The effect of tranexamic acid on postpartum bleeding in women with moderate and severe anaemia (WOMAN-2): an international, randomised, double-blind, placebo-controlled trial

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Summary

Background Tranexamic acid, given within 3 h of birth, reduces bleeding deaths in women with postpartum haemorrhage. We examined whether giving tranexamic acid shortly after birth can prevent postpartum haemorrhage in women with moderate or severe anaemia.

Methods This international, randomised, double-blind, placebo-controlled trial was done in 34 hospitals across four countries (Nigeria, Pakistan, Tanzania, and Zambia). We recruited women of any age in active labour with moderate or severe anaemia (haemoglobin <100 g/L). We randomly assigned women (1:1) who had given birth vaginally to receive 1 g of tranexamic acid or matching placebo by slow intravenous injection (over 10 min) within 15 min of the umbilical cord being cut or clamped. Women were randomly assigned by selection of the lowest numbered treatment pack from a box containing 20 packs that were identical apart from the pack number. Participants, care givers, and those assessing outcomes were masked to group assignment. The primary outcome was a clinical diagnosis of primary postpartum haemorrhage, which might be an estimated blood loss of more than 500 mL or any blood loss sufficient to compromise haemodynamic stability within 24 h of randomisation, analysed on an intention-to-treat basis. Safety analyses were performed in all participants included in the intention-to-treat population. This trial was registered on ISRCTN (ISRCTN62396133), ClinicalTrials.gov (NCT03475342), and the Pan African Clinical Trial Registry (PACTR201909735842379) and is closed to recruitment.

Findings From Aug 24, 2019, to Sept 19, 2023, 16 586 women aged 14–50 years were invited to take part and 1518 were excluded. 7580 women were randomly assigned to receive tranexamic acid and 7488 to receive placebo. Primary outcome data were unavailable for one woman in each group. The median time interval from the start of the administration of the trial treatment to the diagnosis of postpartum haemorrhage was 18·5 min (IQR 5–58); 20 min (8–64) in women with moderate anaemia and 13 min (7–44) in women with severe anaemia. 358 (35%) of 1024 with postpartum haemorrhage for whom time data were available were diagnosed before the trial treatment had been fully administered. Clinically diagnosed postpartum haemorrhage occurred in 530 (7·0%) of 7579 in the tranexamic acid group and in 497 (6·6%) of 7487 in the placebo group (risk ratio [RR] 1·05, 95% CI 0·94–1·19). There was no strong evidence against the null hypothesis of homogeneity of effects for any of the prespecified subgroup analyses: severity of anaemia (p=0·44), antepartum haemorrhage (p=0·044), birth canal trauma (p=0·37), use of pain control (p=0·37), and baseline risk of postpartum haemorrhage (p=0·31). There were no vascular occlusive events (pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction) reported in either group. There were no adverse events related to the treatment and no treatment-related deaths.

Interpretation In women with moderate and severe anaemia, giving tranexamic acid within 15 min of the umbilical cord being clamped did not reduce the risk of clinically diagnosed postpartum haemorrhage.

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Introduction

Worldwide, half a billion women of reproductive age are anaemic and 20 million are severely anaemic.[1] In sub-Saharan Africa and south Asia, nearly half of all pregnant women are anaemic.[2] Women with anaemia have a greatly increased risk of severe bleeding after childbirth,[3,4] and women with severe anaemia are also considerably more likely to die than women with moderate anaemia if they do have severe bleeding.[4] Efforts to reduce the prevalence of anaemia in women of reproductive age have not been successful and in many countries the prevalence has risen.[5] Effective ways to prevent and treat anaemia are urgently needed, but interventions to prevent severe postpartum bleeding in women with anaemia are also required.

Research in context

Evidence before this study

Randomised controlled trials have shown that early treatment with tranexamic acid reduces blood loss in surgery and reduces death due to bleeding after trauma. When given within 3 h of birth, tranexamic acid reduces deaths caused by bleeding in women with postpartum haemorrhage. However, for many women, the initiation of treatment of postpartum haemorrhage is too late to prevent death. Over a third of pregnant women worldwide are anaemic and many are severely anaemic. These women have an increased risk of postpartum haemorrhage and have more severe outcomes if postpartum haemorrhage occurs. A systematic review conducted before the start of the WOMAN-2 trial showed that there was insufficient evidence on whether tranexamic acid prevents postpartum haemorrhage during childbirth, especially in women with anaemia at high risk. There is an urgent need to identify a safe and effective way to reduce postpartum bleeding in women with anaemia. We conducted a systematic review before the start of the WOMAN-2 trial to assess the effects of tranexamic acid on the risk of postpartum haemorrhage and other clinically relevant outcomes. We searched for randomised controlled trials comparing tranexamic acid with no tranexamic acid or a placebo in women delivering vaginally or by caesarean section in the MEDLINE, CENTRAL, Embase, PubMed, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform electronic databases from database inception to May 31, 2015. Search terms have been published previously (Ker and colleagues, 2016). Most of the available trials of tranexamic acid to prevent postpartum haemorrhage were small, unreliable, and did not provide sufficient evidence on whether tranexamic acid could prevent postpartum haemorrhage during childbirth, especially in women with anaemia who were at high risk.

Added value of this study

The WOMAN-2 trial investigated the effect of tranexamic acid on postpartum bleeding in women with moderate or severe anaemia who gave birth vaginally. We found that giving women with moderate or severe anaemia tranexamic acid within 15 min of the umbilical cord being cut or clamped did not reduce the risk of clinically diagnosed postpartum haemorrhage. We found no evidence that tranexamic acid increases thromboembolic events in these women. Also, we did not find strong evidence against the null hypothesis of the homogeneity of effects in our subgroup analysis. However, there appeared to be an increase in the risk of postpartum haemorrhage in the subgroup of women with antepartum haemorrhage who received tranexamic acid.

Implications of all the available evidence

Giving tranexamic acid after cord clamping might be too late to prevent severe bleeding in many women and randomised trials of earlier treatment are needed. Our results also highlight the need to prevent and treat anaemia in women of reproductive age.

Tranexamic acid reduces bleeding after surgery and reduces the risk of death from bleeding in trauma victims by inhibiting the breakdown of blood clots.[6,7] In our previous study, the WOMAN trial,[8] we showed that tranexamic acid, given within 3 h of birth, reduces the risk of death from bleeding in women with postpartum haemorrhage. In women treated within 3 h of giving birth, 1·2% of women in the tranexamic acid group died from bleeding compared with 1·7% in the placebo group (risk ratio [RR] 0·69, 95% CI 0·52–0·91; p=0·008).[8] In this Article we present the results of the WOMAN-2 trial, conducted to investigate whether giving tranexamic acid as soon as possible and no later than 15 min after the umbilical cord was cut or clamped can reduce postpartum haemorrhage in women with moderate and severe anaemia.

