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

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78

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81

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84

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86

87 **Condensation**

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

90

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

93

94 **AJOG at a Glance:**

95 **A. Why was this study conducted?**

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

98 **B. What are the key findings?**

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

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

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

105

106

107 **Abstract**

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

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

115 **Study design:** Secondary analysis of the TRAAP2 trial data including 319 women with multiple
116 pregnancies in this double-blind, randomized controlled trial from March 2018 through January
117 2020 in 27 French maternity hospitals. Women with a cesarean before or during labor at 34 or more
118 gestational weeks were randomized to receive intravenously 1 g of tranexamic acid (n=160) or
119 placebo (n=159), both with prophylactic uterotonics. The primary outcome was a calculated
120 estimated blood loss > 1000 mL or a red blood cell transfusion by 2 days after delivery. Secondary
121 outcomes included clinical and laboratory blood loss measurements.

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

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

131 **Key words:** multiple pregnancy, postpartum hemorrhage, prevention, tranexamic acid, cesarean

132 delivery, blood loss

133

134 **Introduction**

135 Tranexamic acid is an antifibrinolytic acting mainly by inhibiting the fibrinolytic pathway and
136 protecting blood clots from being degraded, thereby promoting hemostasis.¹ In different contexts
137 outside obstetrics, its use has been found to be associated with reductions in the incidence of
138 transfusion for elective surgery^{2,3} and of mortality among patients with traumatic extracranial⁴
139 and mild to moderate intracranial bleeding.⁵ In obstetrics, its reduction of deaths due to bleeding in
140 women with postpartum hemorrhage, in particular when given soon after delivery,⁶ suggests that it
141 may act as a preventive rather than a therapeutic medication on blood loss after childbirth.^{1,6-10}
142 Prophylactic tranexamic acid has not been found to reduce blood loss of at least 500 mL after
143 vaginal delivery (TRAAP trial).¹¹ It did, however, reduce the incidence of a calculated estimated
144 blood loss greater than 1000 mL or red-cell transfusion by day 2 when administered in women with
145 cesarean delivery with a mean between-group difference in calculated blood loss (derived from the
146 preoperative-to-postoperative hematocrit change) of about 100 mL (TRAAP2 trial).¹² Nevertheless,
147 the clinical relevance of this narrow difference is questionable, especially since there were no
148 significant between-group differences in the secondary clinical outcomes (mean gravimetrically
149 estimated blood loss, provider-assessed clinically significant hemorrhage, additional uterotonic,
150 and postpartum blood transfusion). The relevance of the prophylactic use of tranexamic acid at
151 cesarean delivery is thus controversial.^{1,10,13-18}
152 It remains possible that the effects of tranexamic acid differ between women at high and low risk:
153 its preventive impact might be greater in subgroups of women at higher risk of postpartum
154 hemorrhage. Women with multiple pregnancies are a particularly interesting group in this
155 hypothesis since their risk of severe postpartum hemorrhage is four to five times higher than that of
156 women with singleton pregnancies,¹⁹ they give birth more often by cesarean, and no specific
157 prophylaxis is recommended for them.²⁰ Exploring the impact of tranexamic acid in women with

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

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

163

164 **Methods**

165 **Study Design**

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

178 **Study population**

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

183 hemoglobin level \leq 90 g/L the week before delivery or poor comprehension of oral French were not
184 eligible (Table A details the TRAAP2 trial's exclusion criteria).^{12,21} Clinicians provided individual
185 information about the trial to women in late pregnancy. Women confirmed participation and
186 provided written informed consent when the investigator considered that cesarean was likely.
187 The study reported here includes only the women with a multiple pregnancy randomized in the
188 TRAAP2 trial. Women with singleton pregnancies and randomized in the TRAAP2 trial were
189 excluded.

190

191 **Randomization and procedures**

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

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

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

215

216 **Study outcomes**

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

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

233 **Statistical analysis**

234 The main analysis of the primary and secondary outcomes was performed in the modified
235 intention-to-treat population, which included all women who underwent randomization and had a
236 cesarean delivery, with the exception of those who withdrew consent or were determined to be
237 ineligible after randomization. The safety population included all women who received tranexamic
238 acid or placebo. Primary and secondary analyses were conducted with available data.
239 Participants' baseline characteristics, management of their third stage of labor, and protocol
240 adherence were described; qualitative variables were expressed as proportions and quantitative
241 variables as either means with standard deviations or medians with interquartile ranges, as
242 appropriate. Effects of tranexamic acid were expressed as risk ratios (RRs) with 95% CIs for
243 categorical outcomes, estimated with Poisson mixed effect models, and as mean differences with
244 95% CIs for quantitative outcomes, estimated with linear mixed effect models, all models adjusted
245 for center and cesarean timing (before or during labor).²¹
246 Three subgroup analyses examined the primary outcome in subgroups of women according to the
247 timing of the cesarean delivery (before or during labor), the type of prophylactic uterotonic
248 administered (oxytocin or carbetocin), and the women's postpartum hemorrhage risk status,
249 according to a composite definition (at risk or not at risk) defined as having at least one risk factor
250 with an odds ratio of 3 or greater in the literature - in addition to the fact that all participants were at
251 high risk due to multiple pregnancy-: previous postpartum hemorrhage, pregnancy-related
252 hypertensive disorder, or cesarean delivery during labor.²⁷
253 STATA software v14.1 (StataCorp, College Station, TX) was used for all statistical analyses.

