Tranexamic acid for the prevention of postpartum hemorrhage in women undergoing cesarean delivery: an updated meta-analysis

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OBJECTIVE: This study aimed to assess the efficacy and safety of prophylactic tranexamic acid administration vs standard uterotonic agents alone among women undergoing cesarean delivery.

DATA SOURCES: MEDLINE, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Google Scholar were systematically searched from inception to June 30, 2021.

STUDY ELIGIBILITY CRITERIA: Randomized controlled trials comparing intravenous tranexamic acid administration with placebo in women undergoing cesarean delivery and receiving standard prophylactic uterotonic agents were held eligible.

STUDY APPRAISAL AND SYNTHESIS METHODS: The risk of bias of individual studies was appraised with the Risk of Bias 2 tool. Meta-analysis was conducted by fitting random-effects models using restricted maximum likelihood. Subgroup analysis was performed on the basis of country, protocol availability, double-blinding, risk of bias, sample size, and tranexamic acid dose. A 1-stage meta-analysis was performed as a sensitivity analysis. The credibility of outcomes was appraised with the Grading of Recommendations Assessment, Development and Evaluation approach.

RESULTS: Overall, 36 studies with 10,659 women were included. Tranexamic acid administration was associated with significantly lower total blood loss (mean difference, −189.44 mL; 95% confidence intervals, −218.63 to −160.25), lower hemoglobin drop (mean difference, 8.22%; 95% confidence interval, 5.54−10.90), decreased risk of blood loss of >1000 mL (odds ratio, 0.37; 95% confidence interval, 0.22−0.60), transfusion requirement (odds ratio, 0.41; 95% confidence interval, 0.26−0.65), and need of additional uterotonics (odds ratio, 0.36; 95% confidence interval, 0.25−0.52). Subgroup analysis indicated a greater effect of tranexamic acid on total blood loss reduction in low-middle income countries. The outcomes remained stable by separately evaluating women at low bleeding risk. The 1-stage meta-analysis demonstrated similar outcomes with the primary analysis. The quality of evidence was judged to be moderate regarding total blood loss and hemoglobin percentage change and low for the other outcomes.

CONCLUSION: This meta-analysis suggested that prophylactic tranexamic acid administration is effective among women undergoing cesarean delivery in lowering postpartum blood loss and limiting hemoglobin drop. Further research is needed to test its efficacy in high-risk populations and verify its safety profile.

Key words: blood loss, pregnancy, prophylaxis, tranexamic, transfusion

Introduction

Postpartum hemorrhage (PPH) represents a life-threatening pregnancy complication, associated with high rates of maternal morbidity and mortality. The frequency of PPH diagnosis ranges from 1% to 10% of pregnancies affecting approximately 14 million women annually worldwide,[1] although its exact incidence depends on the applied definition criteria.[2] Several risk factors associated with maternal (eg, advanced age, nulliparity, uterine fibroids), gestational (eg, multiple pregnancy, preeclampsia, fetal macrosomia, placenta accreta), and labor (eg, prolonged second stage of labor, episiotomy, retained placenta) characteristics have been recognized[3]; however, an optimal model for PPH prediction is still lacking.[4] Therefore, early identification and prompt initiation of treatment remain the main goals of clinical management to limit the risk of mortality and enhance maternal outcomes. To this end, the prophylactic administration of oxytocin is currently recommended, aiming to promote the contraction of the uterus and reduce blood loss associated with vaginal and cesarean deliveries.[5]

Tranexamic acid (TXA) represents a synthetic competitive lysine receptor inhibitor, which serves as an antifibrinolytic agent by inhibiting plasmin-fibrin interactions and fibrin matrix stabilization.[6] Its administration has been suggested to be able to improve clinical outcomes in patients with trauma[7] and intracerebral hemorrhage[8] and decrease perioperative blood loss in abdominal[9] and orthopedic[10] surgeries. The World Maternal Antifibrinolytic trial[11] has demonstrated that TXA is

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This research was done without patient involvement.

All extracted data are available as supplemental material.

The protocol of the study was registered on June 11, 2021, and is available online (dx.doi.org/10.17504/protocols.io.bvqun5ww).

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AJOG at a Glance

Why was this study conducted?

Postpartum hemorrhage (PPH) is a potentially life-threatening complication of cesarean delivery, necessitating early identification and urgent intervention. Tranexamic acid (TXA) can reduce mortality when administered as a treatment of PPH, although data regarding its preventive effects remain unclear.

Key findings

Prophylactic TXA effectively reduced postpartum blood loss, hemoglobin decline, and transfusion requirements. Preliminary data indicated no increased risk of thromboembolic events. The quality of existing evidence was evaluated as moderate.

What does this add to what is known?

Our meta-analysis provided reinforcing evidence regarding the clinical benefits of TXA, suggesting that its administration in conjunction with standard uterotonics may serve as an effective preventive intervention for women undergoing cesarean delivery.

effective in reducing the risk of death owing to bleeding among women with PPH, without increasing the risk of adverse events. Importantly, the most beneficial outcomes were observed with the earliest administration of TXA within the bleeding onset, proposing that it may exert its action by preventing coagulopathy rather than treating the condition.[12]

Previous meta-analyses[13–15] have suggested the potential use of TXA as a prophylactic agent in women undergoing cesarean delivery, although the applicability of their findings has been limited by the small sample size of the included studies. Knowledge in the field has been enriched by the recent adequately powered Tranexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery (TRAAP2) trial,[16] which sought to assess whether the benefits of routine TXA outweigh its long-term risks. Our meta-analysis aimed to update current clinical evidence and determine the efficacy and safety of prophylactic TXA administration compared with standard uterotonic agents alone among women undergoing cesarean delivery.

Materials and methods

Study design

The meta-analysis was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] The protocol of the study has been prospectively registered and is available online (dx.doi.org/10.17504/protocols.io.bvqun5ww).

Eligibility criteria, information sources, and search strategy

The population of the study consisted of women undergoing cesarean delivery receiving standard uterotonic agent prophylaxis. The intervention of interest was prophylactic intravenous TXA administration and was compared with placebo. The primary endpoint was total blood loss as a continuous variable (in milliliters). The secondary outcomes were blood loss of >1000 mL, red blood cell (RBC) transfusion, need of additional uterotonic agent administration, hemoglobin percentage change, and thromboembolic events. Only randomized controlled trials (RCTs) were held eligible. Quasi-randomized trials, observational studies, conference abstracts, review articles, and in vitro studies were excluded.

The literature search was conducted by systematically searching the following databases: MEDLINE (accessed via PubMed), Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Moreover, Google Scholar was searched to provide gray literature coverage, and the full reference list of the included studies was screened to identify potential missing articles (snowball method). The date of the last search was on June 30, 2021. The search strategy was based on the combination of Medical Subject Headings (MeSH) terms and key words. The main search algorithm was the following: ("Tranexamic Acid"[Mesh] OR tranexamic OR TXA or antifibrinolytic) AND ("Cesarean Section"[Mesh] OR cesarean OR caesarean OR "Postpartum Hemorrhage"[Mesh] OR "postpartum hemorrhage"). No date or language restriction was applied.

Study selection

Studies were selected following 3 consecutive steps. First, the titles and abstracts of all electronic records identified by database search were screened for potential eligibility. Subsequently, all articles that were considered to satisfy the inclusion criteria were retrieved in full text. Next, any study that was found to meet any of the exclusion criteria was not included in the meta-analysis. The process of study selection was performed by 2 researchers, and any discrepancy was resolved after reaching a consensus.

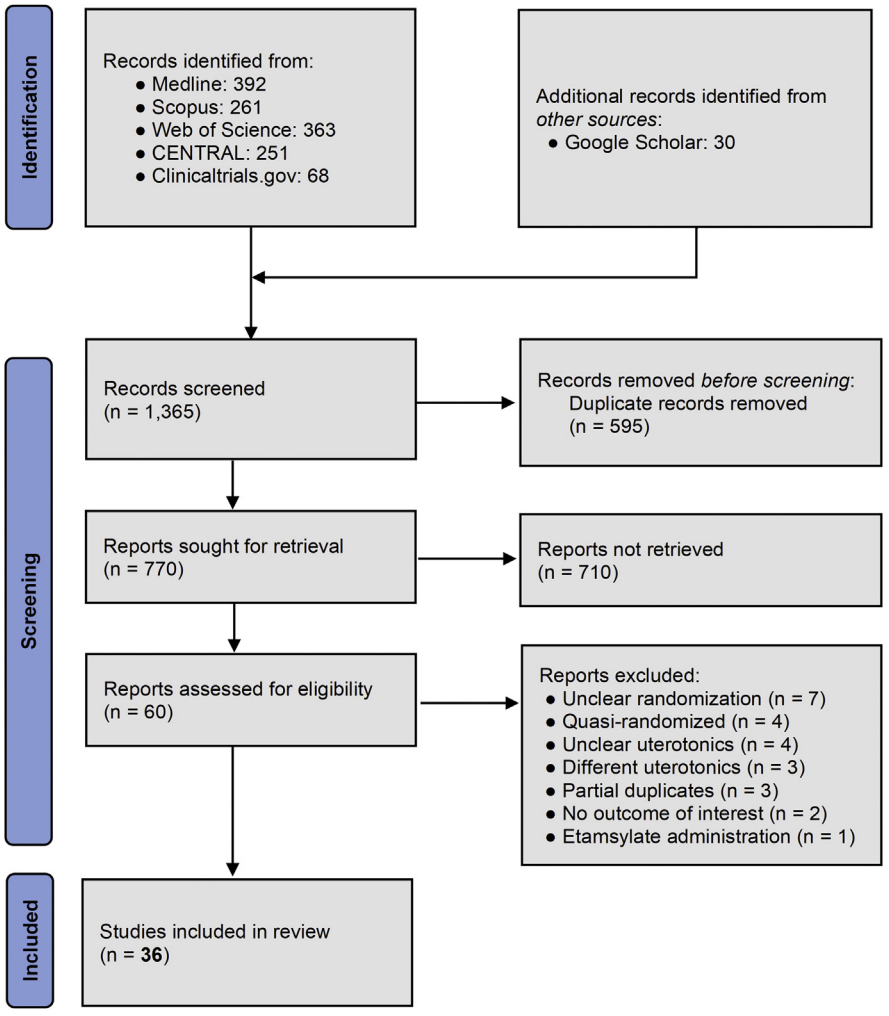
Data extraction

Prepiloted forms were used to extract the following data from each included study: year of publication, country, design, eligibility criteria, type of cesarean delivery (elective or emergent), bleeding risk (low or high), availability of protocol, TXA dose, prophylactic uterotonic agent, patients' number, mean maternal age, gestational age, parity, weight, body mass index, multiple pregnancy, previous cesarean deliveries, and data regarding the primary and secondary outcomes. In case of missing information, the corresponding authors of the original studies were contacted.

Assessment of risk of bias

The methodological quality of the included RCTs was evaluated using the Risk of Bias 2 (RoB-2) tool,[18] taking into account the following domains: randomization, deviations from intended interventions, missing outcome

FIGURE 1
Search plot diagram



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data, measurement of the outcome, and selection of the reported results. The risk of bias was assessed independently by 2 researchers; any possible disagreement was resolved through their consensus.