Methods

Study design and participants

The WOMAN-2 trial is an international, randomised, double-blind, placebo-controlled trial investigating the effect of tranexamic acid on postpartum bleeding in women with moderate to severe anaemia who are giving birth vaginally. Women of any age who were in active labour and had a haemoglobin concentration of less than 100 g/L and no indication or contraindication for tranexamic acid treatment were enrolled at 34 hospitals in Nigeria, Pakistan, Tanzania, and Zambia. We conducted the trial according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines.[9]

The WOMAN-2 trial was approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee (REF 15194) on May 10, 2018; the National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007-29/09/2019) on Sept 29, 2019; the National Bioethics Committee of Pakistan on Nov 27, 2018 (NBC-340); the National Institute of Medical Research of Tanzania (NIMR/HQ/R.8a/Vol.IX/3767) on Aug 19, 2021; and the University of Zambia Biomedical Research Ethics Committee (REF 001-04-19) on Feb 2, 2019. Local site approvals were also obtained where relevant.

Written informed consent was obtained when the woman had the mental and physical capacity to give fully informed consent during labour, otherwise verbal agreement was obtained in the presence of an impartial witness, and written consent was obtained as soon as possible after delivery. If the woman was not legally an adult, consent was obtained from her guardian. If a woman could not give consent herself, we obtained proxy consent from a relative or representative. If neither was

available, we deferred consent. In these instances, the woman was advised about the trial as soon as possible and we obtained her consent to use the trial data. The consent procedures are described in detail in the WOMAN-2 trial protocol.[10] This trial was registered on the International Standard Randomised Controlled Trial Number registry (ISRCTN62396133), ClinicalTrials.gov (NCT03475342), and the Pan African Clinical Trial Registry (PACTR201909735842379).

Randomisation and masking

We randomly assigned (1:1) participants to receive tranexamic acid or matching placebo by administering the lowest numbered treatment pack from a box containing 20 packs that were identical apart from the pack number. The randomisation codes were generated by an information technology expert and a statistician who were not involved in the conduct of the trial. We gave the randomisation codes to the trial drug manufacturer so that treatment packs could be prepared in accordance with the randomisation list. The sponsor representative, who was also not involved in the trial, was sent a copy of the codes so that a backup was available in an emergency. The tranexamic acid was manufactured by Focus Pharmaceuticals (London, UK); the Guy's and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit (London, UK) manufactured the matching placebo (sodium chloride 0·9%) and prepared the trial treatment packs. The Guy's and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit were also responsible for masking, ensuring that the ampoules and treatment packs were identical in appearance except for the randomisation codes. Adherence to the allocation sequence was monitored throughout the trial by the central coordinating team and investigators were retrained if treatment packs were used out of sequence. Participants, trial coordinating team members, and site research teams were masked to the treatment allocation. Correct masking and coding of ampoules was checked by independent random testing of treatment packs by high-performance liquid chromatography to identify the contents of the ampoules. An emergency unblinding service was available to clinicians; however, unblinding was not required for any participant in the trial.

Procedures

Women in active labour who planned to give birth vaginally were offered a point-of-care haemoglobin test (HemoCue Hb 201+ System, Hemocue, Ängelholm, Sweden)[11] and those with a haemoglobin measurement of less than 100 g/L were invited to take part in the trial. Once consent or verbal agreement had been obtained, baseline data were collected before delivery. Final eligibility was confirmed after the delivery of the baby's anterior shoulder and before cutting or clamping the umbilical cord because some women became ineligible if they had a caesarean section or developed postpartum haemorrhage before the cord was cut or clamped.

After eligibility was confirmed, the lowest numbered pack was taken from a box of 20 treatment packs. Each treatment pack contained two ampoules, each containing 500 mg (5 mL) of tranexamic acid or placebo (5 mL), one sterile 10 mL syringe, and one 21 G needle. The women received 1 g (10 mL) of tranexamic acid or placebo by slow intravenous injection (about 1 mL/min) as soon as possible but no later than 15 min after the umbilical cord was cut or clamped. The women were considered randomly assigned when the administration of the trial treatment started. The women were monitored and outcome data related to postpartum haemorrhage were collected 24 h after randomisation or before death or discharge. The remaining outcome data were collected at death, discharge, or 42 days after randomisation, whichever occurred first. The research team at each hospital included the clinical team, research fellows, and other relevant personnel. Adverse events were monitored for up to 42 days after randomisation; those occurring while the woman was in hospital were documented by the research fellow in the case report form. Women discharged within 42 days of randomisation were given an alert card with the principal investigator's contact details and were asked to contact them if they had any medical event within the monitoring period. The research team documented any adverse events reported in the case report form. To prevent reporting delays, the clinician responsible for the woman's care initially graded the seriousness of the adverse event and its relatedness to the trial treatment. All adverse events and serious adverse events were subsequently reviewed by the principal investigator. The clinical team documented estimated blood loss at delivery in the medical record and the research fellow followed up the woman after birth to document postpartum blood loss. The research fellows estimated total blood loss from the medical records, collected data on quality of life, and conducted the exercise tolerance test (a 6 min walk test).

Outcomes

The primary outcome was a clinical diagnosis of postpartum haemorrhage, which might be an estimated blood loss of more than 500 mL or any blood loss sufficient to compromise haemodynamic stability within 24 h of randomisation. The research team at each hospital were trained to estimate blood loss from the point of delivery until 24 h after birth, or until earlier discharge, by monitoring and documenting the number of blood-soaked pads used by the women during this period. Pictograms were provided to help estimation. Haemodynamic instability was based on clinical judgement via clinical signs (low systolic blood pressure, tachycardia, reduced urine output, etc). The suspected cause of bleeding was documented by the research team. Postpartum blood loss, haemoglobin (measured

with the HemoCue Hb 201+ System), use of interventions to control primary postpartum haemorrhage (medical and surgical), and blood transfusion were assessed at 24 h after administration of the trial treatment or at 24 h after discharge from hospital, whichever occurred first. We recorded the lowest blood pressure and its corresponding pulse rate in the 24 h after birth (or until death or discharge).

