Tranexamic acid for the prevention of blood loss after cesarean among women with twins: a secondary analysis of the TRAnexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery randomized clinical trial

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Tranexamic Acid for the Prevention of Blood Loss after Cesarean Among Women With Twins. A Secondary Analysis of the TRAAP2 Randomized Clinical Trial

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Disclosure statement: Dr. Sentilhes reports receiving lecture and consulting fees from Ferring, and lecture fees from Bayer, GSK and SIGVARIS. Dr Daniel reports receiving lecture and consulting fees from LFB. No other potential conflict of interest relevant to this article was reported.

Funding Statement: The TRAAP2 trial was funded by the French Ministry of Health under its Clinical Research Hospital Program (PHRC, 2015, PHRC-15-0011).

Trial registration: ClinicalTrials.gov Identifier: NCT03431805.

Word count of the abstract: 291

Word count of the main text: 2949

Condensation

Among women with a multiple pregnancy and cesarean delivery, prophylactic tranexamic acid did not reduce the incidence of any blood loss-related outcomes.

Short title: Tranexamic acid for the prevention of blood loss after cesarean among women with twins

AJOG at a Glance:

A. Why was this study conducted?

The magnitude effect of prophylactic tranexamic acid at cesarean delivery is unknown in women at high risk of blood loss, including those with multiple pregnancies.

B. What are the key findings?

In this subgroup analysis of a multicenter, double-blind, randomized controlled trial (TRAAP2 trial) that included 319 women with multiple pregnancy, the rates of blood loss-related outcomes did not differ in the tranexamic acid group and the placebo group.

C. What does this study add to what is already known?

These findings do not support superiority of tranexamic acid over placebo for the reduction of any blood loss-related outcomes among women with a multiple pregnancy and cesarean delivery.

Abstract

Background: Although prophylactic tranexamic acid administration at cesarean delivery resulted in a lower incidence of calculated estimated blood loss > 1000 mL or red-cell transfusion by day 2, its failure to reduce the incidence of hemorrhage-related secondary clinical outcomes (TRAAP2 trial) makes its use questionable. The magnitude of its effect may differ in women at higher risk of blood loss, including those with multiple pregnancies.

Objective: To compare the effect of tranexamic acid vs placebo to prevent blood loss at cesarean delivery among women with multiple pregnancies.

Study design: Secondary analysis of the TRAAP2 trial data including 319 women with multiple pregnancies in this double-blind, randomized controlled trial from March 2018 through January 2020 in 27 French maternity hospitals. Women with a cesarean before or during labor at 34 or more gestational weeks were randomized to receive intravenously 1 g of tranexamic acid (n=160) or placebo (n=159), both with prophylactic uterotonics. The primary outcome was a calculated estimated blood loss > 1000 mL or a red blood cell transfusion by 2 days after delivery. Secondary outcomes included clinical and laboratory blood loss measurements.

Results: Of the 4551 women randomized in this trial, 319 had a multiple pregnancy and cesarean delivery, 298 (93.4%) with primary outcome data available. This outcome occurred in 62 of 147 women (42.2%) in the tranexamic acid group and 67 of 152 (44.1%) receiving placebo (adjusted risk ratio, 0.97; 95% CI 0.68-1.38; *P*=.86). No significant between-group differences occurred for any hemorrhage-related clinical outcomes: gravimetrically estimated blood loss, provider-assessed clinically significant hemorrhage, additional uterotonics, postpartum blood transfusion, arterial embolization, and emergency surgery (P>.05 for all comparisons).

Conclusion: Among women with a multiple pregnancy and cesarean delivery, prophylactic tranexamic acid did not reduce the incidence of any blood loss-related outcomes.

Key words: multiple pregnancy, postpartum hemorrhage, prevention, tranexamic acid, cesarean delivery, blood loss

Introduction

Tranexamic acid is an antifibrinolytic acting mainly by inhibiting the fibrinolytic pathway and protecting blood clots from being degraded, thereby promoting hemostasis.[1] In different contexts outside obstetrics, its use has been found to be associated with reductions in the incidence of transfusion for elective surgery[2,3] and of mortality among patients with traumatic extracranial[4] and mild to moderate intracranial bleeding.[5] In obstetrics, its reduction of deaths due to bleeding in women with postpartum hemorrhage, in particular when given soon after delivery,[6] suggests that it may act as a preventive rather than a therapeutic medication on blood loss after childbirth.[1,6-10] Prophylactic tranexamic acid has not been found to reduce blood loss of at least 500 mL after vaginal delivery (TRAAP trial).[11] It did, however, reduce the incidence of a calculated estimated blood loss greater than 1000 mL or red-cell transfusion by day 2 when administered in women with cesarean delivery with a mean between-group difference in calculated blood loss (derived from the preoperative-to-postoperative hematocrit change) of about 100 mL (TRAAP2 trial).[12] Nevertheless, the clinical relevance of this narrow difference is questionable, especially since there were no significant between-group differences in the secondary clinical outcomes (mean gravimetrically estimated blood loss, provider-assessed clinically significant hemorrhage, additional uterotonics, and postpartum blood transfusion). The relevance of the prophylactic use of tranexamic acid at cesarean delivery is thus controversial.[1,10,13-18]

It remains possible that the effects of tranexamic acid differ between women at high and low risk: its preventive impact might be greater in subgroups of women at higher risk of postpartum hemorrhage. Women with multiple pregnancies are a particularly interesting group in this hypothesis since their risk of severe postpartum hemorrhage is four to five times higher than that of women with singleton pregnancies,[19] they give birth more often by cesarean, and no specific prophylaxis is recommended for them.[20] Exploring the impact of tranexamic acid in women with

multiple pregnancies may also contribute to the debate on the value of prophylactic use of tranexamic acid at cesarean delivery.