Data synthesis

Statistical analysis was performed using R software (version 4.0.5; "metafor" package; R foundation for statistical computing, Vienna, Austria).[18] Confidence intervals (CI) were set at 95%. Random-effects models using restricted maximum likelihood were fitted to provided pooled estimates of mean difference (MD) or odds ratio (OR). Heterogeneity was quantified with the inconsistency index (I^2),[19] with I^2>50% indicating significant interstudy heterogeneity. In addition, the 95% prediction intervals were calculated to provide estimates of the effects to be expected by future studies.[20] In case the hemoglobin percentage change was not reported, it was estimated using the delta method.[21] Subgroup analysis was performed on the basis of country (low-middle vs upper-middle or high income), availability of protocol (yes vs no), double-blinding (yes vs no), risk of bias (low vs moderate), sample size (<200 vs ≥200 patients), and TXA dose (1 g vs other). As a sensitivity analysis, estimates were obtained by separately pooling studies, including patients at low risk of bleeding. Publication bias was assessed by the visual inspection of funnel plots and the significance of the Egger regression test (P<.10).[21] Moreover, the potential presence of small-study effects was explored with cumulative meta-analysis sorting studies by sample size from highest to lowest.[22]

To test the robustness of outcomes, a 1-stage meta-analysis was performed to avoid possible concerns regarding hidden normality assumptions and within-study approximations.[23] Specifically, a generalized linear mixed ("hypergeometric normal") model was applied for binary outcomes,[24] whereas a linear mixed model was fitted after reconstruction of pseudo-individual participant data (IPD) for continuous ones.[25]

Quality of evidence

The credibility of outcomes was judged using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach,[26] which evaluates the domains of study limitations, consistency, directness, precision, and publication bias. Specifically, study limitations were assessed according to the RoB-2 evaluation of most studies, whereas consistency was examined by the I^2 values and the agreement of 95% confidence and prediction intervals. Directness referred to whether the interventions and populations of the included studies were appropriate for the research question of the meta-analysis. Precision was judged by taking into account whether clinical decisions may differ if the true effect is at the upper or low end of the 95% CI. The risk of publication bias was assessed by the funnel plot asymmetry and outcomes of cumulative meta-analysis.

Results

Study selection

The literature search process is schematically depicted in Figure 1. After deduplication and initial screening, a total of 60 articles were retrieved as full texts. Of those articles, 24 were excluded for the following reasons: unclear randomization process (n=7),[27–33] quasi-randomized trials (n=4),[34–37] no description of uterotonic agents

TABLE 1
Methodological characteristics of the included studies

Author, year	Country	Sample size	Double-blinding	Public protocol	Elective or emergent	Bleeding risk	Uterotonic agent	Tranexamic acid dose	Timing of intervention	Blood loss quantification	Risk of bias
Gai et al,[61] 2004	China	180	No	No	Elective	Low	Oxytocin	1 g	10 min before incision	Gravimetric	Moderate
Sharma et al,[60] 2010	India	100	No	No	Both	Low	Oxytocin	1 g	5 min before incision	Gravimetric	Moderate
Gungorduk et al,[59] 2011	Turkey	660	Yes	ISRCTN42314355	Elective	Low	Oxytocin	1 g	10 min before incision	Estimated	Low
Movafegh et al,[58] 2011	Iran	100	Yes	No	Elective	Low	Oxytocin	10 mg/kg	20 min before incision	Gravimetric	Low
Abdel-Aleem et al,[58] 2013	Egypt	740	No	ACTRN12612000313831	Elective	Low	Oxytocin	1 g	10 min before incision	Gravimetric	Moderate
Goswami et al,[57] 2013	India	90	Yes	No	Elective	Low	Oxytocin	10-15 mg/kg	10 min before incision	Gravimetric	Low
Sentürk et al,[56] 2013	Turkey	223	Yes	No	Both	Low	Oxytocin	1 g	5 min before incision	Gravimetric	Low
Shahid and Khan,[55] 2013	Pakistan	74	Yes	No	Elective	Low	Oxytocin	1 g	10 min before incision	Gravimetric	Low
Xu et al,[54] 2013	China	174	Yes	No	Elective	Low	Oxytocin plus methylergometrine	10 mg/kg	20 min before incision	Gravimetric	Low
Ahmed et al,[53] 2014	Egypt	124	No	No	Elective	Low	Oxytocin plus ergometrine	10 mg/kg	5 min before incision	Gravimetric	Moderate
Ghosh et al,[86] 2014	India	140	Yes	No	Elective	Low	Oxytocin	1 g	Before incision	Gravimetric	Low
Yehia et al,[85] 2014	Egypt	212	Yes	No	Elective	Low	Oxytocin	1 g	Before incision	Gravimetric	Low
Maged et al,[85] 2015	Egypt	200	No	ACTRN12615000312549	Elective	Low	Oxytocin plus ergometrine	1 g	15 min before incision	Estimated	Moderate
Bhavana et al,[82] 2016	India	200	No	No	Elective	Low	Oxytocin	1 g	Before incision	Gravimetric	Moderate
Lakshmi and Abraham,[81] 2016	India	120	No	No	Elective	Low	Oxytocin	1 g	20 min before incision	Gravimetric	Moderate
Ray et al,[74] 2016	India	100	No	No	Elective	Low	Oxytocin	1 g	20 min before incision	Gravimetric	Moderate
Sujata et al,[63] 2016	India	60	No	CTRI/2015/05/005752	Both	High	Oxytocin	10 mg/kg	10 min before incision	Estimated	Moderate

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(continued)

TABLE 1
Methodological characteristics of the included studies *(continued)*

Author, year	Country	Sample size	Double-blinding	Public protocol	Elective or emergent	Bleeding risk	Uterotonic agent	Tranexamic acid dose	Timing of intervention	Blood loss quantification	Risk of bias
Kamel et al,[52] 2018	Egypt	300	Yes	No	Elective	Low	Oxytocin	1 g	20 min before incision	Gravimetric	Moderate
Milani et al,[51] 2018	Iran	60	Yes	IRCT201405313485N4	Elective	Low	Oxytocin	1 g	15 min before incision	Gravimetric	Moderate
Nargis and Dewan,[64] 2018	Bangladesh	120	Yes	No	Elective	Low	Oxytocin	1 g	After birth	Gravimetric	Low
El-Gaber et al,[62] 2019	Egypt	500	Yes	No	Elective	Low	Oxytocin	1 g	After birth	Gravimetric	Low
El-Sttar et al,[65] 2019	Egypt	150	Yes	No	Elective	Low	Misoprostol	1 g	10 min before incision	Gravimetric	Low
Ifunanya et al,[66] 2019	Nigeria	168	Yes	No	Both	High	Oxytocin	1 g	10 min before incision	Estimated	Low
Obi et al,[68] 2019	Nigeria	115	Yes	No	Elective	Low	Oxytocin	1 g	20 min before incision	Estimated	Low
Shabir et al,[67] 2019	Pakistan	100	No	No	Elective	Low	Oxytocin	1 g	20 min before incision	Gravimetric	Moderate
Hemapriya et al,[70] 2020	India	200	No	No	Both	Low	Oxytocin	10 mg/kg	10 min before incision	Gravimetric	Moderate
Sanad et al,[69] 2020	Egypt	74	No	No	Elective	Low	Oxytocin	1 g	10 min before incision	Estimated	Moderate
Torky et al,[72] 2020	Egypt	120	Yes	No	Elective	Low	Oxytocin	1 g	20 min before incision	Estimated	Low
Adel Nour et al,[71] 2021	Egypt	160	Yes	No	Elective	High	Oxytocin	1 g	15 min before incision	Estimated	Low
Fahmy et al,[68] 2021	Egypt	100	Yes	No	Elective	Low	Oxytocin	2 g	Before incision	Estimated	Low
Jafarbegloo et al,[77] 2021	Iran	50	Yes	IRCT20091010002558N7	Elective	Low	Oxytocin	1 g	10 min before incision	Gravimetric	Low
Naeiji et al,[76] 2021	Iran	200	Yes	IRCT20180819040830N2	Elective	Low	Oxytocin	1 g	Before incision	Gravimetric	Low
Sentilhes et al,[75] 2021	France	4,431	Yes	NCT03431805	Both	Both	Oxytocin or carbetocin	1 g	3 min after birth	Estimated	Low
Soliman et al,[73] 2021	Egypt	100	Yes	No	Elective	Low	Oxytocin	1 g	20 min before incision	Gravimetric	Low

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(continued)

TABLE 1
Methodological characteristics of the included studies *(continued)*

Author, year	Country	Sample size	Double-blinding	Public protocol	Elective or emergent	Bleeding risk	Uterotonic agent	Tranexamic acid dose	Timing of intervention	Blood loss quantification	Risk of bias
Tabatabaie et al,[79] 2021	Iran	60	No	No	Elective	Low	Oxytocin	10 mg/kg	20 min before incision	Gravimetric	Moderate
Halifa et al,[80] 2021	Nigeria	154	Yes	20180402955302	Both	Low	Oxytocin	1 g	10 min before incision	Gravimetric	Low

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(n=4),[38–41] different uterotonic agents in the 2 groups (n=3),[42–44] partial duplicates of studies already included (n=3),[45–47] missing outcome of interest (n=2),[48,49] and etamsylate coadministration (n=1).[50] Therefore, the meta-analysis was based on a cohort of 36 studies,[51–86] comprising 10,659 patients. Of those patients, 5346 were treated with TXA, and 5313 received a placebo.

Study characteristics

The methodological characteristics of the included studies are summarized in Table 1. The median sample size was 132 participants (range, 50−4431). Double-blinding was applied in 23 studies, and a protocol was publicly available for 9 studies. Most studies evaluated women at low bleeding risk undergoing elective cesarean delivery. The most common TXA dose was 1 g intravenously, and oxytocin was used as the prophylactic uterotonic agent in most studies. Blood loss was quantified gravimetrically in 26 studies and was estimated using preoperative and postoperative hematocrit values in 10 studies. The timing of TXA administration ranged from 20 minutes before skin incision to 3 minutes after birth. The trial exclusion criteria are presented in Supplemental Table 1 (Appendix 1), indicating that cases with multiple pregnancy, preterm birth, systemic diseases, or history of coagulation disorders were excluded from most studies. The baseline patients' characteristics are exhibited in Supplemental Table 2 (Appendix 1). The mean participant age ranged from 21.5 to 31.3 years, and the mean gestational age ranged from 37.9 to 39.3 weeks. No significant difference was noted between the 2 groups. The outcomes of the studies regarding the endpoints of interest are presented in Supplemental Table 3 (Appendix 1).

Risk of bias of included studies

The outcomes of the RoB-2 evaluation are presented in Supplemental Figure 1 (Appendix 2). Overall, 21 studies (58.3%) were judged to be at low risk of bias and 15 (41.7%) at moderate risk of bias. Some concerns of bias were raised in the domain of randomization in studies with an unclear description of the allocation concealment process and in the domain of deviation from intended interventions in case of lack of participant and personnel blinding. No high risk of bias was detected in any domain.

Synthesis of Results

Total blood loss

Our meta-analysis indicated that TXA administration was associated with significantly less total blood loss (MD, −189.44 mL, 95% CI, −218.63 to −160.25) than placebo (Supplemental Figure 2, Appendix 3). Heterogeneity was high (I^2, 96.1%), although the 95% prediction interval excluded the null effect, indicating that the expected true effect estimate ranges from −356.33 mL to −22.55 mL (Table 2). Stratified analysis indicated that the association remained significant in all subgroups. The difference between the subgroups was significant in the case of study country (P=.001), demonstrating a greater benefit in studies conducted in low-middle income countries (Figure 2). Table 3 demonstrates the prediction intervals in subgroups, which excluded the null effect in all cases except for the subgroup of studies with an available protocol (95% prediction interval, −367.53 to 9.12). Pooling of studies with patients at low bleeding risk indicated significantly less total blood loss in those treated with TXA (MD, −178.00 mL; 95% CI, −204.94 to −151.06). The funnel plot showed no evident asymmetry (an Egger P value of .241), whereas the cumulative meta-analysis suggested no significant presence of small-study effects (Figure 3). One-stage meta-analysis using pseudo-IPD confirmed the presence of a significant benefit for women treated TXA (MD, −156.27 mL; 95% CI, −175.64 to −136.90). The overall quality of evidence was assessed to be moderate because of downgrading in the domain of consistency (Table 2).

