RESEARCH ARTICLE

No effect of tranexamic acid on platelet function and thrombin generation (ETAPlat) in postpartum haemorrhage: a randomised placebo-controlled trial [version 1; referees: awaiting peer review]

Kastriot Dallaku 1,2, Haleema Shakur-Still 3, Danielle Beaumont 3, Ian Roberts 3, Sumaya Huque 3, Maria Delius 4, Stefan Holdenrieder 5, Orion Gliozheni 2, Ulrich Mansmann 1

1Institute for Medical Informatics, Biometry and Epidemiology, University Hospital LMU, Munich, Germany
2University Hospital of Obstetrics Gynaecology “Koço Gliozheni”, Tirana, Albania
3Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK
4Department of Obstetrics and Gynaecology, University Hospital LMU, Munich, Germany
5Institute of Laboratory Medicine, German Heart Center of the Technical University Munich, Munich, Germany

Abstract

Background: Postpartum hemorrhage (PPH) is a leading cause of maternal mortality and morbidity. The WOMAN trial showed that tranexamic acid (TXA) reduces death due to bleeding in women with PPH. To determine whether TXA has pro-thrombotic effects in women with PPH, we measured endogenous thrombin potential (ETP), coagulation factors V, VIII, von Willebrand (vW), fibrinogen, D-Dimers and platelet function.

Methods: We conducted a sub-study within the WOMAN trial, an international randomized, parallel-group, double blind, placebo-controlled trial. Women with primary PPH were randomly allocated to receive 1 gram of tranexamic acid or matching placebo. Baseline blood samples were collected just prior to the first dose and a follow up sample was collected 30±15 minutes afterwards. We compared before and after changes in coagulation parameters between treatment groups using repeated measurement ANOVA. Change in ETP was the primary outcome. We did an intention-to-treat analysis using ANCOVA with adjustment for baseline and the time interval between the blood samples.

Findings: A total of 187 patients were randomized to receive TXA (n=93) or matching placebo (n=94). Six patients were excluded due to incomplete data. The reduction in ETP from baseline to follow up was 43.2 nM*min (95%CI, -16.6 to 103.1) in the TXA group and 4.6 nM*min (95%CI, -51.4 to 60.6) in the placebo group. The difference was not statistically significant (95%CI, -42.9 to 120). There were no significant effects of TXA treatment on any other parameters (ADPtest, TRAPtest, coagulation factors activity, fibrinogen levels, D-Dimer level).

Conclusion: We found no evidence that tranexamic acid treatment for PPH has substantial pro-coagulant effects. However, larger studies are needed to
confirm or refute more modest effects.

**Trial registration:** ISRCTN76912190 (initially registered 10/12/2008, WOMAN-ETAPI included on 28/10/2013) and NCT00872469 (initially registered 31/03/2009, WOMAN-ETAPI included on 28/10/2013).