We therefore investigated whether the administration of tranexamic acid, in addition to a prophylactic uterotonic agent, decreased the incidence of postpartum hemorrhage after cesarean, compared with the uterotonic agent alone, among women with multiple pregnancies.

Methods

Study Design

This study is a non-prespecified secondary subgroup analysis of the women with multiple pregnancy included in the Tranexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery (TRAAP2) trial, a multicenter, randomized, placebo-controlled, double-blind trial with two parallel groups.[12,21] Women expected to deliver by cesarean were randomly assigned to receive tranexamic acid or placebo immediately after delivery, with a uterotonic agent. Details of the trial's rationale and design have previously been published. [12,21] The TRAAP2 trial's protocol was approved by the Northwest VI Committee for the Protection of Research Subjects and the French Health Products Safety Agency. The funder (French Ministry of Health) had no role in the design of the study, the collection, analysis, or interpretation of the data, or the writing of the report. Drs. Sentilhes, Madar, and Deneux-Tharaux take responsibility for the accuracy and completeness of the data, analysis, and fidelity to the study protocol and statistical analysis plan. No company or manufacturer was involved in the trial.

Study population

For the TRAAP2 trial, eligible participants were women aged 18 years and older with a singleton or multiple pregnancy at 34 gestational weeks or more, expected to deliver by cesarean either before or during labor. They were recruited at 27 French maternity hospitals. Women with known or potential increased risks of venous or arterial thrombosis or of bleeding, a history of epilepsy or seizure, a

hemoglobin level ≤ 90 g/L the week before delivery or poor comprehension of oral French were not eligible (Table A details the TRAAP2 trial's exclusion criteria).[12,21] Clinicians provided individual information about the trial to women in late pregnancy. Women confirmed participation and provided written informed consent when the investigator considered that cesarean was likely.

The study reported here includes only the women with a multiple pregnancy randomized in the TRAAP2 trial. Women with singleton pregnancies and randomized in the TRAAP2 trial were excluded.

Randomization and procedures

Randomization and procedures of the TRAAP2 trial have been previously described in detail.[12,21] Briefly, eligible consenting women were randomly assigned in a 1/1 ratio to receive either 1 g of tranexamic acid (purchased at full cost from Sanofi Aventis, Paris, France) or placebo (normal saline, Fresenius Kabi, Sèvres, France). Computerized randomization (in blocks of four) took place centrally through a secure internet facility (Ennov Clinical Software), stratified by trial site and cesarean timing (before or during labor). The blinded products were prepared in numbered and labeled boxes, each containing a 10-mL vial of the study drug (1 g of tranexamic acid or placebo, depending on randomization number). All boxes and vials were identically labeled, with drug packs differentiated only by treatment number. Neither participants nor investigators were aware of group assignments during the trial.

Clinicians were instructed to administer the intravenous trial regimen slowly (over 30–60 s) during the 3 minutes after birth, after the prophylactic uterotonic (5 or 10 IU oxytocin or 100 micrograms carbetocin, possibly followed by an oxytocin infusion for 2 hours, according to each center's policy) and cord clamping. All these aspects of third-stage management were standardized at each center and adhered to the national guidelines.[22] After the cesarean, women were transferred from the operating room to the postanesthesia care unit (PACU) for at least 2 hours and until clinicians

considered that bleeding had stopped. Gravimetrically estimated blood loss was assessed by measuring the suction volume and swab weight from, among other items, disposable waterproof drapes with pockets that captured blood and amniotic fluid (details in Table B). Women had a venous blood sample taken on day 2 after delivery for outcome assessment. Adverse events were assessed until hospital discharge and by a telephone interview at 3 months postpartum, given the increased thromboembolic risk during this period, compared with women not pregnant within at least the past year.[23]

Study outcomes

For the present study, primary and secondary outcomes in this study are identical to those prespecified and defined in the TRAAP2 trial.[12,21] Thus, the primary outcome was the incidence of postpartum hemorrhage, defined by a calculated estimated blood loss > 1000 mL or a red blood cell (RBC) transfusion by day 2 postpartum.[24] Calculated estimated blood loss = estimated blood volume × (preoperative hematocrit – postoperative hematocrit/preoperative hematocrit (where estimated blood volume (mL) = weight (kg) × 85).[24,25] This quantitative objective estimate of blood loss was chosen because blood loss estimation for cesareans by other subjective methods is limited.[22] Preoperative hematocrit was that most recently measured within 8 days before delivery and postpartum hematocrit that measured closest to day 2 after delivery (without transfusion). Secondary outcomes included clinical and laboratory (blood samples on day 2) measurements of postpartum blood loss,[12,21] adverse events potentially related to tranexamic acid including thromboembolic events up to 3 months after delivery, and maternal satisfaction on day 2. These secondary outcomes are listed in Table B.[21]

The physician responsible for the delivery prospectively recorded the procedures used during the third stage of labor and clinical outcomes identified in the immediate postpartum period. Research assistants, independent of the local medical team, collected all other data from medical charts.