Hemoglobin percentage change

Treatment with TXA was linked to significantly lower hemoglobin

TABLE 2
Summary of findings table

Outcome	Number of studies	Number of patients	Estimate (95% CI)	95% prediction interval	GRADE assessment					
					Study limitations	Consistency	Directness	Precision	Publication bias	Quality of evidence
Blood loss (mL)	36	10,659	−189.44 (−128.63 to −160.25)[a]	(−356.33 to −22.55)[a]	No concerns	Inconsistent	Direct	Precise	Undetected	Moderate ⊕⊕⊕◯
Hemoglobin change (%)	26	4674	8.22 (5.54−10.90)[a]	(−4.77 to 21.21)	No concerns	Inconsistent	Direct	Precise	Undetected	Moderate ⊕⊕⊕◯
Blood loss>1000 mL	10	6867	0.37 (0.23−0.60)[a]	(0.11−1.20)	No concerns	Inconsistent	Direct	Precise	Suspected	Low ⊕⊕◯◯
RBC transfusion	14	7177	0.41 (0.26−0.65)[a]	(0.15−1.13)	No concerns	Inconsistent	Direct	Precise	Suspected	Low ⊕⊕◯◯
Additional uterotonic agents	14	7680	0.36 (0.25−0.52)[a]	(0.13−1.05)	No concerns	Inconsistent	Direct	Precise	Suspected	Low ⊕⊕◯◯

The estimate refers to mean difference for continuous variables and odds ratio for binary variables.

CI, confidence intervals; *GRADE*, Grading of Recommendations Assessment, Development and Evaluation; *RBC*, red blood cell.

[a] The interval excludes the null effect.

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percentage drop (MD, 8.22%; 95% CI, 5.54−10.90) (Supplemental Figure 3, Appendix 3). The estimated heterogeneity was high (I^2, 95.3%), and the 95% prediction intervals ranged from −4.77 to 21.21 (Table 2). No significant difference was noted between the subgroups (Table 4). The 95% prediction intervals of subgroups regarding secondary outcomes are presented in Table 3. Analysis limited to women at low risk of bleeding indicated a significant benefit for those receiving TXA (MD, 7.17%; 95% CI, 5.02−9.32). No funnel plot asymmetry was observed (an Egger P value of .322) (Supplemental Figure 7, Appendix 4). Cumulative meta-analysis indicated that adding small studies did not significantly affect the outcome (Supplemental Figure 8, Appendix 4). A similar significant outcome was obtained through a 1-stage meta-analysis (MD, 7.37%; 95% CI, 6.58−8.16). The credibility of evidence was moderate because of concerns of inconsistency (Table 2).

Blood loss>1000 mL

The rate of PPH (blood loss>1000 mL) was significantly reduced in the TXA group (OR, 0.37; 95% CI, 0.22−0.60) (Supplemental Figure 4, Appendix 3). The interstudy heterogeneity was moderate to large (I^2, 65.6%), and the 95% prediction intervals included the null effect, ranging from 0.11 to 1.20 (Table 2). The subgroup analysis indicated a greater effect in studies with <200 patients (P<.001) (Table 4). The result remained significant in the analysis of low-risk cases (OR, 0.41; 95% CI, 0.28−0.61). The Egger test suggested potential funnel plot asymmetry (P=.043) (Supplemental Figure 9, Appendix 4). Cumulative meta-analysis showed that the addition of small studies may have affected the effect estimate but not the significance of the outcome (Supplemental Figure 10, Appendix 4). One-stage meta-analysis resulted in a similar significant estimate (OR, 0.32; 95% CI, 0.17−0.53). The quality of evidence was judged to be low because of concerns of inconsistency and publication bias.

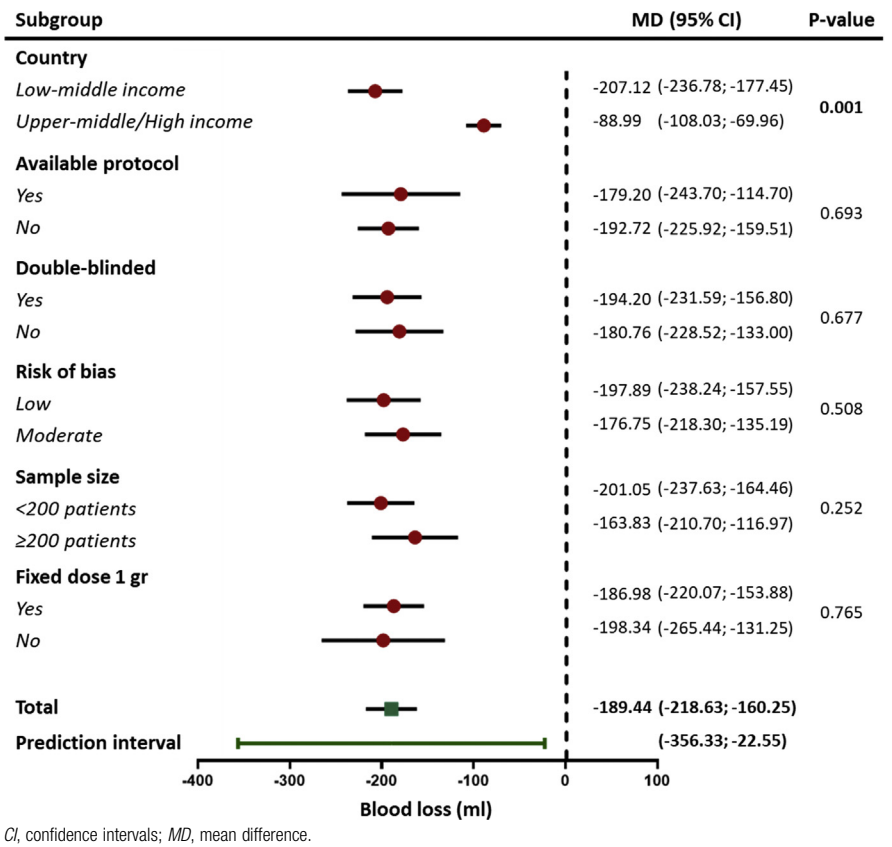
Red blood cell transfusion

The need for RBC transfusion was estimated to be significantly less frequent in women receiving prophylactic TXA (OR, 0.41; 95% CI, 0.26−0.65) than in women receiving placebo (Supplemental Figure 5, Appendix 3). Statistical heterogeneity was small to moderate (I^2, 33.3%), and the 95% prediction interval was wide (range, 0.15−1.13) (Table 2). No significant difference was noted between the subgroups (Table 4). Transfusion risk was significantly lower among women at low bleeding risk (OR, 0.34; 95% CI, 0.21−0.54). Inspection of the funnel plot suggested the presence of asymmetry (an Egger *P* value of .002) (Supplemental Figure 11, Appendix 4); however, no evidence of small-study effects was shown by the cumulative meta-analysis (Supplemental Figure 12, Appendix 4). The 1-stage meta-analysis demonstrated a similar outcome with the 2-stage meta-analysis (OR, 0.38; 95% CI, 0.21−0.60). The credibility of evidence was assessed as low because of downgrading in the domains of inconsistency and publication bias (Table 2).

Additional uterotonic agents

The need for additional uterotonic agents was significantly less common in the TXA arm (OR, 0.36; 95% CI, 0.25−0.52) (Supplemental Figure 6, Appendix 3). Heterogeneity was estimated to be low to moderate (I^2, 68.8%) and the 95% prediction interval ranged from 0.13 to 1.05 (Table 2). The effect estimate was significantly different between the subgroups in the case of study country (*P*=.022), sample size (*P*=.043), and TXA dose (*P*=.017) (Table 4). Funnel plot asymmetry was noted (an Egger *P* value of <.001) (Supplemental Figure 13, Appendix 4), whereas cumulative meta-analysis suggested the impact of small studies on the absolute effect estimate but not on the significance of the outcome (Supplemental Figure 14, Appendix 4). One-stage meta-analysis resulted in a similar outcome (OR, 0.35; 95% CI, 0.24−0.50). The quality of the existing evidence was judged as low because of inconsistency and suspected publication bias (Table 2).

FIGURE 2
Subgroup analysis of the total blood loss outcome



CI, confidence intervals; *MD*, mean difference.

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Thromboembolic events

The outcome of thromboembolic events was assessed qualitatively because of limited data. Xu et al[54] reported a similar risk of deep vein thrombosis between patients treated with TXA (2/88 patients) and patients receiving placebo (2/86 patients) (*P*=.38). Postdischarge follow-up was available in the study of Sentilhes et al,[75] demonstrating that the risk of thromboembolic events does not differ significantly between women in the TXA group (8/2049) and women in the placebo group (2/2056) (*P*=.08).

Comment

Principal findings

This meta-analysis of 36 RCTs comprising 10,659 participants indicated that the prophylactic administration of TXA is associated with significantly lower blood loss in women undergoing cesarean delivery. This effect remained significant in all subgroups of the stratified analysis and in studies that included patients at low risk of bleeding. Analysis of the secondary outcomes revealed that TXA administration was linked to significant benefits regarding hemoglobin drop, risk of PPH, need of transfusion, and additional uterotonic agents. Data regarding the safety of the intervention come mainly from the TRAAP2 trial,[75] suggesting that TXA does not significantly increase the risk of thromboembolic events.

In most studies, TXA was administered at the fixed dose of 1 g, and a weight-adjusted dosing regimen was implemented in 7 trials, typically at the dose of 10 mg/kg. Subgroup analysis demonstrated no significant difference between the 2 strategies regarding blood loss, hemoglobin decline, PPH, and RBC transfusion. Heterogeneity was noted in the outcome of additional uterotonic

TABLE 3
Prediction intervals of subgroups in primary and secondary outcomes, indicating the expected true effect in a new study

Subgroup	Total blood loss (mL)	Hemoglobin change (%)	Blood loss >1000 mL	Red blood cell transfusion	Additional uterotonic agents
Country					
Low-middle income	−362.91 to −69.96[a]	−50.60 to 22.05	0.10−0.88[a]	0.21−0.54[a]	0.13−0.75[a]
Upper-middle or high income	−108.03 to −69.96[a]	2.60−8.20[a]	0.19−1.90	0.11−2.93	0.42−1.18
Available protocol					
Yes	−367.53 to 9.12	−0.71 to 11.55	0.21−1.31	0.09−2.24	0.06−2.41
No	−359.75 to −25.68[a]	−5.36 to 22.98	0.08−0.92[a]	0.22−0.57[a]	0.18−0.63[a]
Double-blinding					
Yes	−367.81 to −20.58[a]	−4.74 to 21.42	0.12−1.26	0.15−1.16	0.16−1.07
No	−347.35 to −14.17[a]	−6.30 to 22.35	0.01−4.59	N/A	0.05−1.12
Risk of bias					
Low	−378.58 to −17.20[a]	−4.88 to 22.84	0.12−1.26	0.15−1.16	0.16−1.07
Moderate	−329.17 to −24.32[a]	−5.87 to 20.46	0.01−4.59	N/A	0.05−1.12
Sample size					
<200 patients	−316.20 to −11.47[a]	−2.57 to 13.55	0.32−1.13	0.16−2.00	0.23−1.29
≥200 patients	−367.83 to −25.26[a]	−5.05 to 24.79	0.10−0.31[a]	0.18−0.51[a]	0.12−0.70[a]
Fixed dose of 1 g					
Yes	−353.76 to −20.19[a]	−3.19 to 19.94	0.12−1.23	0.14−1.27	0.17−0.97[a]
No	−392.49 to −4.20[a]	−11.79 to 26.79	N/A	0.15−0.76[a]	N/A

Estimation of the prediction interval was not feasible in single-study subgroups.

N/A, not applicable.

[a] The 95% prediction interval excludes the null effect.