We also assessed secondary outcomes at death, discharge from hospital, or 42 days after randomisation, whichever occurred first. Secondary outcomes were vascular occlusive events, death or near miss defined as a severe postpartum haemorrhage (blood loss of >1000 mL), surgical intervention for bleeding (eg, hysterectomy, laparotomy, embolisation, uterine compression sutures, and arterial ligation), absence of clot formation, transfusion of more than 5 units of blood, cardiovascular dysfunction (eg, shock, cardiac arrest, continuous vasoactive drugs, severe hypoperfusion, severe acidosis, and cardiopulmonary resuscitation), or renal dysfunction (eg, oliguria non-responsive to fluids or diuretics, dialysis for acute renal failure, and severe acute azotaemia[12]), quality of life assessed with a participant-reported outcomes questionnaire,[13] anaemia symptoms, exercise tolerance (6 min walk test), organ dysfunction, sepsis, in-hospital death, length of hospital stay, admission to and time spent in a higher-level facility, status of baby (eg, livebirth or stillbirth), and any thromboembolic events in the baby or babies. Women were monitored by the research team until discharge, death, or 42 days after randomisation, whichever occurred first. Postpartum haemorrhage prophylaxis was routinely used at all study sites.

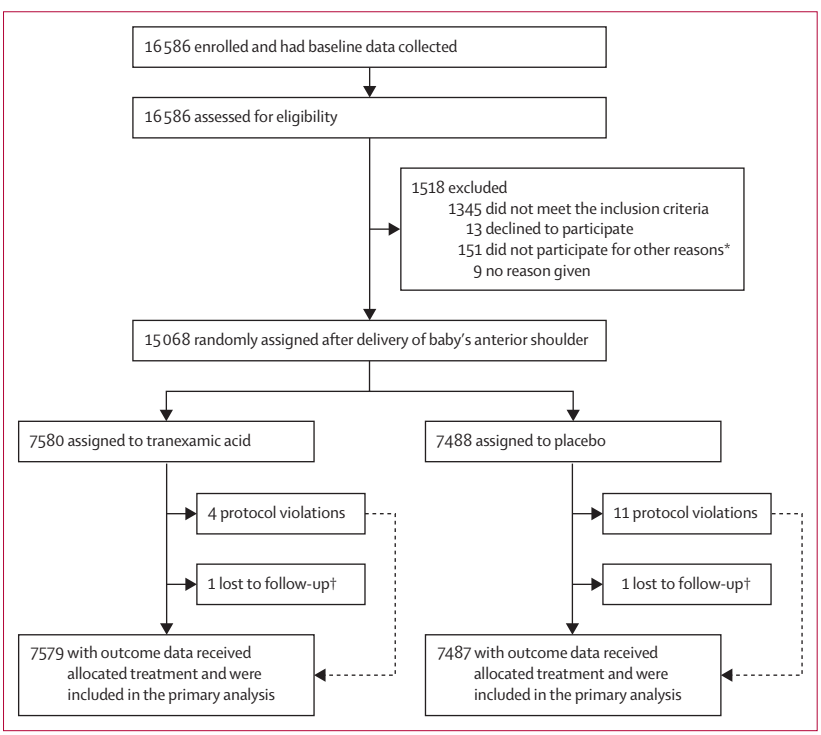

Figure 1: **Trial profile**
*Other reasons recorded by the research team include the woman leaving against medical advice (n=40), fetal distress (n=25), the trial treatment was not available (n=22), the woman was referred to another hospital (n=12), a diagnosis of antepartum haemorrhage was made (n=11), the woman had to undergo emergency surgery (n=11), and various other reasons (n=39). †Participants for whom there is no information about the primary endpoint.

Statistical analysis

We published the statistical analysis plan before the trial treatment allocation was unblinded.[12] This plan has details of the protocol amendment to increase the sample size from 10 000 to 15 000 women. We originally estimated that a trial with 10 000 women would have over 90% power (two-sided α of 5%) to detect a 25% reduction from 10% to 7·5% in the proportion of women with postpartum haemorrhage. While the trial was in progress, several trials of tranexamic acid for the prevention of postpartum haemorrhage were published. When we pooled the results of those trials that included more than 1000 women, we found that the treatment effect, although still important, was more modest (about 15% relative risk reduction) than we had estimated.[14–16] Assuming tranexamic acid reduces the risk of postpartum haemorrhage by 15% with a placebo group event rate of 9%, a trial with 15 000 women would have 85% power to detect a 15% relative risk reduction with a two-side α of 5%. The re-estimation of sample size was done before unblinding and without any knowledge of the trial results. An independent data monitoring committee conducted five unblinded interim analyses to monitor the safety, efficacy, and overall trial progress during the course of the trial. The data monitoring committee had no part in the decision to change the sample size.

All analyses were done on an intention-to-treat basis, regardless of whether the participant received all the allocated treatment. Safety analyses were performed in all participants included in the intention-to-treat population. The results are presented as RRs and 95% CIs. We report the effect of tranexamic acid on cause-specific postpartum haemorrhage (ie, atony, placenta implantation abnormalities, tears, retained placental tissue, uterine rupture, other, and unknown). However, the primary analysis was for all-cause postpartum haemorrhage. We ran two sensitivity analyses for the primary outcome: (1) adjusting for baseline risk factors for postpartum haemorrhage in a logistic regression model (ie, age, haemoglobin before birth, previous postpartum haemorrhage, multiple birth, placental abnormality, and birth canal trauma); and (2) excluding women with continuing antepartum haemorrhage because distinguishing between continuing antepartum and postpartum bleeding in these women is difficult. Analyses were performed on Stata version 18 and R version 4.3.0.

We report heterogeneity p values for all subgroup analyses. We prespecified subgroup analyses on the basis of the severity of anaemia (moderate *vs* severe anaemia), antepartum bleeding, birth canal trauma (traumatic *vs*

non-traumatic), use of pain control (any *vs* none), and baseline risk of postpartum haemorrhage (low, intermediate, or high). For baseline risk of postpartum haemorrhage, we developed a prognostic model using baseline characteristics collected before randomisation as predictors. Unless there was strong evidence against the null hypothesis of homogeneity of effects (ie, p<0·001), we considered the overall effect to be the most reliable guide to the approximate effect in each of the subgroups.[12]

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to publish.