Statistical analysis

The main analysis of the primary and secondary outcomes was performed in the modified intention-to-treat population, which included all women who underwent randomization and had a cesarean delivery, with the exception of those who withdrew consent or were determined to be ineligible after randomization. The safety population included all women who received tranexamic acid or placebo. Primary and secondary analyses were conducted with available data.

Participants' baseline characteristics, management of their third stage of labor, and protocol adherence were described; qualitative variables were expressed as proportions and quantitative variables as either means with standard deviations or medians with interquartile ranges, as appropriate. Effects of tranexamic acid were expressed as risk ratios (RRs) with 95% CIs for categorical outcomes, estimated with Poisson mixed effect models, and as mean differences with 95% CIs for quantitative outcomes, estimated with linear mixed effect models, all models adjusted for center and cesarean timing (before or during labor).[21]

Three subgroup analyses examined the primary outcome in subgroups of women according to the timing of the cesarean delivery (before or during labor), the type of prophylactic uterotonic administered (oxytocin or carbetocin), and the women's postpartum hemorrhage risk status, according to a composite definition (at risk or not at risk) defined as having at least one risk factor with an odds ratio of 3 or greater in the literature - in addition to the fact that all participants were at high risk due to multiple pregnancy-: previous postpartum hemorrhage, pregnancy-related hypertensive disorder, or cesarean delivery during labor.[27]

STATA software v14.1 (StataCorp, College Station, TX) was used for all statistical analyses.

Results

Population

From March 2018 through January 2020, the 27 centers recruited 4551 eligible participants, who were randomly assigned to receive tranexamic acid (2276 women) or placebo (2275); 112 were excluded because they withdrew consent or were ineligible after randomization. Of the remaining 4439 women (intention-to-treat population), 8 had vaginal deliveries, which produced a modified intention-to-treat population of 4431 (2222 in the tranexamic acid group and 2209 in the placebo group) for the TRAAP2 trial. Among them, 319 had multiple pregnancies (160 twins in the tranexamic acid group and 159 twins in the placebo group) and comprised our study population (Figure 1).

Women's baseline characteristics, protocol adherence, and other aspects of third-stage labor management were similar in both groups (Table 1).

Primary outcome

Data on the primary outcome were missing for 13 women in the tranexamic acid group and 7 in the placebo group because of unavailable preoperative or postoperative hematocrit. Postpartum hemorrhage, defined as calculated estimated blood loss > 1000 mL or RBC transfusion by day 2, occurred in 62 of 147 women (42.2%) in the tranexamic acid group and in 67 of 152 (44.1%) in the placebo group (adjusted RR, 0.97; 95% CI, 0.68-1.38; P=.86) (Table 2).

The results of the subgroup analyses are shown in Figure 2. No evidence was observed of differential effects of tranexamic acid by the timing of cesarean delivery (before or during labor), the type of prophylactic uterotonic administered (oxytocin versus carbetocin), or the presence or absence of additional known risk factors for postpartum hemorrhage.

Secondary outcomes

No significant between-group differences were shown in the rates of any hemorrhage-related clinical outcomes: mean gravimetrically estimated blood loss, provider-assessed clinically significant hemorrhage, use of additional uterotonics for excessive bleeding, postpartum blood transfusion, arterial embolization, and emergency surgery (P>.05 for all comparisons). Similarly, there were no significant between-group differences in the rates for blood loss-related laboratory outcomes: mean calculated estimated blood loss and mean peripartum change in hemoglobin and hematocrit (P>.05 for all comparisons) (Table 2).

Adverse events

Neither the incidence rates of vomiting or nausea, dizziness, or kidney function tests on day 2 nor aminotransferase levels on that day differed significantly between the groups (Table 3). Adverse-event data at 3 months after delivery were available for 98.1% of the women. During this period, a thromboembolic event occurred in 0.7% (1/154) of women in the tranexamic acid vs 0% (0/156) in the placebo group (Table 3).

Comparison of primary and secondary outcomes between women with multiple and those with singleton pregnancies in the TRAAP2 trial source population.

The incidence of the primary outcome and the incidences or means of all blood loss-related clinical and laboratory secondary outcomes were higher among the 319 women with multiple pregnancies who comprised this study's population than among the 4112 women of the modified intention-to-treat population of the TRAAP2 trial with singleton pregnancies (P<.05 for all comparisons) (Table C).