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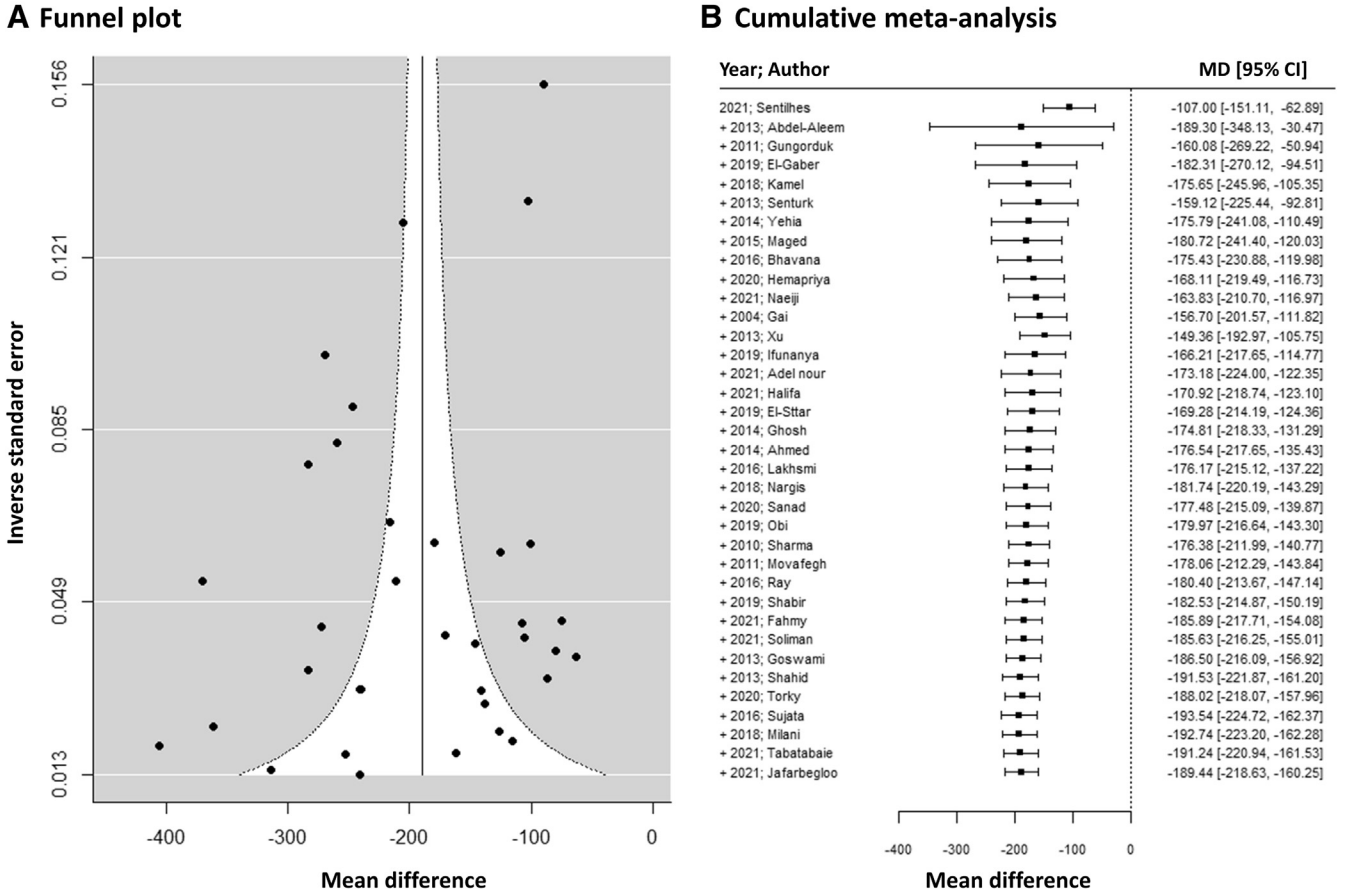
agents, although the effect remained significant in both subgroups. Nonetheless, it should be noted that recent pharmacokinetic and pharmacodynamic data have indicated the lower dose of 600 mg as the optimal one for the prevention of PPH,[87] although the clinical effects of such an approach remain unclear. It is important to state that, in all studies, TXA was administered on top of conventional uterotonics, which are recommended to promote the contraction of the uterus and limit the risk of PPH; oxytocin was the uterotonic of choice in most trials. Moreover, the combination of oxytocin and ergometrine was used in 3 studies.

Analysis of the study country impact demonstrated that pooling of evidence coming from low-middle income countries leads to inflated effects compared with upper-middle or high-income countries concerning the primary outcome of total blood loss, pointing toward a greater benefit from the use of TXA (MD, −207.12 vs −88.99 mL). This discrepancy may reflect a true difference among countries, which should be interpreted in the context of the clinical difficulties of managing PPH in low-resource settings. Alternatively, one may speculate that this difference may indicate the presence of bias because of lower sample sizes and presumed inferior quality of trials in low-middle income countries. However, it should be noted that subgroup analysis showed no significant impact on protocol availability, double-blinding, risk of bias, and sample size. In addition, no evidence of small-study effects and publication bias was observed in either subgroup of countries. No significant influence of study country was noted in the outcomes of hemoglobin drop, PPH, and transfusion requirement.

Comparison with existing literature

Our findings were similar with the outcomes of previous meta-analyses in the field. Specifically, a Cochrane systematic review of 9 trials with 2453 women undergoing cesarean delivery has suggested a significant decrease of PPH with TXA prophylaxis, evaluating the quality of evidence as moderate.[13] Moreover, the meta-analysis of Li et al,[14] including 15 studies with 3353 patients, showed a significant decrease of total blood loss with TXA use (MD, −154.25 mL). Moreover, similar outcomes were obtained by a more recent meta-analysis (21 studies, 3852 participants).[15]

FIGURE 3
Publication bias assessment for the total blood loss outcome



A, The funnel plot shows no asymmetry (P=.241). **B,** Cumulative meta-analysis sorting studies by sample size indicates no evidence of small-study effects.

CI, confidence intervals; *MD*, mean difference.

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Therefore, our meta-analysis confirmed and extended the results of previous ones in the field, by including a significantly larger sample size despite the use of strict eligibility criteria, enabling the exploration of heterogeneity and a more accurate appraisal of evidence quality.

Strengths and limitations

This study has several strengths. A comprehensive literature search was conducted based primarily on 5 databases, and gray literature coverage was ensured by Google Scholar screening. Simultaneously, rigorous inclusion criteria were applied, and thus, none of the meta-analysis studies was judged to be at high risk of bias. Several subgroup analyses were performed, and potential sources of heterogeneity were determined. Furthermore, a 1-stage meta-analysis using pseudo-IPD was implemented as a sensitivity analysis, which avoids the normality assumption of the standard 2-stage analysis, supporting the robustness of outcomes. In contrast, it should be noted that the estimated benefit in blood loss was <100 mL in high-income countries, which although significant is of low clinical importance; hence, other than coagulopathy, other preventable risk factors should be targeted for PPH prevention, such as anemia, infection, and surgical technique. Moreover, secondary outcomes were reported in a smaller number of studies, which raised concerns about publication bias. In addition, the prediction interval of the secondary outcomes was wide, suggesting the existence of uncertainty for the effects to be expected in future populations. It should be noted that postdischarge follow-up was only available in the TRAAP2 trial[75]; hence, data regarding the long-term safety of the intervention remain limited.

Conclusions and implications

PPH accounts for a considerable proportion of preventable maternal morbidity and mortality in low-middle income countries, and its incidence is estimated to rise even in developed regions.[88] Therefore, an effective

TABLE 4
Subgroup analysis of the secondary outcomes

Subgroup	Hemoglobin change (%)	*P* value	Blood loss >1000 mL	*P* value	RBC transfusion	*P* value	Additional uterotonic agents	*P* value
Country								
Low-middle income	8.49 (5.59–11.39)[a]	.527	0.30 (0.17–0.52)[a]	.150	0.33 (0.21–0.54)[a]	.085	0.31 (0.22–0.44)[a]	.022[b]
Upper-middle or high income	5.40 (2.60–8.20)[a]		0.60 (0.29–1.24)		0.57 (0.22–1.47)		0.70 (0.49–1.01)	
Available protocol								
Yes	5.42 (2.42–8.42)[a]	.367	0.52 (0.31–0.87)[a]	.166	0.45 (0.19–1.07)	.274	0.38 (0.17–0.85)[a]	.465
No	8.81 (5.63–11.99)[a]		0.27 (0.13–0.55)[a]		0.35 (0.22–0.57)[a]		0.34 (0.24–0.47)[a]	
Double-blinding								
Yes	8.34 (4.99–11.70)[a]	.908	0.39 (0.23–0.65)[a]	.560	0.42 (0.26–0.67)[a]	.618	0.42 (0.29–0.61)[a]	.181
No	8.02 (3.35–12.69)[a]		0.20 (0.03–1.50)		0.22 (0.02–2.14)		0.24 (0.11–0.54)[a]	
Risk of bias								
Low	8.98 (5.23–12.73)[a]	.550	0.39 (0.23–0.65)[a]	.560	0.42 (0.26–0.67)[a]	.618	0.42 (0.29–0.61)[a]	.181
Moderate	7.29 (3.32–11.27)[a]		0.20 (0.03–1.50)		0.22 (0.02–2.14)		0.24 (0.11–0.54)[a]	
Sample size								
<200 patients	9.87 (6.08–13.66)[a]	.112	0.17 (0.10–0.31)[a]	<.001[b]	0.31 (0.18–0.51)[a]	.052	0.29 (0.19–0.43)[a]	.043[b]
≥200 patients	5.49 (2.77–8.21)[a]		0.60 (0.41–0.87)[a]		0.57 (0.28–1.16)		0.55 (0.35–0.86)[a]	
Fixed dose of 1 g								
Yes	8.38 (5.67–11.08)[a]	.781	0.39 (0.24–0.63)[a]	.204	0.42 (0.25–0.71)[a]	.643	0.40 (0.29–0.56)[a]	.017[b]
No	7.50 (−0.31 to 15.32)		0.05 (0.00–0.95)[a]		0.33 (0.15–0.76)[a]		0.06 (0.02–0.22)[a]	
Total	8.22 (5.54–10.90)[a,b]		0.37 (0.23–0.60)[a,b]		0.41 (0.26–0.65)[a,b]		0.36 (0.25–0.52)[a,b]	

P value refers to the significance of the difference between the 2 subgroups.

RBC, red blood cell.

[a] Values are statistically significat; [b] *P*-vlaue <.05.

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preventive intervention among women undergoing cesarean delivery is expected to yield remarkable benefits and improve the quality of peripartum care. Our meta-analysis indicated that prophylactic TXA on top of routine uterotonics is effective in limiting PPH, without increasing the risk of serious adverse effects. The benefit in terms of total blood loss was estimated to be clinically meaningful, especially for low-middle income countries, a finding requiring further replication. TXA administration has been suggested as a cost-saving intervention when given as prevention in vaginal deliveries[89] or as a treatment in PPH cases[90]; hence, its cost-effectiveness as prophylaxis in women undergoing cesarean delivery remains to be confirmed. Further research is needed to elucidate the effects of TXA in special high-risk populations; to this end, the outcomes of the TRAAPrevia trial,[91] which included women with placenta previa, are expected. Furthermore, it is important to state that future studies exploiting pharmacokinetic and pharmacodynamic data should focus on defining the optimal TXA dosing strategy,[92] and real-world studies with adequate follow-up are needed to shed more light on the risk of thromboembolic events and the influence of the intervention on quality-of-life parameters.