Results

From Aug 24, 2019, to Sept 19, 2023, 16 586 women were invited to take part in the trial, of whom 1518 were excluded (figure 1). The age range of those included was

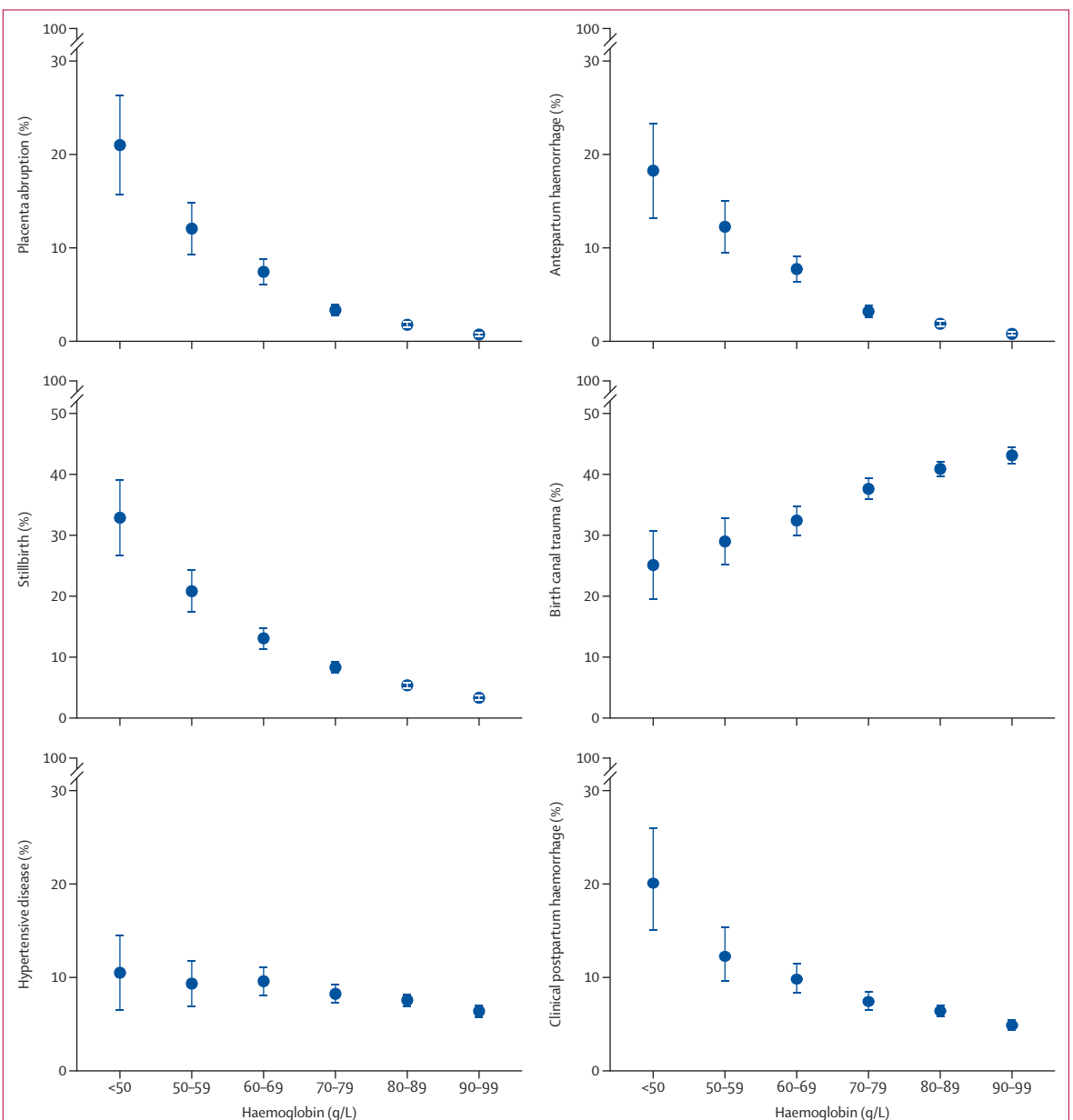

Figure 2: **Baseline characteristics within the current pregnancy of the women by haemoglobin before birth and association between haemoglobin before birth and a clinical diagnosis of postpartum haemorrhage (N=15 066)**

Datapoints show the proportion of women and error bars show the corresponding 95% CI. Stillbirth refers to stillborn in at least one baby at baseline. Birth canal trauma includes episiotomy, vaginal, perineal, or cervical tear, or uterine rupture. Clinical postpartum haemorrhage might have been an estimated blood loss of >500 mL or any blood loss sufficient to compromise haemodynamic stability.

14–50 years. We randomly assigned 15 068 women to receive tranexamic acid (n=7580) or placebo (n=7488). Seven (<0·1%) women (one [<0·1%] in the tranexamic acid group and six [<0·1%] in the placebo group) received only one of the two ampoules of the trial treatment because the other ampoule was found to be broken when the pack was opened, but these women were included in the primary analysis. There were 15 (0·1%) protocol violations: four (<0·1%) women in the tranexamic acid group and three (<0·1%) in the placebo group received previous non-trial tranexamic acid, seven (0·1%) women in the placebo group had postpartum haemorrhage before randomisation, and one (<0·1%) woman in the placebo group was having a miscarriage and not in an active stage of labour when randomly assigned. All 15 participants with protocol violations were included in the main analysis. We obtained primary outcome data for all but two women (one [<0·1%] in the tranexamic acid group and one [<0·1%] in the placebo group); therefore, the primary analysis includes data for 15 066 (99·9%) of 15 068 women. The median time interval between birth and cord clamping was 2 min (IQR 1–2). The median time interval between birth and the start of the trial treatment was 5 min (3–6). The median time interval from the start of the administration of the trial treatment to the diagnosis of postpartum haemorrhage was 18·5 min (IQR 5–58): 20 min (8–64) in women with moderate anaemia and 13 min (7–44) in women with severe anaemia.