Comment

Principal findings

Among women with a multiple pregnancy and a cesarean delivery who received prophylactic uterotonics, the use of tranexamic acid did not significantly reduce the incidence of either the primary outcome ─ calculated estimated blood loss > 1000 mL or red-cell transfusion by day 2 ─ compared with placebo, or of the clinical or laboratory secondary outcomes related to blood loss.

Results in the Context of What is Known

Comparison with the existing literature is challenging because none of the few trials assessing the prophylactic effect of tranexamic acid on blood loss after childbirth that included multiple pregnancies reported results among that specific subgroup.[1,8-10]

While we hypothesized that the prophylactic effect of tranexamic acid, statistically significant but narrow, found for the primary outcome and laboratory secondary outcomes related to blood loss among a general population of women undergoing cesarean delivery (TRAAP2 trial results), might have a greater magnitude in women with multiple pregnancies, who are at increased risk of blood loss, this subgroup analysis provides some evidence against this hypothesis, in particular because no tendency to reduced blood loss-related outcomes was found in favor of tranexamic acid.

Clinical Implications

These results provide additional key findings in the ongoing debate on the relevance of prophylactic tranexamic acid to reduce blood loss among women undergoing cesarean delivery, in general. In particular, they call into question the most recent guidelines from the Royal College of Obstetricians and Gynaecologists, which recommend that obstetricians "consider the use of intravenous tranexamic acid (0.5–1.0 g), in addition to oxytocin, at caesarean section to reduce blood loss in women at increased risk of postpartum hemorrhage"[28] and, to a lesser extent, those

from the United Kingdom's National Institute of Health and Care Excellence (NICE), recommending the use of prophylactic tranexamic acid for any surgical procedure expected to have a blood loss>500 mL.[29]

The relevance of the routine implementation of prophylactic administration of tranexamic acid for all cesareans is currently debated. Arguments in favor of routine use are (1) the finding of a prophylactic effect of tranexamic acid on peripartum hematocrit decrease in the TRAAP2 trial[12,16]; (2) any volume of blood loss even low must be prevented[16] because anemia and postpartum hemorrhage have a potential detrimental effect on woman's postpartum mental health[30-32]; (3) strong evidence coming from different bleeding contexts including postpartum hemorrhage[2-6] demonstrates the effectiveness of tranexamic acid for reducing blood loss or mortality[16]; and (4) meta-analyses of summary data from trials,[33-37] including the last one containing the TRAAP2 trial,[14] have found prophylactic tranexamic acid reduces moderate and severe postpartum hemorrhage and blood transfusion. On the other hand, some argue that (1) the numerous small single-center trials, which have all found a reduction of blood loss-related outcomes with prophylactic tranexamic acid, have significant methodological flaws[1,9,10,38,39] and the results of meta-analyses that aggregate their data[15] are prone to biases[40]; (2) the clinical relevance of the 100-mL reduction of calculated blood loss, in light of the lack of difference for either blood loss-related secondary clinical outcomes or postnatal depression scores found in the TRAAP2 trial, is questionable[1,12,17]; and (3) the gastrointestinal effects of the tranexamic acid are uncomfortable for women in the supine position after cesarean delivery.[17] In addition, other aspects of the use of tranexamic acid need to be studied in greater depth in order to complete the elements necessary for defining a policy. Thus, although tranexamic acid is not expensive, it does have a cost, and a medico-economic analysis would make it possible to support or not its systematic use. Moreover, concern that widespread prophylactic use at cesarean may lead to tranexamic acid being kept at hand on the anesthetic trolley and increase the risk of inadvertent spinal injection, has emerged with

cases of spinal tranexamic acid, sometimes lethal, being reported.[41] Our finding of an absence of impact of tranexamic acid in women with multiple pregnancy is an indirect additional argument for the need to gather further data before considering the routine use of prophylactic tranexamic acid to prevent blood loss for all cesarean deliveries.

Research Implications

Further randomized controlled trials studies are required to determine whether prophylactic tranexamic acid plus a prophylactic uterotonic agent would be associated with a lower incidence of postpartum hemorrhage after cesarean delivery than the uterotonic agent alone in high risk populations, such as women with placenta previa or those with preeclampsia, and to determine whether prophylactic tranexamic acid administration for the prevention of blood loss is cost-effective.

Strengths and Limitations

Our study presents several strengths. It is the first intention-to-treat analysis on multiple pregnancy assessing the effect of prophylactic tranexamic acid on the prevention of blood loss after cesarean delivery, before or during labor. Data came from a large, robust, multicenter, randomized, placebo-controlled, double-blind trial.[12] Blood loss for the primary outcome was assessed with an objective validated calculation based on the change from preoperative to postoperative hematocrit; the latter was measured at most 8 days before delivery to standardize measurement timing and avoid heterogeneity due to possible third-trimester changes. Notably, the volume of blood loss was similar to calculated and gravimetric estimation methods in both groups, and the incidences of all blood loss-related laboratory and clinical outcomes were significantly higher among women with multiple compared with singleton pregnancy, confirming that this study population was at high risk of

postpartum hemorrhage. Finally, women with hemoglobin levels below 90 g/L were excluded to limit the risk of postpartum transfusion without significant blood loss.