Our meta-analysis suggested that prophylactic TXA administration is effective among women undergoing cesarean delivery in reducing postpartum blood loss and limiting hemoglobin decline. The quality of the existing evidence was evaluated as moderate. Future research should verify the long-term safety of TXA and elucidate its efficacy in high-risk populations. ■

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SUPPLEMENTARY APPENDIX

Contents

Appendix 1: Study Data

1.1. Exclusion criteria

SUPPLEMENTAL TABLE 1
Exclusion criteria of the included studies

Year; author	Exclusion criteria
2004; Gai	Multiple pregnancy; gestational age of <37 weeks; any systemic disease; history of thromboembolic disorders; placenta previa; placental abruption; severe preeclampsia; macrosomia; polyhydramnios; uterine fibroids
2010; Sharma	Multiple pregnancy; gestational age of <37 weeks; history of thromboembolic disorders; polyhydramnios; anemia requiring transfusion; any systemic disease
2011; Gungorduk	Multiple pregnancy; gestational age of <38 weeks; anemia requiring transfusion; antepartum hemorrhage; placenta previa; placental abruption; uterine fibroids; polyhydramnios; history of uterine atony or postpartum bleeding; any systemic disease
2011; Movafegh	Multiple pregnancy; age of <20 or >40 years; gestational age of <38 or >40 weeks; history of thromboembolic disorders; any systemic disease; preeclampsia; macrosomia; polyhydramnios; abnormal placentation; history of cesarean delivery or abdominal surgery
2013; Abdel-Aleem	Multiple pregnancy; gestational age of <37 weeks; preeclampsia; antepartum hemorrhage; history of thromboembolic disorders; polyhydramnios; macrosomia; anticoagulant therapy; any systemic disease
2013; Goswami	Age of <18 years; hemoglobin of <7 or >10 g/dL; history of thromboembolic disorders; anticoagulant therapy; any systemic disease
2013; Sentürk	History of thromboembolic disorders; obesity; uterine fibroids; polyhydramnios; any systemic disease
2013; Shahid	Multiple pregnancy; gestational age of <37 weeks; history of thromboembolic disorders; severe preeclampsia; polyhydramnios; macrosomia; abnormal placentation; anemia requiring transfusion; any systemic disease; parity of >2
2013; Xu	Multiple pregnancy; age of <18 years; multiparity; macrosomia; polyhydramnios; history of bleeding or thromboembolic disorders; any systemic disease
2014; Ahmed	Multiple pregnancy; placenta previa; uterine fibroids; anticoagulant therapy any systemic disease
2014; Ghosh	Age of <20 or >40 years; gestational age of <38 or >40 weeks; multiple pregnancy; history of bleeding or thromboembolic disorders; any systemic disease; macrosomia; polyhydramnios; antepartum hemorrhage; anemia requiring transfusion; severe preeclampsia; previous cesarean delivery
2014; Yehia	Multiple pregnancy; history of bleeding or thromboembolic disorders; macrosomia; polyhydramnios; abnormal placentation; antepartum hemorrhage; any systemic disease
2015; Maged	Multiple pregnancy; gestational age of <37 weeks; any systemic disease; anemia; history of thromboembolic disorders; antepartum hemorrhage; abnormal placentation; history of uterine atony or postpartum bleeding; polyhydramnios; uterine fibroids
2016; Bhavana	Multiple pregnancy; gestational age of <37 weeks; any systemic disease; macrosomia; polyhydramnios; uterine fibroids; previous cesarean delivery; history of thromboembolic disorders; placenta previa; placental abruption
2016; Lakshmi	Multiple pregnancy; age of <19 or >34 years; gestational age of <37 or >42 weeks; history of bleeding or thromboembolic disorders; gestational or chronic hypertension; preeclampsia; any systemic disease; placenta previa; placental abruption; abnormal placentation; polyhydramnios; anemia requiring transfusion; ≥2 previous cesarean deliveries
2016; Ray	Multiple pregnancy; age of <20 or >40 years; gestational age of <37 weeks; history of bleeding or thromboembolic disorders; any systemic disease; anemia requiring transfusion; preeclampsia; polyhydramnios; macrosomia; placenta previa; placental abruption
2016; Sujata	History of bleeding or thromboembolic disorders; urgent cesarean delivery; hemodynamic instability; ischemic heart or kidney disease; anticoagulant therapy
2018; Kamel	Multiple pregnancy; age of <18 or >37 years; gestational age of <37 or >42 weeks; gestational or chronic hypertension; preeclampsia; any systemic disease; history of bleeding or thromboembolic disorders; polyhydramnios; anemia requiring transfusion; ≥2 previous cesarean deliveries; parity of >2

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 1

Exclusion criteria of the included studies *(continued)*

Year; author	Exclusion criteria
2018; Milani	Multiple pregnancy; gestational age of <37 or >40 weeks; any systemic disease; history of bleeding or thromboembolic disorders; severe preeclampsia; abnormal placentation; macrosomia; polyhydramnios; anemia requiring transfusion; intrauterine growth restriction; obesity
2018; Nargis	Multiple pregnancy; age of <18 years; gestational age of <35 weeks; history of thromboembolic disorders; any systemic disease; anticoagulant therapy; history of epilepsy; eclampsia; HELLP syndrome; placenta previa; abnormal placentation; in utero fetal demise
2019; El-Gaber	Multiple pregnancy; gestational age of <37 weeks; history of bleeding disorders; any systemic disease; preeclampsia; polyhydramnios; macrosomia; uterine fibroids; anemia requiring transfusion; placenta previa; placental abruption; intrauterine fetal demise; anticoagulant therapy
2019; El-Sttar	Multiple pregnancy; gestational age of <37 weeks; history of bleeding or thromboembolic disorders; any systemic disease; preeclampsia; polyhydramnios; macrosomia; uterine fibroids; anemia requiring transfusion; placenta previa; placental abruption; antepartum hemorrhage; anticoagulant therapy
2019; Ifunanya	History of thromboembolic disorders; anticoagulant therapy; any systemic disease
2019; Obi	Multiple pregnancy; gestational age of <37 or >42 weeks; history of bleeding or thromboembolic disorders; any systemic disease; antepartum hemorrhage
2019; Shabir	Multiple pregnancy; age of <20 or >40 years; gestational age of <37 weeks; history of bleeding or thromboembolic disorders; preeclampsia; polyhydramnios; macrosomia; placenta previa; placental abruption; anemia requiring transfusion; any systemic disease
2020; Hemapriya	Age of <18 or >35 years; gestational hypertension; antepartum hemorrhage; moderate to severe anemia; any systemic disease; history of bleeding or thromboembolic disorders; polyhydramnios; oligohydramnios
2020; Torky	History of bleeding or thromboembolic disorders; placenta previa
2020; Sanad	Multiple pregnancy; age of <20 or >35 years; gestational age of <37 weeks; multiparity; history of thromboembolic disorders; severe preeclampsia; macrosomia; polyhydramnios; placenta previa; placental abruption; uterine fibroids; anemia requiring transfusion; any systemic disease
2021; Adel Nour	Age of <20 or >40 years; gestational age of <37 or >41 weeks; history of thromboembolic disorders; morbidly adherent placenta
2021; Fahmy	Multiple pregnancy; gestational age of <37 weeks; history of bleeding or thromboembolic disorders; any systemic disease; preeclampsia; polyhydramnios; macrosomia; placenta previa; placental abruption
2021; Jafarbegloo	Multiple pregnancy; gestational age of <38 or >42 weeks; preeclampsia; polyhydramnios; macrosomia; placenta previa; placental abruption; history of bleeding or thromboembolic disorders; anemia; any systemic disease
2021; Naeiji	Multiple pregnancy; gestational age of <37 or >42 weeks; history of bleeding or thromboembolic disorders; any systemic disease; gestational or chronic hypertension; preeclampsia; abnormal placentation; polyhydramnios; aspirin therapy
2021; Sentilhes	Age of <18 years; gestational age of <34 weeks; history of bleeding or thromboembolic disorders; anticoagulant therapy; any systemic disease; history of epilepsy; eclampsia; HELLP syndrome; placenta previa; abnormal placentation; anemia requiring transfusion; cesarean delivery for the second twin or second or third triplets after vaginal birth of the first
2021; Soliman	Multiple pregnancy; age of <18 or >35 years; fetal death
2021; Tabatabaie	Multiple pregnancy; age of <18 or >40 years; gestational age of <37 or >42 weeks; history of bleeding or thromboembolic disorders; preeclampsia; macrosomia; polyhydramnios; abnormal placentation; history of previous cesarean delivery or intra-abdominal surgery; anemia requiring transfusion; any systemic disease; body mass index of >30 kg/m^2; general anesthesia
2021; Halifa	Multiple pregnancy; history of thromboembolic disorders; placenta previa; abnormal placentation; uterine fibroids; previous myomectomy; any systemic disease

HELLP, hemolysis, elevated liver enzymes, and low platelet count.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

1.2. Baseline patients' characteristics

SUPPLEMENTAL TABLE 2

Baseline patients' characteristics of the included studies

Year; author	Age (y)	Gestational age (wk)	Weight (kg)	BMI (kg/m^2)	Primiparity (%)	Parity	Multiple pregnancy (%)	Previous cesarean delivery (%)
2004; Gai	29.7 vs 29.8	38.8 vs 38.7	72.7 vs 71.3	—	100.0 vs 100.0	0 vs 0	0 vs 0	0 vs 0
2010; Sharma	25.6 vs 25.9	39.3 vs 39.1	50.1 vs 50.5	—	—	—	0 vs 0	—
2011; Gungorduk	26.3 vs 26.6	38.7 vs 38.8	—	31.0 vs 31.2	2.4 vs 1.5	—	0 vs 0	97.6 vs 98.5
2011; Movafegh	27.0 vs 27.6	38.9 vs 39.0	—	—	—	—	0 vs 0	0 vs 0
2013; Abdel-Aleem	26.3 vs 26.6	39.3 vs 39.3	—	—	—	1.6 vs 1.6	0 vs 0	40.6 vs 61.1
2013; Goswami	23.2 vs 24.3	—	57.6 vs 57.7	22.6 vs 22.8	—	—	—	—
2013; Sentürk	30.2 vs 29.2	—	75.5 vs 74.2	—	—	—	—	—
2013; Shahid	24.2 vs 24.9	38.3 vs 38.5		—	—	—	0 vs 0	—
2013; Xu	26.7 vs 27.1	38.7 vs 38.8	65.3 vs 66.5	—	100.0 vs 100.0	0 vs 0	0 vs 0	0 vs 0
2014; Ahmed	28.6 vs 26.9	38.5 vs 38.5	—	27.6 vs 28.2	12.9 vs 9.8	—	0 vs 0	80.6
2014; Ghosh	25.9 vs 26.0	38.6 vs 38.7	68.5 vs 67.7	—	—	—	0 vs 0	0 vs 0
2014; Yehia	28.4 vs 28.6	39.1 vs 39.0	—	27.2 vs 27.5	—	2.0 vs 1.8	0 vs 0	—
2015; Maged	24.9 vs 25.3	—	75.8 vs 76.3	—	—	1.0 vs 1.0	0 vs 0	—
2016; Bhavana	—	—	—	—	—	—	0 vs 0	0 vs 0
2016; Lakshmi	26.8 vs 26.8	—	71.4 vs 72.5	29.4 vs 29.1	11.7 vs 11.7	—	0 vs 0	83.3 vs 81.7
2016; Ray	25.0 vs 25.9	38.9 vs 39.0	65.2 vs 64.9	—	66.0 vs 72.0	—	0 vs 0	18.0 vs 22.0
2016; Sujata	29.4 vs 30.3	—	73.2 vs 73.8	28.2 vs 28.7	—	—	7.0 vs 3.0	13.0 vs 7.0
2018; Kamel	29.4 vs 29.8	39.5 vs 39.3	—	—	—	—	0 vs 0	—
2018; Milani	29.3 vs 31.2	37.9 vs 37.9	—	—	—	—	0 vs 0	—
2018; Nargis	25.3 vs 25.7	38.8 vs 38.6	66.6 vs 67.5	—	—	—	0 vs 0	—
2019; El-Gaber	27.1 vs 26.8	38.3 vs 38.2	—	32.9 vs 33.6	—	1.7 vs 1.6	0 vs 0	—
2019; El-Sttar	27.8 vs 28.3	38.2 vs 38.2	—	29.2 vs 29.6	10.7 vs 18.7	—	0 vs 0	—
2019; Ifunanya	28.2 vs 28.6	38.0 vs 38.0	—	25.0 vs 25.0	—	2.0 vs 1.8	2.4 vs 4.8	—
2019; Obi	29.5 vs 28.2	39.6 vs 39.3	77.4 vs 75.4	28.8 vs 29.2	—	1.9 vs 1.5	0 vs 0	64.9 vs 69.0
2019; Shabir	26.0 vs 26.8	38.0 vs 39.0	66.6 vs 64.5	—	—	—	0 vs 0	22.0 vs 18.0
2020; Hemapriya	—	38.3 vs 38.4	—	—	47.0 vs 47.0	—	—	—