**Keywords**
Tranexamic Acid, Postpartum Haemorrhage, Thrombin Generation, Platelet Function

| Corresponding author: Kastriot Dallaku (k_dallaku@hotmail.com) |
| Author roles: Dallaku K: Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Resources, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Shakur-Still H: Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Beaumont D: Formal Analysis, Investigation, Software, Writing – Original Draft Preparation, Writing – Review & Editing; Roberts I: Conceptualization, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Huque S: Formal Analysis, Software, Writing – Original Draft Preparation, Writing – Review & Editing; Holdenrieder S: Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Gliozheni O: Conceptualization, Investigation, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Mansmann U: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing |
| Competing interests: No competing interests were disclosed. |
| Grant information: The WOMAN Trial was funded by the Department of Health (UK), grant number HICF-T2-0510-007, the Wellcome Trust, grant number WT094947, the Bill & Melinda Gates Foundation (grant number OPP1095618), and LSHTM (London, UK). An educational grant was given by Erasmus Mundus program ERAWEB [D2.12.048] and Rudolf Marx Foundation (Munich, Germany). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. |
| Copyright: © 2019 Dallaku K et al. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. |
| How to cite this article: Dallaku K, Shakur-Still H, Beaumont D et al. No effect of tranexamic acid on platelet function and thrombin generation (ETAPI) in postpartum haemorrhage: a randomised placebo-controlled trial [version 1; referees: awaiting peer review] Wellcome Open Research 2019, 4:21 (https://doi.org/10.12688/wellcomeopenres.14977.1) |
| First published: 05 Feb 2019, 4:21 (https://doi.org/10.12688/wellcomeopenres.14977.1) |
Background
Postpartum haemorrhage (PPH) is a leading cause of maternal mortality worldwide and the incidence appears to be increasing¹. Most deaths are in low- and middle-income countries. Immediate and appropriate management of PPH is essential to reduce mortality and morbidity. The antifibrinolytic tranexamic acid (TXA) reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots. Plasminogen is converted into the fibrinolytic enzyme plasmin by tissue plasminogen activator. TXA is a synthetic lysine analogue which blocks the lysine binding sites on plasminogen, as a result inhibits binding of plasminogen or plasmin with fibrin and thereby inhibiting fibrin degradation. It has the half-life about two hours and is excreted mostly by the kidneys².

The CRASH 2 trial³ showed that TXA significantly reduces death due to bleeding in trauma patients without any increase in thromboembolic events when given within 3 hours of injury. More recently, the WOMAN trial⁴ showed that TXA significantly reduces death due to bleeding in women with PPH. Once again there was no evidence of any increase in thromboembolic events. On the basis of these results, TXA is recommended for the treatment of PPH and should be administered as soon as possible after onset of bleeding and within 3 hours of birth⁵.

Although plasmin increases fibrin clot breakdown, it may also have effects on coagulation and platelets. Plasmin activates coagulation factors V and VIII⁶,⁷ and increases thrombin generation⁶. Plasmin stimulates platelet aggregation, degranulation, complement activation and platelet activation⁶,⁸,⁹,10. If these effects are mediated via lysine binding sites then it is possible that they might be affected by TXA administration. We conducted a sub-study within the WOMAN trial to investigate the effects of TXA on coagulation and platelets.

Objective
To assess the effects of TXA treatment on endogenous thrombin potential (ETP) and platelet function. If plasmin activation increases ETP and stimulates platelet activation, we would expect TXA to reduce ETP and inhibit platelets.

Methods and study design
The full ETAPlaT protocol is available from 11.

Study design and participants
We conducted a sub-study within the WOMAN trial, an international randomized, parallel-group, double blinded, placebo-controlled trial. The study included adult women with primary PPH. The PPH diagnosis was based on the visual estimation of blood loss (>500 mL after vaginal birth or ≥1,000 mL after caesarean birth or blood loss sufficient to cause hemodynamic instability). In addition to the usual treatment for PPH, women were randomized in the study as soon as possible after informed consent had been obtained. The main criterion for eligibility was the uncertainty of clinician to use or not use TXA in a particular woman diagnosed with PPH. The study was carried out according to the guidelines of good clinical practice¹² and adhered to the regulatory requirements for Albania.

Ethical approvals for the study were obtained from the London School of Hygiene and Tropical Medicine (LSHTM) and the National Ethics Committee in Tirana, Albania. Brief information about the study was given to pregnant women. All eligible women underwent the informed consent procedure for the WOMAN trial as well as for the ETAPlaT sub-study before randomization. The detailed consent procedure is reported at the ETAPlaT protocol¹³. The ETAPlaT study was carried out at the Obstetric Gynaecology University Hospital “Koço Gliozheni” in Tirana, Albania. There are approximately 4500 deliveries per year in this hospital, which offers tertiary level health care and is a referral centre for other maternity hospitals at the country.

Randomization and blinding
Women with PPH, who fulfilled the eligibility criteria and completed the consent procedures, were randomized in the study and were allocated to receive either TXA or placebo. ETAPlaT as a sub-study of WOMAN trial utilised the same randomization and blinding procedures. In summary, the trial treatment packs were identical, so both patients and healthcare workers were blinded to treatment allocation. Each box contained eight individual treatment packs, each pack contained two doses of study drugs (one dose contained: 2 vials each TXA 500mg-5 mL, or 2 vials each 5 mL sodium chloride 0.9%). The packs were used in sequential order by the caregiver starting from the lowest numbered pack.