This analysis has some limitations. It is a subgroup analysis from a randomized controlled trial with a randomization that was not stratified on multiple pregnancies. Nonetheless, the proportion of women with multiple pregnancies and their characteristics were very similar in the two groups. No prespecified sample size calculation to detect a relevant between-group difference in the incidence of the primary outcome among women with multiple pregnancy was performed, and the study was underpowered to detect potentially meaningful differences in the risk of severe maternal complications. Nonetheless, our sample size was sufficient to show a decrease in the primary outcome related to tranexamic acid corresponding to a RR of 0.66 with a power of 80%, 5% alpha risk, and assessed according to the observed incidence of the primary outcome in the placebo group. In addition, the RR point estimates we found for the primary and main secondary outcomes are all very close to 1, which does not suggest an existing impact that does not reach statistical significance because of limited power.

Conclusion

Among women with multiple pregnancy undergoing cesarean delivery and receiving prophylactic uterotonics, tranexamic acid administration did not result in significantly lower rates than placebo of calculated estimated postpartum blood loss > 1000 mL or of transfusion by day 2, or of blood loss-related secondary clinical or laboratory outcomes.

Acknowledgements

The authors thank the women who participated in the trial and the staff from the participating maternity units: Angers University Hospital, Bicêtre University Hospital, Besançon University Hospital, Bordeaux University Hospital, Caen University Hospital, Centre Hospitalier Inter-Communal de Créteil University Hospital, Clermont-Ferrand University Hospital, Marseille Saint Joseph Hospital, Marseille University Hospital, Montpellier University Hospital, Nancy University Hospital Nantes University Hospital, Nîmes University Hospital, Necker-Enfants Malades Hospital, Paris Saint Joseph Hospital, Poissy/Saint-Germain Hospital, Port-Royal Maternity University Hospital, Pau Hospital, Rennes University Hospital, Robert Debré University Hospital, Rouen University Hospital, Saint-Etienne University Hospital, Schiltigheim University Hospital, Strasbourg University Hospital, Tours University Hospital, Toulouse University Hospital, Trousseau University Hospital,.

The authors want to thank the members of the independent safety monitoring committee: Pr Cyril Huissoud (chair), Pr Sophie Alexander, Pr Hawa Keita-Meyer, and Dr Sophie Gautier. The independent safety monitoring committee met yearly to examine baseline data and adverse events.

The authors thank the clinical research assistants particularly Aurélie Darmaillacq, Aline Bibes, Melissa Charvet, Fatima-Zahra Makhoukhi, Laure Estève, and Elodie Labbé as well as the members of the Department of Clinical Research and Innovation of the Bordeaux University Hospital who worked on this trial (Jérôme Gallet, Bellabes Ghezzoul, Sébastien Marchi, Anne Gimbert, and Jonathan Belcastro).

The authors thank Jo Ann Cahn for her help in editing this manuscript.

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List and titles of figures and tables

Figure 1 – Flowchart of Study Population Selection

Legend:

* All multiple pregnancies were twin pregnancies.

** Pre- and/or postoperative hematocrit were not available.

Figure 2 – Subgroup Analyses of the Primary Outcome: Women with Multiples Pregnancies in the TRAAP2 Trial, Modified Intention-to-Treat Population.

Legend:

Figure 2 shows the risk ratio for postpartum hemorrhage (PPH) (tranexamic acid vs placebo), adjusted for randomization stratification variables (center and timing of cesarean delivery, that is, before or during labor). PPH was defined as a calculated estimated blood loss > 1000 mL or receipt of a red-cell transfusion within 2 days after delivery. Women defined as at risk for PPH were those with one or more risk factors for PPH with an odds ratio of at least 3 in the literature, that is, previous PPH, pregnancy-related hypertensive disorder, or cesarean delivery during labor.27

Table 1 - Characteristics of Participants at Baseline and Management of the Third Stage of Labor: Women with Multiple Pregnancies in the TRAAP2 trial, Modified Intention-to-Treat Population

Table 2 - Primary and Secondary Outcomes in Women with Multiples Pregnancies in the TRAAP2 trial, Modified Intention-to-Treat Population

Table 3 – Adverse Events, Women with Multiple Pregnancies in the TRAAP2 trial, Safety Population

571 **Table 1.** Characteristics of Participants at Baseline and Management of the Third Stage of Labor, Women
572 with Multiple Pregnancies in the TRAAP2 trial, Modified Intention-to-Treat Population*