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 2

Baseline patients' characteristics of the included studies *(continued)*

Year; author	Age (y)	Gestational age (wk)	Weight (kg)	BMI (kg/m^2)	Primiparity (%)	Parity	Multiple pregnancy (%)	Previous cesarean delivery (%)
2020; Torky	30.7 vs 30.8	—	—	26.9 vs 27.2	—	1.8 vs 1.9	—	—
2020; Sanad	26.1 vs 26.7	39.0 vs 38.7	—	—	100.0 vs 100.0	0 vs 0	0 vs 0	0 vs 0
2021; Adel Nour	27.4 vs 29.5	38.1 vs 37.9	88.7 vs 94.1	—	10.0 vs 12.0	—	7.5 vs 11.3	42.5 vs 42.5
2021; Fahmy	27.6 vs 26.9	—	71.3 vs 71.8	—	0 vs 0	1.0 vs 1.0	0 vs 0	100 vs 100
2021; Jafarbegloo	30.5 vs 31.5	38.2 vs 37.8	64.9 vs 67.7	25.3 vs 26.4	—	1.2 vs 1.13	0 vs 0	—
2021; Naeiji	27.2 vs 27.9	38.7 vs 38.5	—	29.3 vs 28.6	—	—	0 vs 0	52.0 vs 55.0
2021; Sentilhes	33.3 vs 33.5	39.0 vs 39.0	—	26.3 vs 26.1	37.2 vs 36.6	—	7.2 vs 7.2	51.8 vs 52.4
2021; Soliman	21.5 vs 21.5	39.3 vs 39.3	73.9 vs 72.0	29.0 vs 28.2	—	0.7 vs 0.7	0 vs 0	—
2021; Tabatabaie	—	—	—	—	72.0 vs 76.0	—	0 vs 0	0 vs 0
2021; Halifa	31.1 vs 31.4	—	—	—	—	—	0 vs 0	—

Values of continuous variables represent their means. Data express the comparison of results between the tranexamic acid group and placebo group. No significant difference was noted between the 2 groups.

BMI, body mass index.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

1.3. Outcomes of interest

SUPPLEMENTAL TABLE 3
Outcomes of the included studies

Year; author	Number of patients	Total blood loss (mL)	Blood loss >1000 mL	RBC transfusion	Additional uterotonic agents	Hemoglobin before (g/dL)	Hemoglobin after (g/dL)	Hemoglobin change (%)
2004; Gai	91 vs 89	359.29±152.02 vs 439.36±191.48	—	—	—	—	—	—
2010; Sharma	50 vs 50	378.43±39.32 vs 481.39±36.25	—	—	—	—	—	—
2011; Gungorduk	330 vs 330	499.90±206.40 vs 600.70±215.70	7 vs 19	2 vs 7	28 vs 48	—	—	—
2011; Movafegh	50 vs 50	329.60±40.13 vs 545.70±100.30	—	—	—	12.50±1.40 vs 12.80±1.00	11.40±1.50 vs 11.00±1.10	−8.80±15.76 vs −14.06±10.91
2013; Abdel-Aleem	373 vs 367	241.61±126.02 vs 510.70±144.52	2 vs 2	—	1 vs 1	—	—	−1.82±2.93 vs −4.30±3.364
2013; Goswami	60 vs 30	316.00±74.08 vs 527.17±88.67	—	—	—	—	—	—
2013; Sentürk	101 vs 122	272.05±143.23 vs 346.87±189.49	—	—	—	11.06±1.02 vs 11.86±1.32	10.55±0.97 vs 10.52±1.24	−4.61±14.25 vs −11.30±14.38
2013; Shahid	38 vs 36	392.12±145.08 vs 753.85±218.53	—	—	—	9.76±0.85 vs 9.88±1.26	8.67±0.715 vs 8.0±0.94	−11.17±10.65 vs −19.03±14.04
2013; Xu	88 vs 86	379.20±160.10 vs 441.70±189.50	—	8 vs 19	—	12.40±1.30 vs 12.60±1.20	11.30±1.30 vs 11.00±1.40	−8.87±14.18 vs −12.70±13.88
2014; Ahmed	62 vs 62	391.00±48.50 vs 596.70±38.02	—	—	—	11.30±0.90 vs 11.60±0.80	10.30±1.90 vs 9.20±0.70	2.65±10.82 vs −20.69±8.14
2014; Ghosh	70 vs 70	367.80±36.77 vs 627.80±95.15	—	—	12 vs 26	—	—	—
2014; Yehia	106 vs 106	454.50±201.00 vs 737.60±217.00	—	0 vs 2	—	11.80±1.50 vs 11.90±1.20	11.20±1.50 vs 9.60±1.20	−5.08±17.53 vs −19.33±12.96
2015; Maged	100 vs 100	459.40±75.40 vs 700.30±143.90	0 vs 6	—	5 vs 23	11.05±0.7 vs 11.06±0.7	10.03±0.7 vs 9.08±0.6	−9.23±8.56 vs −17.90±7.51
2016; Bhavana	100 vs 100	511.30±164.45 vs 637.90±429.77	—	—	—	11.20±1.28 vs 11.10±1.24	10.50±1.25 vs 9.90±1.14	−6.25±15.47 vs −10.81±14.31

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022. *(continued)*

SUPPLEMENTAL TABLE 3

Outcomes of the included studies *(continued)*

Year; author	Number of patients	Total blood loss (mL)	Blood loss >1000 mL	RBC transfusion	Additional uterotonic agents	Hemoglobin before (g/dL)	Hemoglobin after (g/dL)	Hemoglobin change (%)
2016; Lakshmi	60 vs 60	347.17±108.60 vs 517.72±150.00	—	—	3 vs 9	11.88±0.96 vs 11.94±1.01	11.60±1.28 vs 10.87±1.25	−2.36±13.35 vs −8.96±13.00
2016; Ray	50 vs 50	559.68±113.80 vs 800.91±200.26	—	—	—	10.33±1.26 vs 9.80±1.34	10.08±1.18 vs 8.81±1.18	−2.42±16.50 vs −10.10±17.21
2016; Sujata	30 vs 30	422.00±124.50 vs 827.70±263.10	0 vs 7	1 vs 4	7 vs 25	11.62±1.05 vs 11.84 vs 1.36	10.54±0.99 vs 9.50±1.17	−9.29±11.82 vs −19.76±65.13
2018; Kamel	150 vs 150	332.00±196.20 vs 478.00±234.00	—	—	—	11.90±1.50 vs 11.90±1.20	10.70±1.50 vs 10.20±1.20	−10.08±16.95 vs −14.29±13.28
2018; Milani	30 vs 30	551.80±207.80 vs 713.10±233.10	—	—	—	12.41±1.16 vs 12.77±1.13	11.78±1.0 vs 11.7±1.69	−5.08±11.99 vs −8.38±15.52
2018; Nargis	60 vs 60	409.86±29.79 vs 692.83±95.37	—	0 vs 3	10 vs 24	—	—	—
2019; El-Gaber	250 vs 250	546.84±106.13 vs 793.99±141.21	10 vs 17	5 vs 9	25 vs 42	11.29± 0.97 vs 11.33±1.03	10.81±0.92 vs 10.27±0.89	−4.25±11.58 vs −9.36±11.38
2019; El-Sttar	75 vs 75	501.28±119.20 vs 647.43±178.77	—	0 vs 1	—	12.16±1.28 vs 11.90±1.24	11.44±1.24 vs 9.55±1.18	−5.92±14.21 vs −19.75±12.97
2019; Ifunanya	84 vs 84	450.00±125.00 vs 820.00±118.00	10 vs 42	5 vs 12	6 vs 28	11.10±2.40 vs 12.00±2.60	11.00±1.60 vs 7.80±1.20	−0.90±25.82 vs −35.00±17.27
2019; Obi	57 vs 58	566.80±267.40 vs 819.10±348.40	5 vs 16	2 vs 5	13 vs 25	10.70±0.90 vs 10.80±1.10	9.80±0.70 vs 9.20±0.90	−8.41±10.11 vs −14.81±12.03
2019; Shabir	50 vs 50	561.64±113.79 vs 801.71±200.12	—	—	—	10.33±1.26 vs 9.80±1.34	10.08±1.00 vs 8.81±1.18	−2.42±15.34 vs −10.10±17.21
2020; Hemapriya	100 vs 100	590.50±190.39 vs 696.20±148.18	—	—	—	11.40±0.80 vs 11.30±0.60	10.00±0.80 vs 9.10±0.60	−12.28±9.33 vs −10.10±17.21
2020; Torky	60 vs 60	591.55±162.08 vs 678.37±171.49	3 vs 9	3 vs 9	—	10.81±0.77 vs 10.89±0.84	9.07±1.32 vs 7.74±1.25	−16.10±13.60 vs −28.93±12.72
2020; Sanad	37 vs 37	364.82±24.94 vs 454.50±29.82	—	—	17 vs 27	11.78±1.08 vs 11.88±0.89	11.39±1.08 vs 10.77±0.85	−3.31±12.75 vs −9.34±9.87
2021; Adel Nour	80 vs 80	583.23±379.62 vs 896.81±519.60	—	1 vs 5	11 vs 37	10.90±1.10 vs 11.00±1.00	10.10±1.20 vs 9.20±1.60	−7.34±14.44 vs −16.36±16.41
2021; Fahmy	50 vs 50	416.12±89.95 vs 688.68±134.77	—	—	—	12.63±0.82 vs 12.18±1.08	11.66±0.79 vs 10.53±1.07	−7.68±8.66 vs −13.55±11.45

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

(continued)

SUPPLEMENTAL TABLE 3

Outcomes of the included studies *(continued)*

Year; author	Number of patients	Total blood loss (mL)	Blood loss >1000 mL	RBC transfusion	Additional uterotonic agents	Hemoglobin before (g/dL)	Hemoglobin after (g/dL)	Hemoglobin change (%)
2021; Jafarbegloo	25 vs 25	616.32±176.87 vs 731.45±178.79	—	—	—	—	—	—
2021; Naeiji	100 vs 100	431.10±68.24 vs 556.60±154.23	12 vs 22	5 vs 13	—	12.16±0.46 vs 12.48±0.67	11.77±0.5 vs 11.31±0.56	−3.21±5.51 vs −9.38±6.62
2021; Sentilhes	2222 vs 2209	680.00±748.00 vs 787.00±750.00	550/2084 vs 650/2066	35/2221 vs 30/2209	130/2217 vs 159/2206	—	—	—
2021; Soliman	50 vs 50	430.28±71.03 vs 610.10±90.87	—	—	—	10.36±0.66 vs 10.26±0.76	9.79±0.67 vs 9.22±0.76	−5.50±8.84 vs −10.14±9.96
2021; Tabatabaie	30 vs 30	500.90±102.24 vs 642.07±148.42	—	—	—	—	—	
2021; Halifa	77 vs 77	613.05±195.63 vs 751.17±250.66	—	1 vs 6	12 vs 17	—	—	