Interventions and laboratory procedures
As soon as the patient was randomized in the study, alongside with the usual treatment for PPH, the trial treatment was administered by slow intravenous injection, 1 mL/minute, of 1 gram TXA or placebo. A second dose of study drugs was administered if haemorrhage did not stop after 30 minutes or restart within 24 hours of the first dose.

Baseline blood sample was collected immediately after randomization and before the first dose was administered. Three mL of venous blood was collected in hirudine (25μgr/mL) test tube - double wall (Dynabyte, Munich, Germany) for multiple electrode aggregometry (MEA) and 5 mL in tri-sodium citrate 0.106 mol/l⁻¹ (S-Monovette, Sarstedt, Germany) for coagulation tests. The same procedure for blood collection was performed at 30±15 minutes after the first dose study drug administration. Follow-up blood collection procedure was performed always before administration of the second dose of study treatment, if it was needed.

Baseline and follow-up samples were analysed for platelet function (ADPtest and TRAPtest) performing MEA with Multiplate. Details of methods used for ADPtest have been previously reported¹⁴ and for TRAPtest¹⁴. All material used for TRAPtest and ADPtest including Multiplate equipment, were obtained from the manufacturer (Dynabyte GmbH, Munich, Germany). The recorded platelet aggregation measured by MEA was expressed as area under curve (AUC) AU*min. The platelet function analysis using MEA was performed by the laboratory at Hospital “KoçoGliozheni” in Tirana, Albania.

The blood samples obtained in 5 mL in sodium citrate test tubes for coagulation analysis were immediately centrifuged at 3000xg for 20 min. The acquired platelet poor plasma was divided in two aliquots and preserved in deep freeze (-80°C)
The laboratory analysis at the end of the study. The coagulation tests were performed at the Institute of Laboratory Medicine, German Heart Centre in Munich, Germany. The thrombin generation assay (TGA) was performed with Calibrated Automated Thrombogram (Stago Deutschland GmbH). The coagulation factors V, VIII, von Willebrand, Fibrinogen (Claus method) and D-Dimer were analyzed with SIEMENS BCS XP Coagulation Analyzer, using reagents FV and FVIII deficient plasma, Multifibrin* U fibrinogen reagent, BC von Willebrand reagent and INNOVANCE® D-Dimer reagent, all reagents were obtained from Siemens Healthcare Diagnostic Products GmbH, Marburg, Germany.

Outcomes
The primary outcome was the change (baseline versus follow-up) in ETP. Secondary outcomes included the change (baseline versus follow-up) in platelet function (ADP test and TRAP test) and coagulation factors V, VIII, von Willebrand, Fibrinogen, D-Dimer on baseline and follow-up blood samples. Thrombin generation was chosen as the primary outcome because it is a surrogate for coagulation activity and factors that increase thrombin formation can potentially increase thrombotic risk.

Statistical analysis
The statistical analysis plan to the ETAPlat Study was published and reviewed before database lock. The study evaluates the effect of TXA compared to placebo by quantifying the change over time (baseline minus follow-up) in the primary outcome ETP and a series of secondary outcomes. The study therefore compares the changes between baseline and follow up in the TXA and placebo groups (the difference in the differences).

We compared before and after changes in coagulation parameters between treatment groups using repeated measurement ANOVA. An intention-to-treat analysis was performed by using analysis of covariance (ANCOVA) with adjustment of baseline measurement as well as adjustment of the length of time between two blood sample collection (30±15 minutes). The same analysis was carried out for secondary outcomes. Site monitoring, source data verification and trial master file review was carried out by the Sponsor and data management was performed by LSHTM using a bespoke electronic system.