Characteristic	**Tranexamic acid group (N=160)**	**Placebo group (N=159)**	***P* Value**
Age — yr	33.6±5.0	34.3±4.8	.20
Body-mass index before pregnancy †	25.1±6.0	24.9±6.2	.73
Primiparous — no./total no. (%)	41/160 (25.6)	40/159 (25.2)	.92
Previous cesarean delivery — no./total no. (%)	40/160 (25.0)	48/160 (30.2)	.30
One previous cesarean delivery (%)	29/160 (18.1)	35/159 (22.0)	.39
At least 2 previous cesarean deliveries (%)	11/160 (6.9)	13/159 (8.2)	.66
History of postpartum hemorrhage — no./total no. (%)	5/160 (3.1)	4/159 (2.5)	>.99
Gestational diabetes — no./total no. (%)	22/160 (13.8)	26/159 (16.4)	.52
Gestational hypertensive disorders — no./total no. (%)	14/160 (8.8)	20/159 (12.6)	.27
Hospitalization during pregnancy longer than 24 hours — no./total no. (%)	43/160 (26.9)	39/159 (24.5)	.63
Median gestational age at delivery (IQR) — wk	37 (36-38)	37 (36-38)	.16
Timing of cesarean delivery — no. (%)			.53
Before labor	120 (75.0)	124 (78.0)	
During labor	40 (25.0)	35 (22.0)	
Median duration of cesarean delivery (IQR) — min	35 (30-44)	37 (30-43)	.42
Epidural or spinal anesthesia — no./total no. (%)	156/158 (98.7)	157/159 (98.7)	>.99
General analgesia — no./total no. (%)	8/156 (5.1)	9/156 (5.8)	.80
Induction of labor — no./total no. (%)	26/160 (16.3)	25/159 (15.7)	.90
Oxytocin during labor — no./total no. (%)	30/160 (18.8)	24/159 (15.1)	.38
Prophylactic uterotonic at birth — no./total no. (%)	156/160 (97.5)	157/158 (99.4)	.18
Prophylactic carbetocin at birth	68/160 (42.5)	72/158 (45.6)	.58
Prophylactic oxytocin at birth	89/160 (55.6)	86/158 (54.4)	.83
Median interval between delivery and administration of tranexamic acid of placebo (IQR) — min	3 (2-5)	4 (2-5)	.35
Controlled cord traction — no./total no. (%)	84/142 (59.2)	87/143 (60.8)	.77
Anticoagulant prophylaxis after delivery — no./total no. (%)	114/158 (72.2)	125/157 (79.6)	.12

573 * Plus-minus values are mean ±SD. Data on body-mass index were missing for 1 woman in the placebo
574 group; on duration of cesarean delivery for 11 women in the tranexamic acid group and 14 women in the
575 placebo group; and on interval between delivery and administration of tranexamic acid or placebo for 8
576 and 3, respectively. IQR denotes interquartile range.

577 † The body-mass index is the weight in kilograms divided by the square of the height in meters

Table 2. Primary and Secondary Outcomes in Women with Multiple Pregnancies in the TRAAP2 trial, Modified Intention-to-Treat Population*

Outcome or Event	**Tranexamic acid group (N=160)**	**Placebo group (N=159)**	**Unadjusted Difference (95% CI)†**	**Unadjusted Risk Ratio (95% CI)**	**Adjusted Risk Ratio or Mean Difference (95% CI)‡**	***P* Value§**
Postpartum hemorrhage — no./total no. (%)¶	62/147 (42.2)	67/152 (44.1)	-1.9 (-13.1 to 9.3)	0.96 (0.74to 1.24)	0.97 (0.68 to 1.38)	.86
Calculated estimated blood loss > 1000 mL	60/146 (41.1)	66/152 (43.4)	-2.3 (-13.5 to 8.9)	0.95 (0.73 to 1.23)	0.96 (0.67 to 1.38)	.83
Red-cell transfusion by day 2	11/160 (6.9)	7/159 (4.4)	2.5 (-2.6 to 7.5)	1.56 (0.62 to 3.93)	1.49 (0.56 to 3.93)	.43
Gravimetrically estimated blood loss — mL‖	1186±1169	1283±1264	-96.6 (-404.2 to 211.0)	—	-128.5 (-381.1 to 124.2)	.32
Gravimetrically estimated blood loss category — no./total no. (%)						
> 500 mL	95/122 (77.9)	94/121 (77.7)	0.2 (-10.3 to 10.6)	1.00 (0.88 to 1.15)	1.01 (0.75 to 1.36)	.95
> 1000 mL	70/122 (57.4)	56/121 (46.3)	11.1 (-1.4 to 23.6)	1.24 (0.97 to 1.58)	1.20 (0.83 to 1.73)	.33
Clinically significant postpartum hemorrhage according to health care providers — no./total no. (%)	44/160 (27.5)	49/159 (30.8)	-3.3 (-13.3 to 6.7)	0.89 (0.63 to 1.26)	0.89 (0.59 to 1.35)	.58
Additional uterotonic agents for excessive bleeding — no./total no. (%)	26/160 (16.3)	27/159 (17.0)	-0.7 (-8.9 to 7.4)	0.96 (0.59 to 1.56)	0.96 (0.56 to 1.67)	.89
Blood transfusion — no./total no. (%)	13/160 (8.1)	8/159 (5.0)	3.1 (-2.3 to 8.5)	1.61 (0.69 to 3.79)	1.62 (0.66 to 4.00)	.30
No. of red-cell units transfused	3.5±2.2	4.8±3.7	-1.3 (-3.9 to 1.4)	—	0.5 (-2.0 to 3.0)	.69
Postoperative iron sucrose infusion — no./total no. (%)	14/159 (8.8)	6/158 (3.8)	5.0 (-0.3 to 10.3)	2.3 (0.9 to 5.9)	2.7 (1.0 to 7.0)	.05
Arterial embolization, emergency surgery for postpartum hemorrhage, or hysterectomy — no./total no. (%)**	5/160 (3.1)	1/159 (0.6)	2.5 (-0.5 to 5.5)	4.97 (0.59 to 42.05)	4.27 (0.49 to 37.01)	.19
Transfer to intensive care unit — no./total no. (%)	4/160 (2.5)	6/159 (3.8)	-1.3 (-5.1 to 2.6)	0.66 (0.19 to 2.30)	0.52 (0.15 to 1.85)	.31
Calculated estimated blood loss — mL††	997±1160	1010±1051	-12.8 (-265.0 to 239.4)	—	-16.8 (-263.5 to 229.9)	.89
Calculated estimated blood loss category — no./total no. (%)††						
> 500 mL	98/146 (67.1)	110/152 (72.4)	-5.2 (-15.7 to 5.2)	0.93 (0.80 to 1.08)	0.92 (0.70 to 1.22)	.58