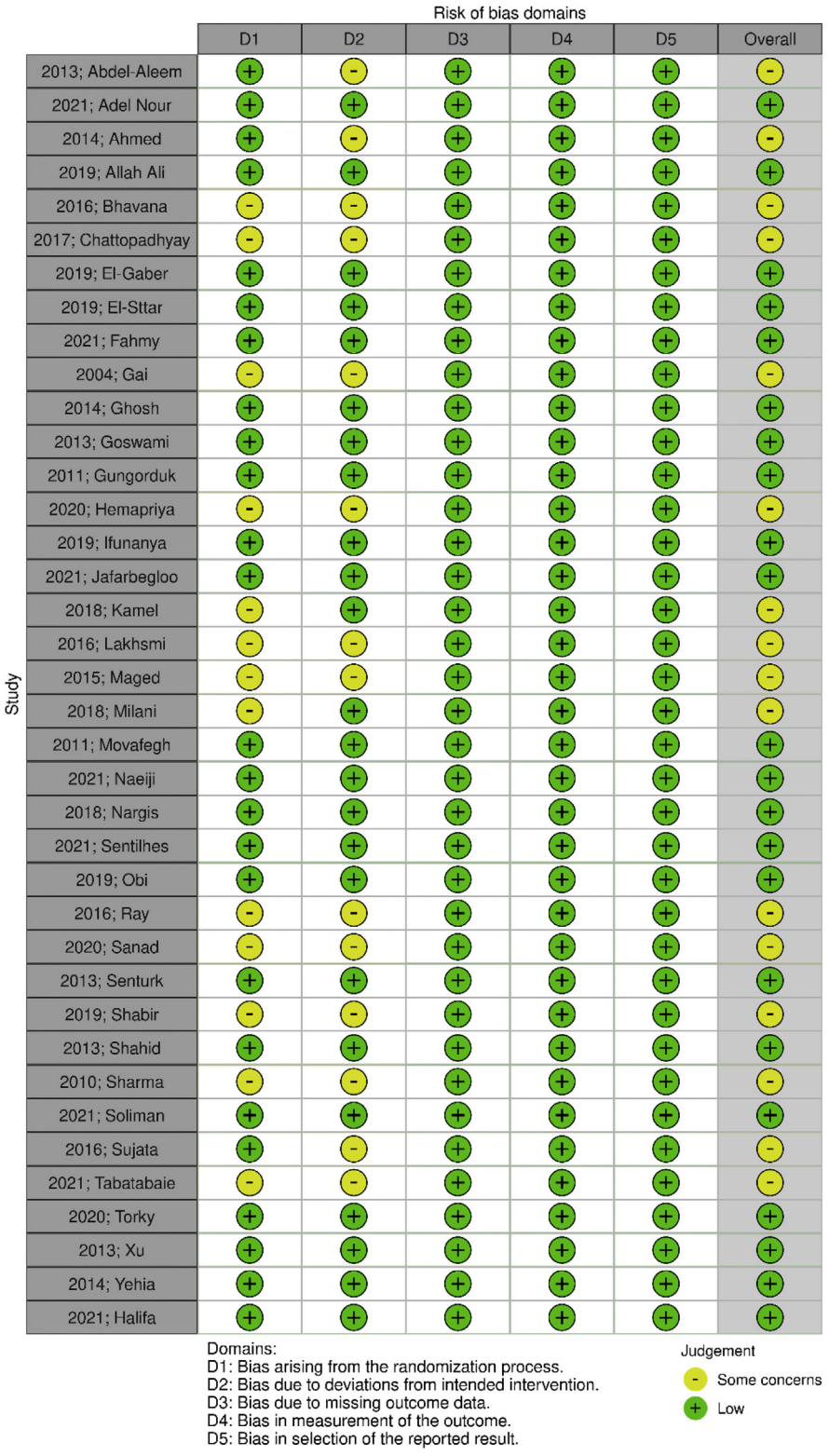
Data express the comparison of results between the tranexamic acid group and placebo group.

RBC, red blood cell.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

Appendix 2: Quality Assessment

SUPPLEMENTAL FIGURE 1
Outcomes of the RoB-2 tool



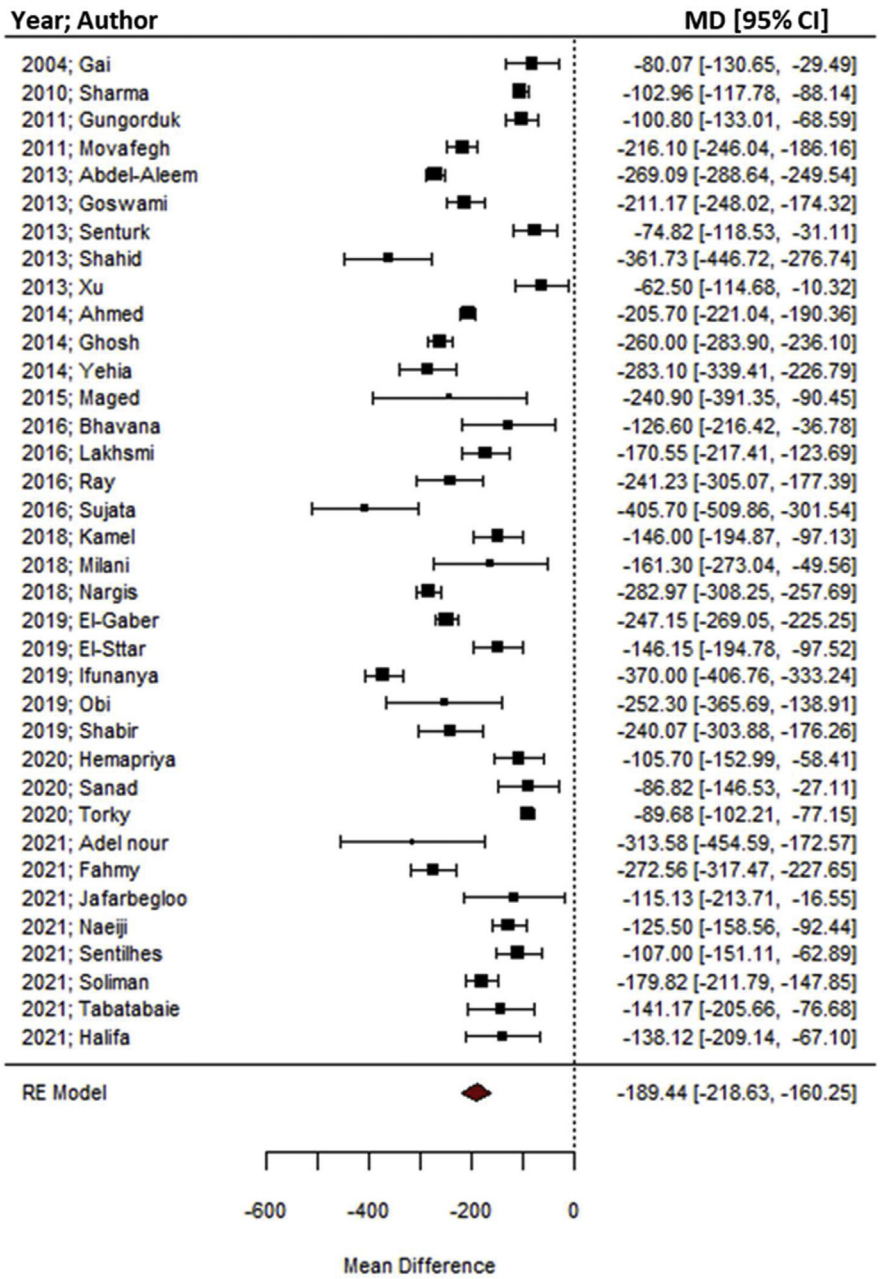
RoB-2 tool, Risk of Bias 2 tool.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

Appendix 3: Forest Plots

3.1. Total blood loss

SUPPLEMENTAL FIGURE 2
Forest plot of the total blood loss outcome

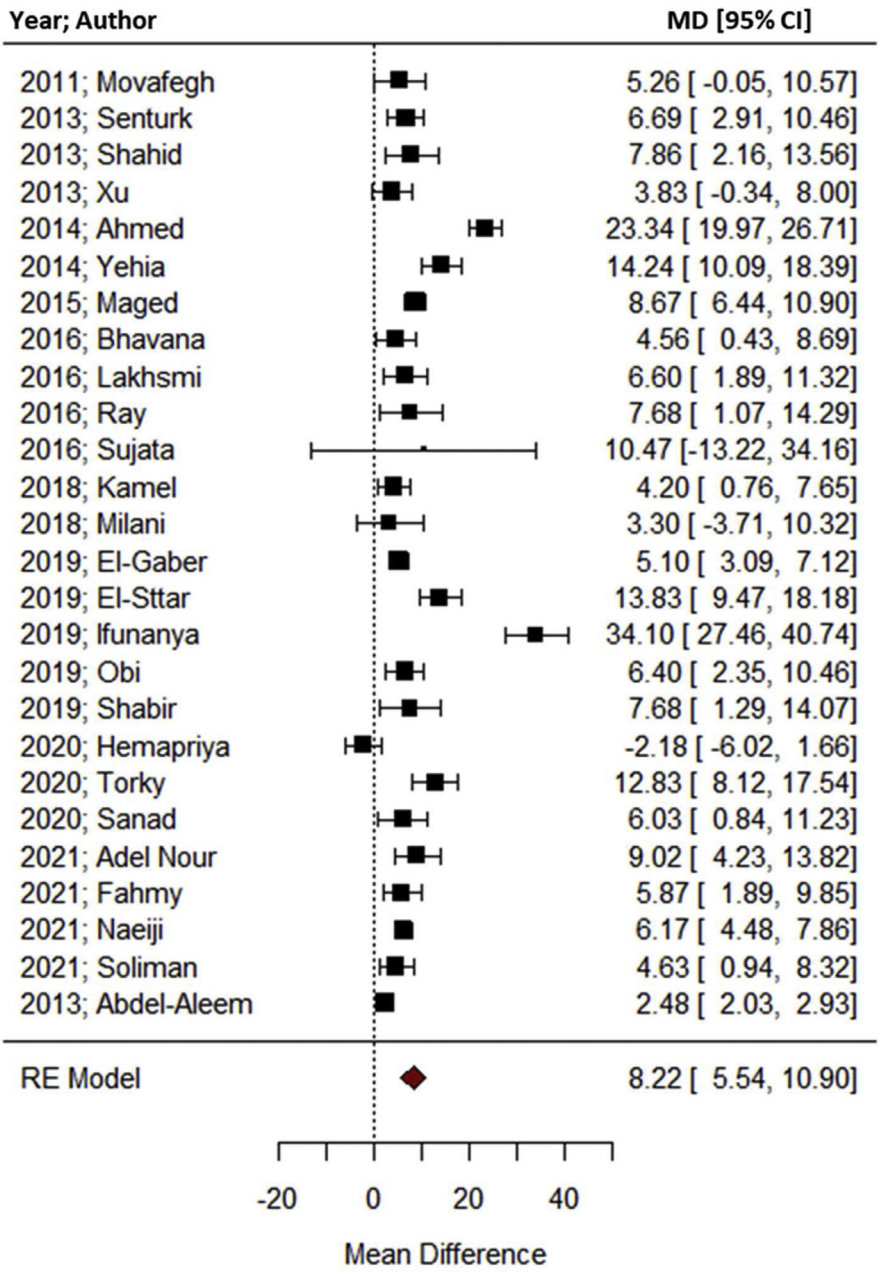


CI, confidence intervals; *MD*, mean difference; *RE*, random effects.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