	Tranexamic acid group (n=7580)	Placebo group (n=7488)
Mean age, years	27·3 (5·6)	27·1 (5·6)
Haemoglobin, g/L		
Mean	82·7 (11·8)	82·8 (11·9)
Moderate (70–99 g/L)	6527 (86·1%)	6462 (86·3%)
Severe (<70 g/L)	1053 (13·9%)	1026 (13·7%)
Mean estimated gestation, weeks	37·4 (2·7)	37·4 (2·7)
Number of fetuses		
1	7290 (96·2%)	7195 (96·1%)
2	283 (3·7%)	285 (3·8%)
3	7 (0·1%)	8 (0·1%)
Placental abnormalities		
Abruption	210 (2·9%)	221 (2·3%)
Previa	15 (0·2%)	26 (0·4%)
Accreta	1 (<0·1%)	2 (<0·1%)
Antepartum haemorrhage	207 (2·7%)	228 (3·0%)
Pre-eclampsia	162 (2·1%)	159 (2·1%)
Stillbirths per mother		
1	507 (6·7%)	509 (6·8%)
2	7 (0·1%)	13 (0·2%)
Macrosomia (>4000 g)	57 (0·8%)	51 (0·7%)
Assisted delivery		
Ventouse	119 (1·6%)	116 (1·5%)
Forceps	61 (0·8%)	63 (0·8%)
Other	35 (0·5%)	33 (0·4%)
Lacerations and tears		
Perineal	865 (11·4%)	923 (12·3%)
Cervical	165 (2·2%)	169 (2·3%)
Vaginal	85 (1·1%)	78 (1·0%)
Prophylactic uterotonics		
Oxytocin	7569 (99·9%)	7479 (99·9%)
Misoprostol	27 (0·4%)	22 (0·3%)
Ergometrine	3 (<0·1%)	8 (0·1%)
Prostaglandins	1 (<0·1%)	3 (<0·1%)

Data are mean (SD) or n (%).

Table 1: **Baseline characteristics for the current pregnancy of participants before random assignment**

Figure 2 shows the characteristics of the women at baseline according to pre-birth haemoglobin concentrations. For women with haemoglobin concentration less than 50 g/L, 44 (20%) of 219 had postpartum haemorrhage. Baseline characteristics were balanced between the tranexamic acid and placebo groups (table 1). A clinically diagnosed postpartum haemorrhage occurred in 1027 (6·8%) of the 15 066 women (table 2). 358 (35%) of 1024 women with postpartum haemorrhage for whom data giving the time of diagnosis were available were diagnosed before the trial treatment had been completely administered.

Clinically diagnosed postpartum haemorrhage occurred in 530 (7·0%) of 7579 women in the tranexamic acid group and in 497 (6·6%) of 7487 women in the placebo group (RR 1·05, 95% CI 0·94–1·19; table 2). Similar results were obtained in the two prespecified sensitivity analyses: first, after adjusting for the baseline risk factors of age, pre-birth haemoglobin, previous postpartum haemorrhage, number of babies in this pregnancy, placental abnormality in this pregnancy, and birth canal trauma in this pregnancy (1·09, 0·97–1·22), and second, after excluding women with continuing antepartum haemorrhage (1·03, 0·91–1·17). The presumed primary causes of the postpartum haemorrhage were atony (348 [4·6%] in the tranexamic acid group *vs* 341 [4·6%] in the placebo group), tears (101 [1·3%] *vs* 91 [1·2%]), retained placenta tissue (52 [0·7%] *vs* 47 [0·6%]), placenta implantation abnormalities (9 [0·1%] *vs* 6 [0·1%]), uterine rupture (0 *vs* 1 [<0·1%]), and other or unknown (20 [0·3%] *vs* 11 [0·1%]).

The prespecified subgroup analyses are presented in figure 3. There was no strong evidence against the null hypothesis of homogeneity of effects for any of the prespecified subgroup analyses: severity of anaemia (p=0·44), antepartum haemorrhage (p=0·044), birth canal trauma (p=0·37), use of pain control (p=0·37), and baseline risk of postpartum haemorrhage (p=0·31).

The key secondary outcomes are presented in table 2. Estimated blood loss data were missing for four (0·1%) women in the tranexamic acid group and four (0·1%) in the placebo group. The mean blood loss was 309·8 mL (SD 193·9) for women in the tranexamic acid group and 310·8 mL (191·5) in the placebo group.

2547 (33·6%) women in the tranexamic acid group and 2503 (33·4%) in the placebo group had an estimated blood loss less than 250 mL; 31 (0·4%) women in the tranexamic acid group and 24 (0·3%) in the placebo group had an estimated blood loss of at least 1500 mL. Postpartum haemoglobin data were missing for 112 (1·5%) women in the tranexamic acid group and 91 (1·2%) in the placebo group. Mean postpartum haemoglobin, measured within 24 h of birth and corrected for blood transfusion, was 82·2 g/L (SD 15·5) in the tranexamic acid group and 82·1 g/L (15·7) in the placebo group; 1402 (18·8%) women with available data in the tranexamic acid group and 1360 (18·4%) in the placebo group had a 24 h corrected haemoglobin less than 70 g/L; 167 (2·2%) women with available data in the tranexamic acid group and 182 (2·5%) in the placebo group had a 24 h corrected haemoglobin of at least 110 g/L.

There were 122 (1·6%) deaths or near misses in the tranexamic acid group and 137 (1·8%) in the placebo group (RR 0·88, 95% CI 0·69–1·12). There were no vascular occlusive events (ie, pulmonary embolism, deep vein thrombosis, stroke, or myocardial infarction) in either group. The number of adverse events and serious adverse events did not differ in the tranexamic acid group versus the placebo group (appendix p 9). None of the adverse events were suspected to be related to the trial treatment. There were no cases of inadvertent intrathecal injection of tranexamic acid.

There were no significant between-group differences in quality of life assessed with a participant-reported outcomes questionnaire, anaemia symptoms, exercise tolerance (ie, 6 min walk test), use of medical and surgical interventions to control primary postpartum haemorrhage, blood transfusion, organ dysfunction, sepsis, in-hospital death, length of hospital stay, admission to and time spent in a higher-level facility, status of baby (ie, livebirth or stillbirth), and any thromboembolic events in the baby (table 3; appendix pp 4–8).

In a post-hoc exploratory analysis in which we used an objective measure of blood loss based on the change in maternal haemoglobin before and 24 h after birth, after adjusting for blood transfusion, we found that the results were similar to the main analysis (appendix p 9).