> 1500 mL	33/146 (22.6)	33/152 (21.7)	0.9 (-8.5 to 10.3)	1.04 (0.68 to 1.59)	1.04 (0.63 to 1.72)	.87
Hemoglobin‡‡						
Peripartum change — g/dL	-1.6±1.8	-1.7±1.7	0.07 (-0.34 to 0.47)	—	0.07 (-0.32 to 0.47)	.71
Peripartum decrease >2 g/dL— no./total no. (%)	41/148 (27.7)	50/152 (32.9)	-5.2 (-15.6 to 5.2)	0.84 (0.60 to 1.19)	0.86 (0.56 to 1.32)	.49
Hematocrit††						
Peripartum change — percentage points	-4.9±5.7	-5.0±5.4	0.08 (-1.19 to 1.35)	—	0.14 (-1.10 to 1.39)	.82
Peripartum decrease >10 percentage points — no./total no. (%)	14/146 (9.6)	12/152 (7.9)	1.7 (-4.7 to 8.1)	1.21 (0.58 to 2.54)	1.15 (0.51 to 2.57)	.74

* Plus–minus values are means ±SD. No hypovolemic shock or maternal death occurred in either group. Data on gravimetrically estimated blood loss were not available for 38 women in the tranexamic acid group and 38 in the placebo group; on red-cell units transfused for 147 and 151, respectively; on calculated estimated blood loss for 14 and 7, respectively; on peripartum change in hemoglobin level for 12 and 7, respectively; and on peripartum change in hematocrit for 14 and 7, respectively.

† Differences between the groups are given in percentage points, and differences between mean values in the units of the mean values.

‡ Adjusted risk ratios and adjusted mean differences were estimated with the use of Poisson mixed-effects regression models and linear mixed-effects models, respectively, with systematic adjustment for randomization stratification variables (center and timing of cesarean delivery, that is, before or during labor).

§ All *P* value were related to adjusted risk ratio or mean difference.

¶ Postpartum hemorrhage was defined as a calculated estimated blood loss of greater than 1000 mL or receipt of a red-cell transfusion within 2 days after delivery.

‖ Gravimetrically estimated blood loss was assessed by measuring the suction volume and swab weight from, among other items, disposable waterproof drapes with pockets that captured blood and amniotic fluid. Only data for women enrolled on or after August 7, 2018, are considered (data monitoring before that date showed a lack of reliability).

** In the tranexamic acid group, 1 woman underwent arterial embolization, and 4 a uterus-sparing surgical procedure (vessel ligation or uterine compression suture). In the placebo group, 1 woman underwent a hysterectomy.

†† Preoperative hematocrit was defined as the most recent hematocrit measured in the 8 days before delivery, and postoperative hematocrit as the measurement closest to day 2. For patients who received a transfusion before the blood sample was obtained, the value of the postoperative hematocrit was calculated as the hematocrit on day 2 (%) − (3 × number of units of red cells transfused). Preoperative hematocrit was measured at a mean (±SD) of

36.8±1.5 weeks of gestation in the tranexamic acid group and at 37.0±1.5 weeks in the placebo group. Postoperative hematocrit was measured on day 2 in 144 women (90.6%) in the tranexamic acid and in 135 women (84.9%) in the placebo group and on day 1 or day 3 in 15 (9.4%) and 24 (15.1%), respectively. ‡‡ Preoperative hemoglobin was defined as the most recent hemoglobin level measured in the 8 days before delivery, and postpartum hemoglobin was defined as the measurement closest to day 2. For patients who received a transfusion before the blood sample was obtained, the value of the postpartum hemoglobin was calculated as the value of the hemoglobin on day 2 (in grams per deciliter)−(1 × number of units of red cells transfused).