Results
Recruitment to the ETAPlat sub-study started on November 2013 and finished on January 2015, with final follow-up completed in March 2015. During this time 187 patients were randomized to receive TXA (n=93) or placebo (n=94). Of these 17 patients in TXA group and 31 in placebo group received a second dose of TXA or placebo. We were unable to collect baseline or follow up blood samples as emergency situation was ongoing in six patients and these patients were excluded from the analyses.

![Diagram: WOMAN ETAPlat trial Consort Flowchart.](https://example.com/flowchart.png)

* Patients for whom there is no information on the primary endpoint.

(2 patients had missing baseline and follow-up thrombin potential measurements, 3 patients with missing baseline thrombin potential, and 1 patient with missing follow-up thrombin potential)
The baseline data for TXA and placebo groups were similar (Table 1). One patient (TXA group) was known to have von Willebrand disease. The main cause of PPH in both groups was uterine atony. In the TXA group, the median (mean) time difference between both samples is 31.00 (32.98) minutes. In the placebo group, the median (mean) time difference between both samples is 30.00 (31.74) minutes. In TXA group, the minimum (maximum) time difference between both samples is 20.00 (45.00) minutes. In placebo group, the minimum (maximum) time difference between both samples is 15.00 (63.00) minutes. There is no evidence that time differences differ between both treatment groups (Wilcoxon-Mann-Whitney-Test, \( p = 0.1336 \)).

**Primary outcome - results**

The change in ETP (expressed in nM*min) between baseline and follow-up was 43.2 (95%CI, -16.6 to 103.1) in the TXA treated group and 4.6 (95%CI, -51.4 to 60.6) in the placebo group. The difference in differences (DiD) of 36.63 (TXA minus Placebo) was not statistically significant (\( p_{raw} =0.350, \) 95%CI \( raw, -42.9 \) to 120.0). The detailed values are given in Table 2.
Table 2. Effect of TXA on primary and secondary endpoints.