	Tranexamic acid group (N=7579)	Placebo group (N=7487)	Estimate (95% CI)*	p value
Postpartum haemorrhage	530 (7·0%)	497 (6·6%)	1·05 (0·94 to 1·19)	0·39
Primary cause of postpartum haemorrhage				
Atony	348 (4·6%)	341 (4·6%)	..	..
Tears	101 (1·3%)	91 (1·2%)	..	..
Retained placenta tissue	52 (0·7%)	47 (0·6%)	..	..
Placenta implantation abnormalities	9 (0·1%)	6 (0·1%)	..	..
Uterine rupture	0	1 (<0·1%)	..	..
Other	9 (0·1%)	7 (0·1%)	..	..
Unknown	11 (0·1%)	4 (0·1%)	..	..
Sensitivity analysis				
Adjusted RR	..	..	1·09 (0·97 to 1·22)	0·14
Adjusted RR with exclusions†	..	..	1·03 (0·91 to 1·17)	0·62
Estimated blood loss, mL				
Mean	309·8 (193·9)	310·8 (191·5)	–0·95 (–7·10 to 5·21)	0·76
Blood loss category	..	..	0·99 (0·93 to 1·06)	0·80
<250 mL	2547/7575 (33·6%)	2503/7483 (33·4%)	..	..
250–499 mL	4489/7575 (59·3%)	4444/7483 (59·4%)	..	..
500–999 mL	437/7575 (5·8%)	422/7483 (5·6%)	..	..
1000–1499 mL	71/7575 (0·9%)	90/7483 (1·2%)	..	..
≥1500 mL	31/7575 (0·4%)	24/7483 (0·3%)	..	..
Corrected 24-h haemoglobin, g/L‡				
Mean	82·2 (15·5)	82·1 (15·7)	0·12 (–0·26 to 0·50)	0·54
Haemoglobin category	..	..	0·97 (0·91 to 1·05)	0·47
<70 g/L	1402/7467 (18·8%)	1360/7396 (18·4%)	..	..
70–99 g/L	5314/7467 (71·2%)	5276/7396 (71·3%)	..	..
100–109 g/L	584/7467 (7·8%)	578/7396 (7·8%)	..	..
≥110 g/L	167/7467 (2·2%)	182/7396 (2·5%)	..	..
Death or near-miss death at 24 h§	122 (1·6%)	137 (1·8%)	0·88 (0·69 to 1·12)	0·30

Data are mean (SD) or n (%). Differences in N are due to missing data. Adjusted RR is adjusted for age, pre-birth haemoglobin, previous postpartum haemorrhage, number of babies in this pregnancy, placental abnormality in this pregnancy, and any birth canal trauma in this pregnancy. For estimated blood loss we reported the number and percentage of women in each category by group, then estimated an OR and 95% CI using an ordinal logistic regression model. We used a likelihood ratio test to confirm the proportional odds assumption was not violated. We found no evidence that the proportional odds assumption was violated (p=0·34). No vascular occlusive events (ie, pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction) were recorded in either group. *Mean difference for continuous variables (estimated blood loss and corrected 24-h haemoglobin), common OR for categorical variables (blood loss category and corrected 24-h haemoglobin category), and RR for the binary variable (death or near-miss death at 24 h). †Excluding 234 women with ongoing antepartum haemorrhage at the time of birth. ‡Corrected for blood transfusion. §Death from any cause or near-miss death from postpartum haemorrhage, defined as severe postpartum haemorrhage (ie, blood loss of >1000 mL), surgical intervention for bleeding (ie, hysterectomy for bleeding, laparotomy, embolisation, uterine compression sutures, or arterial ligation), failure to form clots, transfusion of >5 units, cardiovascular dysfunction (ie, shock, cardiac arrest, continuous vasoactive drugs, severe hypoperfusion, severe acidosis, or CPR), or diagnosed renal dysfunction (ie, oliguria non-responsive to fluids or diuretics, dialysis for acute renal failure, or severe acute azotaemia). OR=odds ratio. RR=risk ratio.

Table 2: **Effect of tranexamic acid on women with moderate or severe anaemia (primary and secondary outcomes)**

Discussion

In women with moderate or severe anaemia, giving tranexamic acid shortly after the umbilical cord is clamped did not reduce the risk of clinically diagnosed postpartum haemorrhage. Our study has many strengths, but also some limitations. The randomisation method ensured that participating clinicians had no foreknowledge of treatment allocation. Baseline prognostic factors were balanced, and because almost all trial participants were followed up, there is minimal potential for bias. We initially planned to enrol 10 000 women; however, while the trial was in progress and without knowledge of the interim results, we increased the sample size to 15 000 women to have more power to reliably support or refute a modest treatment effect. We have previously shown that our primary outcome measure, clinically diagnosed postpartum

See Online for appendix

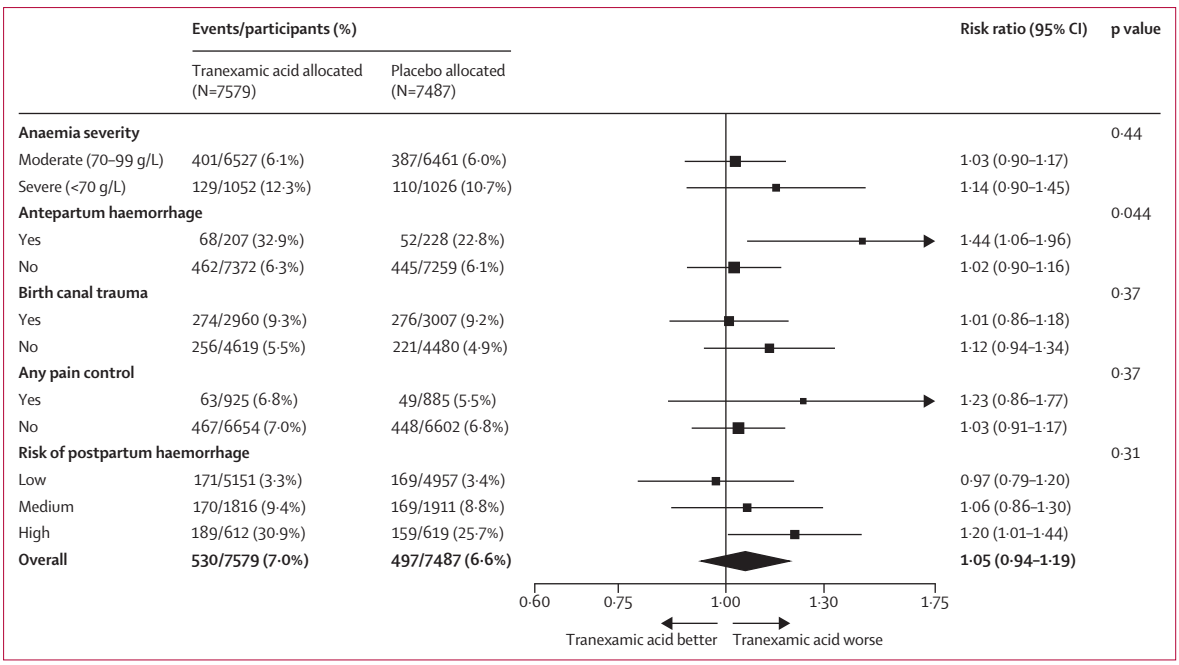

Figure 3: **Effect of tranexamic acid on clinically diagnosed postpartum haemorrhage overall and by subgroup**
p values are for heterogeneity. Birth canal trauma includes episiotomy, vaginal, perineal, or cervical tear, or uterine rupture. Baseline variables included in the risk of postpartum haemorrhage model can be found in the appendix (p 2).