Table 3. Adverse Events, Women with Multiple Pregnancies in the TRAAP2 trial, Safety Population*

Event or Measure	Tranexamic acid group (N=159)	Placebo group (N=157)	Unadjusted Difference (95% CI)†	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio or Mean Difference (95% CI)‡	*P* Value§
In the operating room or PACU						
Vomiting or nausea — no. (%)	70/159 (44.0)	61/155 (39.4)	4.7 (-6.2 to 15.6)	1.12 (0.86 to 1.45)	1.10 (0.78 to 1.57)	.58
Photopsia — no. (%)¶	0/159 (0)	1/155 (0.7)	-0.6 (-1.9 to 0.6)	—	—	—
Dizziness — no. (%)	10/159 (6.3)	7/155 (4.5)	1.8 (-3.2 to 6.8)	1.39 (0.54 to 3.57)	1.78 (0.61 to 5.15)	.29
Day 2 after delivery‖						
Urea nitrogen — mmol/L	3.6±2.0	3.6±1.6	0.03 (-0.38 to 0.44)	—	0.04 (-0.42 to 0.34)	.83
Creatinine — µmol/L	57.5±12.5	58.9±14.1	-1.4 (-4.5 to 1.6)	—	-2.11 (-5.0 to 0.8)	.15
Alanine aminotransferase >2 × ULN — no. (%)	7/148 (4.7)	2/152 (1.3)	3.4 (-0.4 to 7.2)	3.6 (0.8 to 17.0)	6.6 (0.8 to 54.2)	.08
Aspartate aminotransferase >2 × ULN — no. (%)	6/148 (4.1)	6/152 (4.0)	0.1 (-4.3 to 4.5)	1.03 (0.34 to 3.11)	1.15 (0.34 to 3.85)	.82
Up to 3 mo after delivery						
Completed interviews at 3 mo — no. (%)	154/159 (96.9)	156/157 (99.4)	-2.5 (-5.5 to 0.5)	0.97 (0.95 to 1.01)	0.98 (0.78 to 1.23)	.83
Deep-vein thrombosis or pulmonary embolism — no. (%)**	1/154 (0.7)	0/156 (0)	0.6 (-0.6 to 1.9)	—	—	—

* Plus–minus values are means ±SD. The safety population included 159 women who received tranexamic acid (158 who had been randomly assigned to the tranexamic acid group and 1 who had been randomly assigned to the placebo group), and 157 women who received placebo (all randomly assigned to the placebo group). No retinal vascular occlusion, myocardial infarction, kidney failure treated with dialysis, or seizure occurred in either group. PACU denotes postanesthesia care unit, and ULN upper limit of the normal range.

† Differences between percentages are presented in percentage points, and differences between mean values are given in the units of the mean values.

‡ Adjusted risk ratios and adjusted mean differences were estimated with the use of Poisson mixed-effects regression models and linear mixed-effects models, respectively, with systematic adjustment for randomization stratification variables (center and timing of cesarean delivery, that is, before or during labor).

§ All *P* values were related to adjusted risk ratio or mean difference

¶ Photopsia is the sensation of seeing lights, sparks, or colors.

‖ If no blood sample was available on day 2, blood measures were assessed from a day 3 blood sample, if available. If no blood sample was available from day 2 or 3, blood measures were assessed from a day 1 blood sample, if available. Data on the urea nitrogen level at postpartum day 2 were not available for 9 women in the tranexamic acid group and 10 women in the placebo group, and data on creatinine at postpartum day 2 were not available for 10 women and 6 women, respectively.

** In the tranexamic acid group, 1 woman had pelvic-vein thrombosis (ovarian vein).

4551 Women were enrolled and underwent randomization in the TRAAP2 trial

2276 Were assigned to the tranexamic acid group

2275 Were assigned to the placebo group

50 Were excluded before delivery
44 Met exclusion criteria
6 Withdrew consent

62 Were excluded before delivery
54 Met exclusion criteria
8 Withdrew consent

2226 Underwent vaginal or cesarean delivery
(intention-to-treat population)

2213 Underwent vaginal or cesarean delivery
(intention-to-treat population)

4 Underwent vaginal delivery

4 Underwent vaginal delivery

2222 Underwent cesarean delivery
(modified intention-to-treat population)

2209 Underwent cesarean delivery
(modified intention-to-treat population)

2062 Singleton pregnancies

2050 Singleton pregnancies

319 Women with multiple pregnancies underwent cesarean delivery*

160 With multiple pregnancies underwent cesarean delivery

159 With multiple pregnancies underwent cesarean delivery

13 Had missing value for primary outcome**

7 Had missing value for primary outcome**

147 Were assessed for primary outcome in the
modified intention-to-treat population

152 Were assessed for primary outcome in the
modified intention-to-treat population

Subgroup	No. of patients	Adjusted Risk Ratio (95% CI)
Cesarean delivery before labor	233	0.87 (0.58-1.32)
Cesarean delivery during labor	66	1.16 (0.61-2.20)
Prophylactic oxytocin at birth	159	0.91 (0.56-1.50)
Prophylactic carbetocin at birth	133	0.92 (0.56-1.51)
At risk for PPH	94	1.03 (0.59-1.80)
Not at risk for PPH	205	0.90 (0.58-1.40)