3 Vogel JP, Oladapo OT, Dowswell T, Gülmezoglu AM. Updated WHO recommendation on intravenous tranexamic acid for the treatment of post-partum haemorrhage. *Lancet Glob Health* 2018; **6:** e18–19.
4 James AH. More than menorrhagia: a review of the obstetric and gynaecological manifestations of von Willebrand disease. *Thromb Res* 2007; **120:** S17–20.
5 Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: a systematic review. *Br J Haematol* 2006; **132:** 171–96.
6 Higgins JPT, Green S, eds. Cochrane handbook for systematic seviews of interventions, version 5.1.0 (updated March 2011). London: The Cochrane Collaboration, 2011.
7 Hancock A, Weeks AD, Lavender DT. Is accurate and reliable blood loss estimation the 'crucial step' in early detection of postpartum haemorrhage: an integrative review of the literature. *BMC Pregnancy Childbirth* 2015; **15:** 230.