	Total (N=15 066)	Tranexamic acid (N=7579)	Placebo (N=7487)
Oxytocin	1962 (13·0%)	993 (13·1%)	969 (12·9%)
Ergometrine	19 (0·1%)	10 (0·1%)	9 (0·1%)
Carbetocin	2 (<0·1%)	1 (<0·1%)	1 (<0·1%)
Prostaglandins	12 (0·1%)	7 (0·1%)	5 (0·1%)
Misoprostol	1527 (10·1%)	773 (10·2%)	754 (10·1%)
Non-trial tranexamic acid	844 (5·6%)	439 (5·8%)	405 (5·4%)
Perineal sutures	5743 (38·1%)	2849 (37·6%)	2894 (38·7%)
Cervical sutures	334 (2·2%)	165 (2·2%)	169 (2·3%)
Perineal or vaginal packing	239 (1·6%)	123 (1·6%)	116 (1·5%)
Uterine tamponade			
Any	160 (1·1%)	81 (1·1%)	79 (1·1%)
Balloon*	66 (0·4%)	31 (0·4%)	35 (0·5%)
Packing*	96 (0·6%)	51 (0·7%)	45 (0·6%)
Bimanual compression	234 (1·6%)	113 (1·5%)	121 (1·6%)
External aortic compression	6 (<0·1%)	3 (<0·1%)	3 (<0·1%)
Anti-shock garment	7 (<0·1%)	5 (0·1%)	2 (<0·1%)
Removal of placenta	289 (1·9%)	157 (2·1%)	132 (1·8%)
Uterine compression sutures	4 (<0·1%)	2 (<0·1%)	2 (<0·1%)
Arterial ligation	4 (<0·1%)	2 (<0·1%)	2 (<0·1%)
Arterial embolisation	0	0	0
Hysterectomy	19 (0·1%)	9 (0·1%)	10 (0·1%)
Type of hysterectomy			
Subtotal hysterectomy	17/19 (89·5%)	9/9 (100·0%)	8/10 (80·0%)
Total hysterectomy	2/19 (10·5%)	0	2/10 (20·0%)

(Table 3 continues on next page)

haemorrhage, has high specificity for clinical signs of shock (95% specificity for shock index ≥1) and was strongly associated with postpartum fatigue and breathlessness after vaginal birth.[17] An important weakness of our study is that we did not use calibrated drapes to quantify postpartum blood loss. The use of drapes was not standard clinical practice when our trial was conducted. Furthermore, because there is no established definition of postpartum haemorrhage for women with anaemia, we could not rely on any particular blood loss criterion.[18] Instead, we asked clinicians to estimate the blood loss and its effect on the woman's haemodynamic status, as they would do in their usual clinical practice. However, when our analyses were repeated (a post-hoc exploratory analysis) with an objective measure of blood loss,[15] based on the change in maternal haemoglobin before and 24 h after birth after adjusting for blood transfusion, the results were similar (appendix p 9). We measured haemoglobin using the HemoCue Hb 201+ System;[11] although this device has high accuracy compared with laboratory measurements, some error is inevitable.[19] Because we did not run coagulation tests, such as those used to diagnose disseminated intravascular coagulation (eg, prothrombin time, fibrinogen, platelet count, and D-dimers), we cannot describe the frequency or type of coagulation abnormalities seen in women giving birth with moderate or severe anaemia.

Women with moderate and severe anaemia have a greatly increased risk of postpartum haemorrhage.[4] The

monotonic biological gradient between pre-birth haemoglobin and postpartum haemorrhage suggests a causal relationship. The reduced blood viscosity and the increased heart rate and cardiac output caused by anaemia can increase blood loss.[20–22] Anaemic blood clots also appear to be more susceptible to fibrinolysis.[23–24] Furthermore, as the haemoglobin concentration falls, the risk of serious obstetric complications, including antepartum bleeding, abruption, and stillbirth, increases. Whether these complications are directly caused by anaemia or whether both anaemia and these serious obstetric complications are caused by other factors, such as poverty or limited access to quality health care, is not certain. Nevertheless, the prenatal activation of coagulation caused by these conditions leads to the consumption and depletion of coagulation factors and platelets causing severe bleeding that occurs soon after birth.[25,26]

When 1 g of tranexamic acid is given by slow intravnous injection, the mean time to reach the blood concentration needed to inhibit fibrinolysis is estimated to be 3 min (range 2–7) after the end of the injection.[27] In our trial, given that 35% of postpartum haemorrhage diagnoses were made before the trial treatment had been fully administered, it is possible that many postpartum haemorrhage diagnoses were made before the trial treatment had any therapeutic effect. Furthermore, if bleeding from birth canal trauma or from the placental bed started at the time of birth, a considerable amount of blood might have been lost before the trial treatment started. Although the diagnosis of postpartum haemorrhage was made after the start of the trial treatment, earlier severe blood loss could have made this diagnosis inevitable in some women. Because of the rapid onset of severe postpartum bleeding in women with anaemia, tranexamic acid given after cord clamping could be too late to prevent postpartum haemorrhage.

Tranexamic acid appeared to increase the risk of postpartum haemorrhage in the subgroup of women with antepartum haemorrhage. Although our case report form did not collect data on the presumed cause of this antepartum haemorrhage, given the similarly high prevalence of placental abruption, it is probable that abruption accounted for most of these instances. In this subgroup analysis we did not find strong evidence against the null hypothesis of the homogeneity of effects, and because we conducted several statistical tests for heterogeneity, there is a moderate chance of making a false positive claim even when there is no heterogeneity. However, if this increase is real, temporal changes in coagulation activation might be the explanation. Randomised trials of tranexamic acid in traumatic and postpartum bleeding show that early treatment is beneficial, but late treatment might be harmful.[28] Treatment with tranexamic acid is only recommended for patients who are within 3 h of injury from trauma or