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>Follow-Up Mean (SD)</th>
<th>Baseline/Follow-Up Mean Difference (95% CI)</th>
<th>DID: TXA / Placebo groups Mean DID (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ETP (nM*min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TXA (N=87)</td>
<td>1537 (375.9)</td>
<td>1494 (369.1)</td>
<td>43.2 [-16.6; 103.1]</td>
<td>36.63 [-42.9; 120.0] p raw = 0.350**</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=94)</td>
<td>1491 (378.7)</td>
<td>1487 (390.5)</td>
<td>4.6 [-51.4; 60.6]</td>
<td>29.81 [-47.8; 107.4] p adj = 0.453**</td>
<td></td>
</tr>
<tr>
<td><strong>ADP test (AU*min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TXA (N=89)</td>
<td>1043.0 (343.6)</td>
<td>964.7 (312.4)</td>
<td>78.0 [15.4; 140.6]</td>
<td>13.2 (-65.8; 92.2) p raw = 0.7*</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=91)</td>
<td>961.6 (339.6)</td>
<td>896.8 (356.8)</td>
<td>64.8 (15.8; 113.7)</td>
<td>-0.9 (-72.7; 70.9) p adj = 1.0**</td>
<td></td>
</tr>
<tr>
<td><strong>TRAP test (AU*min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TXA (N=89)</td>
<td>1199 (362.3)</td>
<td>1070 (336.8)</td>
<td>85.3 (31.2; 139.4)</td>
<td>20.9 (-65.3; 107.1) p raw = 0.6*</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=91)</td>
<td>1156 (347.9)</td>
<td>970 (336.8)</td>
<td>78.8 (28.7; 128.7)</td>
<td>1.5 (-72.8; 75.7) p adj = 1.0**</td>
<td></td>
</tr>
<tr>
<td><strong>Factor V (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TXA (N=88)</td>
<td>103.4 (27.7)</td>
<td>95.9 (25.7)</td>
<td>0.1 (-4.6; 4.8)</td>
<td>-4.2 (-10.0; 1.7) p raw = 0.2*</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=94)</td>
<td>100.2 (28.5)</td>
<td>95.9 (25.7)</td>
<td>0.1 (-4.6; 4.8)</td>
<td>-4.9 (-10.4; 0.7) p adj = 0.1**</td>
<td></td>
</tr>
<tr>
<td><strong>Factor VIII (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TXA (N=88)</td>
<td>221.9 (102.4)</td>
<td>209.7 (98.5)</td>
<td>5.4 (-9.2; 21.2)</td>
<td>5.9 (-13.9; 25.6) p raw = 0.6*</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=94)</td>
<td>195.2 (87.0)</td>
<td>195.2 (87.0)</td>
<td>0.0 (-12.7; 12.7)</td>
<td>-0.9 (-18.6; 17.6) p adj = 1.0**</td>
<td></td>
</tr>
<tr>
<td><strong>Factor vW (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TXA (N=88)</td>
<td>216.3 (98.9)</td>
<td>202.2 (91.5)</td>
<td>2.7 (-15.5; 17.2)</td>
<td>-0.4 (-16.6; 19.5) p raw = 1.0*</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=94)</td>
<td>212.6 (92.6)</td>
<td>212.6 (92.6)</td>
<td>0.0 (-12.7; 12.7)</td>
<td>-0.1 (-14.6; 13.5) p adj = 0.9**</td>
<td></td>
</tr>
<tr>
<td><strong>Fibrinogen (g/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TXA (N=87)</td>
<td>3.64 (1.09)</td>
<td>3.59 (1.07)</td>
<td>0.05 (-0.1; 0.2)</td>
<td>-0.08 (-0.29; 0.12) p raw = 0.4*</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=93)</td>
<td>3.49 (1.2)</td>
<td>3.49 (1.1)</td>
<td>0.0 (-0.2; 0.2)</td>
<td>-0.09 (-0.28; 0.1) p adj = 0.4**</td>
<td></td>
</tr>
<tr>
<td><strong>D-Dimer (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TXA (N=88)</td>
<td>7.4 (9.3)</td>
<td>7.4 (9.3)</td>
<td>0.0 (-0.1; 0.1)</td>
<td>0.9 (-1.3; 3.0) p raw = 0.4*</td>
<td></td>
</tr>
<tr>
<td>Placebo (N=94)</td>
<td>9.6 (24.6)</td>
<td>9.6 (24.6)</td>
<td>1.2 (-3.4; 0.8)</td>
<td>1.5 (-2.1; 3.1) p adj = 0.1**</td>
<td></td>
</tr>
</tbody>
</table>

Population: Patients were difference could be calculated (N); DID: Difference in Differences
Analysis: * raw (simple 95% CI of DID); ** adjusted for baseline and time between samples

Secondary outcomes - results
Table 2 also summarizes the exploratory results for the secondary outcomes. The change in platelet activity (expressed in AU*min) in the ADP test was larger with TXA (mean change 78.0, 95% CI, 15.4 to 140.6) compared to placebo group (mean change 64.8, 95% CI, 15.8 to 113.7), but with no significant difference in difference (DiD 13.2, 95% CI, -65.8 to 92.2). The mean difference of the TRAP test for the TXA group was 106.2, (95% CI, 38.5 to 174.0) compared to the placebo group 85.3, (95% CI, 31.2 to 139.4). The difference in difference was not significant (DiD -20.9, 95% CI, -65.3 to 107.1). There was no significant DiD between treatment groups for coagulation factors activity (expressed in % of the norm). The results are as follows: factors V DiD -4.2, 95% CI, -10.0 to 1.7, factor VIII DiD 5.9, 95% CI, -13.9 to 25.6, and von Willebrand factor DiD -0.1, 95% CI, -16.9 to 16.0. No significant difference in difference was observed for Fibrinogen, expressed in g/L, (DiD 0.9 with 95% CI, -1.3 to 3.0). Detailed changes in the single treatment groups are presented in Table 2.