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259 **Results**

260 **Population**

261 From March 2018 through January 2020, the 27 centers recruited 4551 eligible participants, who
262 were randomly assigned to receive tranexamic acid (2276 women) or placebo (2275); 112 were
263 excluded because they withdrew consent or were ineligible after randomization. Of the remaining
264 4439 women (intention-to-treat population), 8 had vaginal deliveries, which produced a modified
265 intention-to-treat population of 4431 (2222 in the tranexamic acid group and 2209 in the placebo
266 group) for the TRAAP2 trial. Among them, 319 had multiple pregnancies (160 twins in the
267 tranexamic acid group and 159 twins in the placebo group) and comprised our study population
268 (Figure 1).

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

271 **Primary outcome**

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

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

281

282

283 **Secondary outcomes**

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

291

292 **Adverse events**

293 Neither the incidence rates of vomiting or nausea, dizziness, or kidney function tests on day 2 nor
294 aminotransferase levels on that day differed significantly between the groups (Table 3).

295 Adverse-event data at 3 months after delivery were available for 98.1% of the women. During this
296 period, a thromboembolic event occurred in 0.7% (1/154) of women in the tranexamic acid vs 0%
297 (0/156) in the placebo group (Table 3).

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

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

305

306

307 **Comment**

308 **Principal findings**

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

313 **Results in the Context of What is Known**

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

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

323 **Clinical Implications**

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

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

333 The relevance of the routine implementation of prophylactic administration of tranexamic acid for
334 all cesareans is currently debated. Arguments in favor of routine use are (1) the finding of a
335 prophylactic effect of tranexamic acid on peripartum hematocrit decrease in the TRAAP2 trial^{12,16};
336 (2) any volume of blood loss even low must be prevented¹⁶ because anemia and postpartum
337 hemorrhage have a potential detrimental effect on woman's postpartum mental health³⁰⁻³²; (3)
338 strong evidence coming from different bleeding contexts including postpartum hemorrhage²⁻⁶
339 demonstrates the effectiveness of tranexamic acid for reducing blood loss or mortality¹⁶; and (4)
340 meta-analyses of summary data from trials,³³⁻³⁷ including the last one containing the TRAAP2
341 trial,¹⁴ have found prophylactic tranexamic acid reduces moderate and severe postpartum
342 hemorrhage and blood transfusion. On the other hand, some argue that (1) the numerous small
343 single-center trials, which have all found a reduction of blood loss-related outcomes with
344 prophylactic tranexamic acid, have significant methodological flaws^{1,9,10,38,39} and the results of
345 meta-analyses that aggregate their data¹⁵ are prone to biases⁴⁰; (2) the clinical relevance of the 100-
346 mL reduction of calculated blood loss, in light of the lack of difference for either blood loss-related
347 secondary clinical outcomes or postnatal depression scores found in the TRAAP2 trial, is
348 questionable^{1,12,17}; and (3) the gastrointestinal effects of the tranexamic acid are uncomfortable for
349 women in the supine position after cesarean delivery.¹⁷ In addition, other aspects of the use of
350 tranexamic acid need to be studied in greater depth in order to complete the elements necessary for
351 defining a policy. Thus, although tranexamic acid is not expensive, it does have a cost, and a
352 medico-economic analysis would make it possible to support or not its systematic use. Moreover,
353 concern that widespread prophylactic use at cesarean may lead to tranexamic acid being kept at
354 hand on the anesthetic trolley and increase the risk of inadvertent spinal injection, has emerged with

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

359

360 **Research Implications**

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

367 **Strengths and Limitations**

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

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

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

392 **Conclusion**

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

397

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419

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549 **List and titles of figures and tables**

550 Figure 1 – Flowchart of Study Population Selection

551 Legend:

552 * All multiple pregnancies were twin pregnancies.

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

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

556 Legend:

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

563

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

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

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

570

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 or 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 (0.74 to 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).