	Total (N=15 066)	Tranexamic acid (N=7579)	Placebo (N=7487)
(Continued from previous page)			
Reason for hysterectomy			
Postpartum haemorrhage	18/19 (94·7%)	8/9 (88·9%)	10/10 (100·0%)
Rupture	1/19 (5·3%)	1/9 (11·1%)	0
Laparotomy to control bleeding	9 (0·1%)	2 (<0·1%)	7 (0·1%)
Any blood product	3822 (25·4%)	1926 (25·4%)	1896 (25·3%)
Whole blood or packed cells, units			
0	11 265 (74·8%)	5664 (74·7%)	5601 (74·8%)
1	3017 (20·0%)	1523 (20·1%)	1494 (20·0%)
2	668 (4·4%)	336 (4·4%)	332 (4·4%)
≥3	116 (0·8%)	56 (0·7%)	60 (0·8%)
Fresh frozen plasma, units			
0	14 918 (99·0%)	7506 (99·0%)	7412 (99·0%)
1	65 (0·4%)	32 (0·4%)	33 (0·4%)
2	30 (0·2%)	14 (0·2%)	16 (0·2%)
≥3	53 (0·4%)	27 (0·4%)	26 (0·3%)
Platelets, units			
0	15 033 (99·8%)	7564 (99·8%)	7469 (99·8%)
1	10 (0·1%)	6 (0·1%)	4 (0·1%)
2	5 (<0·1%)	2 (<0·1%)	3 (<0·1%)
≥3	18 (0·1%)	7 (0·1%)	11 (0·1%)
Cryoprecipitate, units			
0	15 065 (100·0)	7578 (100·0%)	7487 (100·0%)
1	0	0	0
2	1 (<0·1%)	1 (<0·1%)	0
≥3	0	0	0
Maternal death in hospital	18 (0·1%)	9 (0·1%)	9 (0·1%)
Time to maternal death, h			
Mean (SD)	77·31 (124·56)	79·84 (82·81)	74·77 (161·55)
Median (IQR)	8·80 (4·08–138·83)	56·73 (4·08–179·28)	8·18 (5·63–12·33)
Range	1·50–489·35	2·25–188·25	1·50–489·35
Cause of maternal death			
Bleeding	7/18 (38·9%)	4/9 (44·4%)	3/9 (33·3%)
Sepsis	2/18 (11·1%)	2/9 (22·2%)	0
Other	9/18 (50·0%)	3/9 (33·3%)	6/9 (66·7%)
MedDRA-defined cause of other maternal death			
Acute kidney injury	1/9 (11·1%)	1/3 (33·3%)	0
Acute respiratory distress syndrome	1/9 (11·1%)	1/3 (33·3%)	0
Anaemia	2/9 (22·2%)	0	2/6 (33·3%)
Eclampsia	1/9 (11·1%)	1/3 (33·3%)	0
HELLP syndrome	1/9 (11·1%)	0	1/6 (16·7%)
Multiple organ dysfunction syndrome	2/9 (22·2%)	0	2/6 (33·3%)
Shock haemorrhagic	1/9 (11·1%)	0	1/6 (16·7%)
Babies breastfed	12 843/14 604 (87·9%)	6445/7354 (87·6%)	6398/7250 (88·2%)

Data are n (%) unless otherwise specified. HELLP=haemolysis, elevated liver enzymes, and low platelet count. MedDRA=Medical Dictionary for Regulatory Activities. *Participants could have more than one type of uterine tamponade.

Table 3: **Interventions given after randomisation, in-hospital maternal death, and breastfeeding**

postpartum haemorrhage from childbirth. The idea that for women with antepartum haemorrhage, the bleeding might have started many hours before birth is possible.

In women with moderate and severe anaemia, giving tranexamic acid within 15 min of the umbilical cord being clamped did not reduce the risk of clinically diagnosed postpartum haemorrhage. Giving tranexamic acid after cord clamping might be too late to prevent severe bleeding in many women and randomised trials of earlier treatment are needed. The I'M Woman trial[29] is currently evaluating the effect of giving tranexamic acid just before childbirth on the risk of postpartum haemorrhage. Our results also highlight the need to prevent and treat anaemia in women of reproductive age. Because anaemia in pregnancy increases the risk of abruption and stillbirth, efforts to prevent anaemia should begin early, ideally before conception.[30,31] The WOMAN-3 trial (NCT06519422), due to begin in 2025, will examine the role of giving tranexamic acid during menstruation in addition to iron and folic acid for the treatment of anaemia in women of reproductive age.

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EB did the project administration and writing of the original draft. IR did the study design, conceptualisation, methodology, supervision, funding acquisition, writing of the original draft, and draft revisions. HS-S did the study design, conceptualisation, methodology, supervision, funding acquisition, and review and editing of the manuscript. SA did the protocol development and the review and drafting of the manuscript. RC, OOl, FAB, PM, BV, MKL, LEM, MM-O, OOO, FJR, C-HT, AK, KJ, and OOk did the data collection, data interpretation, and review and editing of the manuscript. RM and TJC did the formal statistical analysis, visualisation, and review and editing of the manuscript. DP and AG did the data curation and review and editing of the manuscript. KK did the study design, funding acquisition, and review and editing of the manuscript. AB did the review and editing of the manuscript. IR, HS-S, EB, RM, TJC, DP, AG verified the data. All members of the writing committee were allowed to access the raw data if they wished. All members of the writing committee accept responsiblity for the decision to submit for publication.

Declaration of interests

KK, IR, and HS-S declare support for the current study and manuscript as co-applicants of grants awarded by the Wellcome Trust and the Bill & Melinda Gates Foundation for the conduct of this study, paid to their institution (London School of Hygiene & Tropical Medicine [LSHTM], London, UK). HS-S declares funding from the UK National Institute for Health and Care Research (NIHR) for other research on tranexamic acid, paid to their institution (LSHTM). IR declares receipt of support from the NIHR, Wellcome Trust, and John Moulton Foundation for other research into the effects of tranexamic acid, paid to their institution (LSHTM); and an unpaid role as convenor of an ad hoc group, the Joint Royal Colleges Tranexamic Acid in Surgery Implementation Group, to increase the use of tranexamic acid in surgical patients as per National Institute for Health and Care Excellence guidance. All other members of the writing committee declare no competing interests.

Data sharing

After publication of primary and secondary analyses detailed in the statistical analysis plan, individual de-identified patient data, including the data dictionary, will be made available via our data sharing portal, The Free Bank of Injury and Emergency Research Data (FreeBIRD), indefinitely to allow maximum use of the data to improve patient care and advance medical knowledge. The trial protocol and statistical analysis plan are freely available online. Trial publications will be available online at publication.

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