Discussion
We found no evidence that tranexamic acid (TXA) has large effects on thrombin generation or platelet function. However, we cannot exclude the possibility of more modest effects. Thrombin plays a crucial role in coagulation and increased thrombin generation is associated with an increased risk of thrombosis. Plasmin has been shown to increase thrombin formation in the blood of healthy volunteers in vitro. An increase in thrombin generation by plasmin was also reported during treatment with tissue plasminogen activators. ETP was decreased about 30% after administration of very effective anticoagulant agents such as low-molecular-weight heparin, in postpartum period soon after caesarean delivery and also during pregnancy at an in-vitro study. In our study there was a small decrease (3%) in ETP with TXA administration (DiD 0.9 with 95% CI, -1.3 to 3.0). Detailed changes in the single treatment groups are presented in Table 2.
not statistically different to that seen in the placebo group. This study provides no evidence TXA has a pro-thrombotic effect.

Plasmin has multifactorial pro-coagulant effects on platelet activation. Activation of platelets may contribute to thrombus formation. The inhibition of fibrinolysis with TXA can help to maintain fibrinogen levels. In our study, the drop in fibrinogen was smaller in the TXA group but the difference was not statistically significant. Once again, these results provide no evidence that TXA has pro-thrombotic effects.

In the last trimester of pregnancy, plasma levels of plasminogen and fibrinogen increase by about 50% whilst levels of plasminogen activator inhibitors 1 and 2 increase 3-fold and 25-fold, respectively. Immediately following delivery there is early fibrinolytic activation and this can be inhibited by TXA. The inhibition of fibrinolysis with TXA has the potential to increase thrombotic risk. By reducing fibrinolysis, TXA can help to maintain fibrinogen levels. In our study, the drop in fibrinogen was smaller in the TXA group but the difference was not statistically significant.

Study limitations

The study was designed to prove a difference (more relevant changes with the use of TXA compared to placebo) and was not planned to establish therapeutic equivalence. There are no predefined therapeutic equivalence bounds which would allow an objective comparison between derived Dd confidence intervals. The study uses a large series of secondary endpoints and multiple testing performed in an explorative setting. In the ETAPlaT study, although we did not measure plasmin directly but evaluated thrombin generation and platelet function as an indirect effect of TXA on plasmin inhibition. Some post-randomization exclusions were performed, because of the emergency situation of PPH it was difficult to collect the baseline or follow up or both blood samples.

Conclusion

Although the inhibition of fibrinolysis with TXA has the potential to increase thrombotic risk, we found no increase in thrombin generation and no increase in platelet activity with TXA.

Ethics approval and consent to participate

Ethical approval for WOMAN ETAPlaT protocol was obtained from the London School of Hygiene and Tropical Medicine Ethics Committee, United Kingdom, and by the National Ethics Committee in Tirana, Albania. ETAPlaT study was undertaken according to local regulatory requirements, and adhered the ICH-GCP guidelines. The consent procedure was approved by each Ethics Committee and is detailed in the previously published WOMAN trial and ETAPlaT protocols. Briefly, consent was obtained from a woman if her physical and mental capacity allowed (as judged by the treating clinician). If a woman was unable to give consent, proxy consent was obtained from a relative or representative (who was not involved in the trial and was approved by the hospital). If a proxy was unavailable, then as permitted by local ethics approval, consent was deferred. When consent was deferred or given by a proxy, the woman was informed about the trial as soon as possible, and consent was obtained for ongoing data collection, if needed.

Data availability

The anonymised data used for this publication is available from the freeBIRD data portal at https://freebird.lshtm.ac.uk/index.php/data-sharing/downloads/etaplat/ following free registration: http://www.doI.org/10.17037/DATA.00000970. Data are available under an Open Data Commons Attribution License (ODC-By) licence.

Reporting guidelines

This study is compliant with CONSORT guideline recommendations.

Grant information

The WOMAN Trial was funded by the Department of Health (UK), grant number HICF-T2-0510-007, the Wellcome Trust, grant number WT094947, the Bill & Melinda Gates Foundation (grant number OPP1095618), and LSHTM (London, UK). An educational grant was given by Erasmus Mundus program ERAWEB [D2.12.048] and Rudolf Marx Foundation (Munich, Germany).

The Sponsor (LSHTM) and the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.


29. CONSORT statement. accessed online on January 2019. Reference Source