3.2. Hemoglobin percentage change

SUPPLEMENTAL FIGURE 3
Forest plot of the hemoglobin percentage change outcome

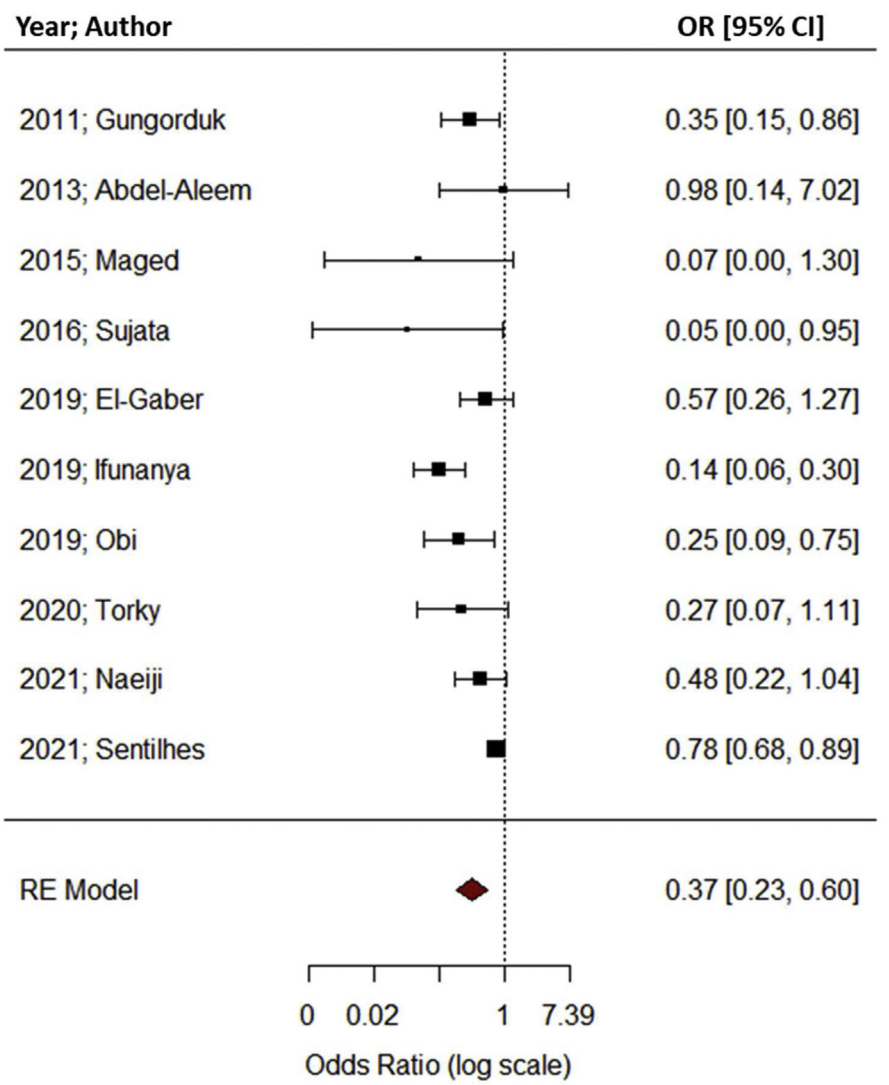


CI, confidence intervals; *MD*, mean difference; *RE*, random effects.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

3.3. Blood loss>1000 milliliter

SUPPLEMENTAL FIGURE 4
Forest plot of the postpartum hemorrhage outcome

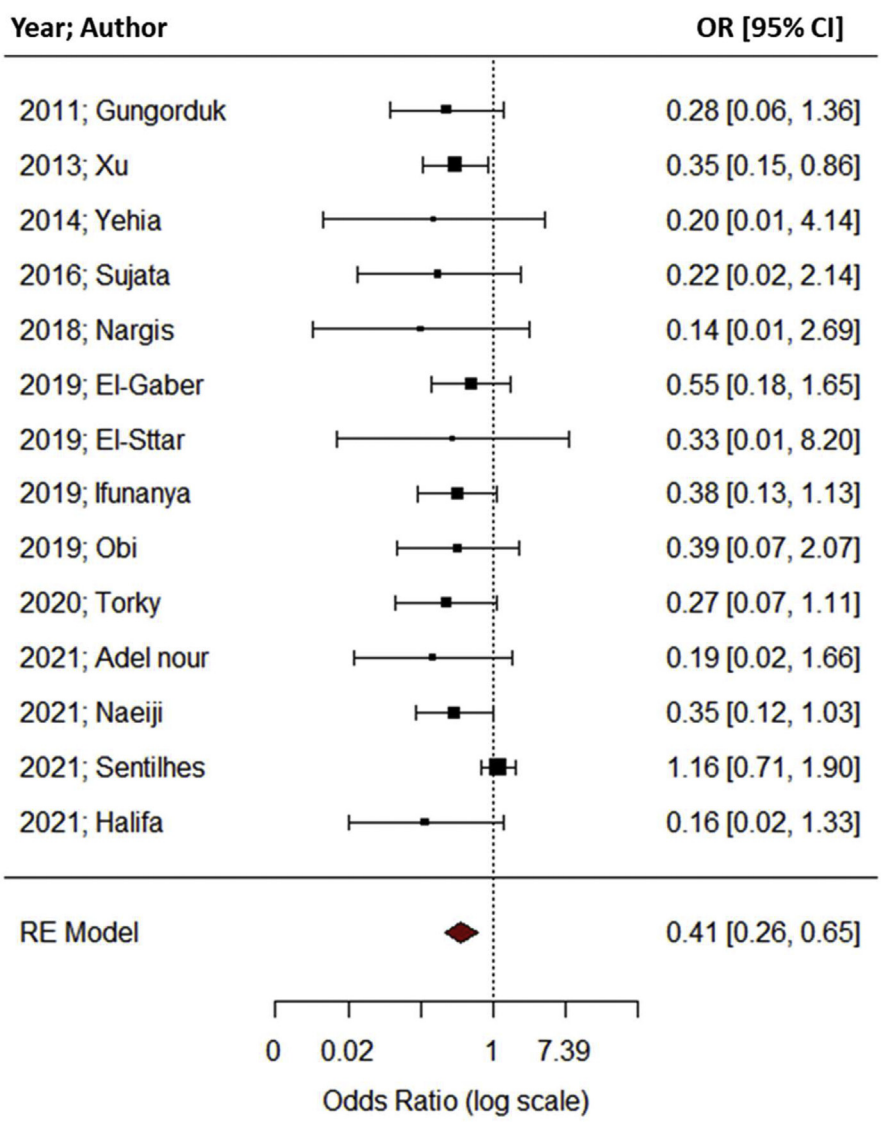


CI, confidence intervals; *OR*, odds ratio; *RE*, random effects.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

3.4. Red blood cell transfusion

SUPPLEMENTAL FIGURE 5
Forest plot of the red blood cell transfusion outcome

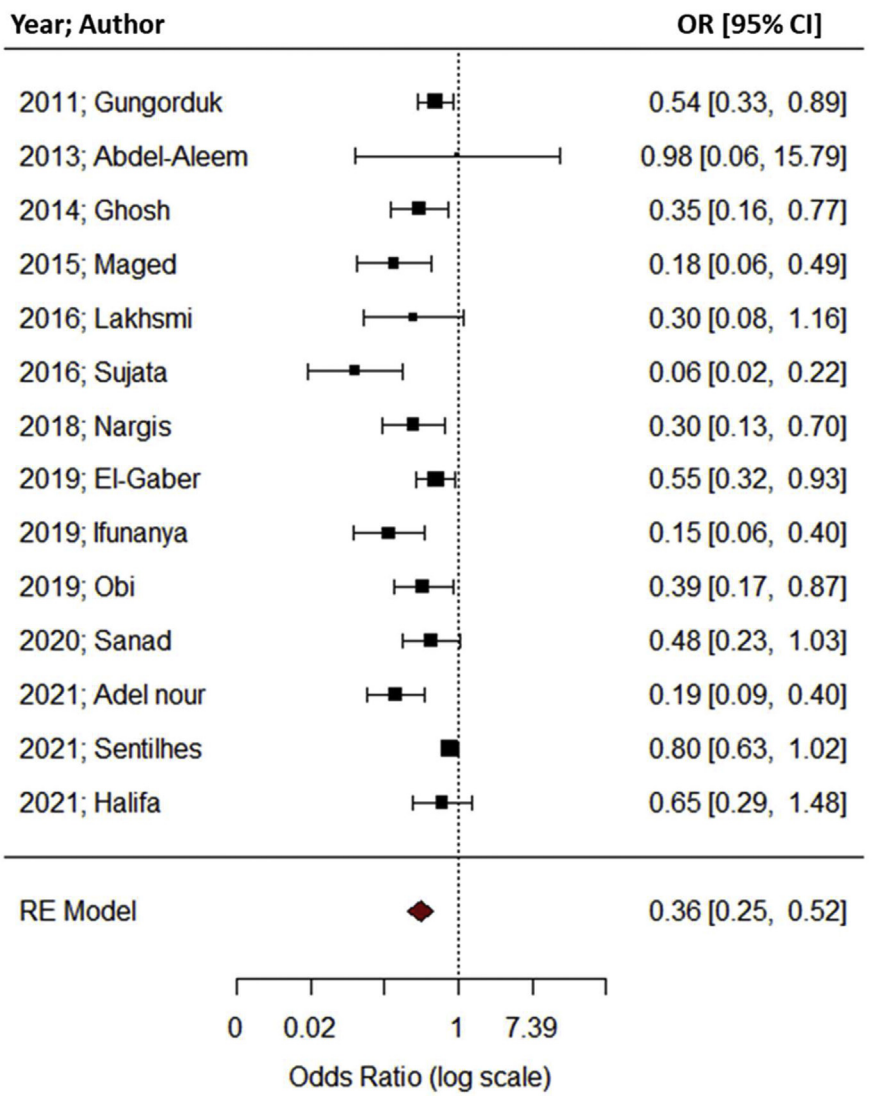


CI, confidence intervals; *OR*, odds ratio; *RE*, random effects.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

3.5. Additional uterotonic agents

SUPPLEMENTAL FIGURE 6
Forest plot of the need of additional uterotonic agents outcome



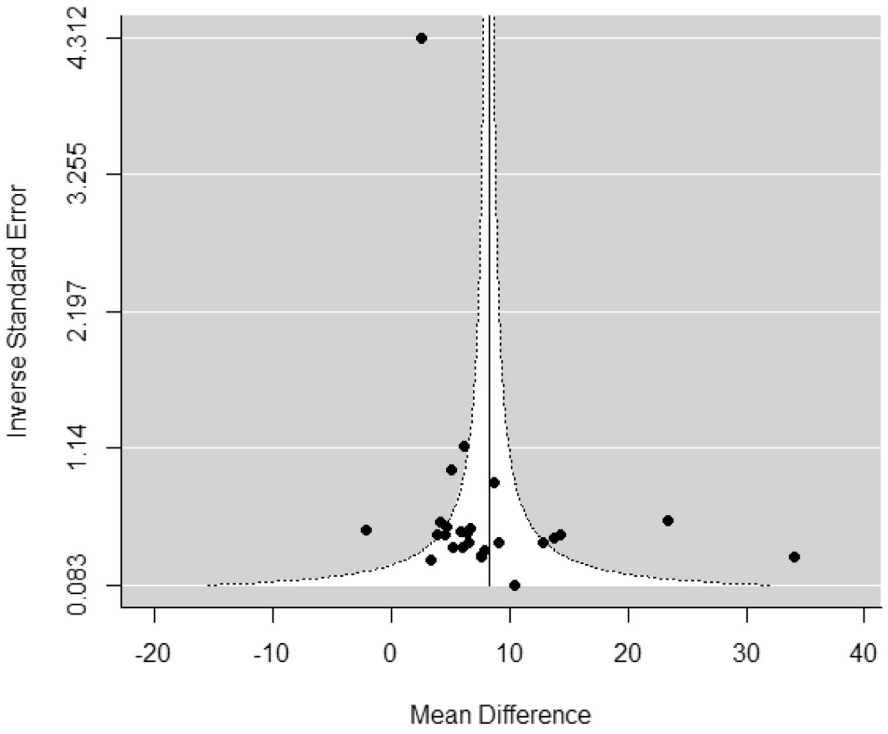
CI, confidence intervals; *OR*, odds ratio; *RE*, random effects.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

Appendix 4: Publication Bias

4.1. Hemoglobin percentage change

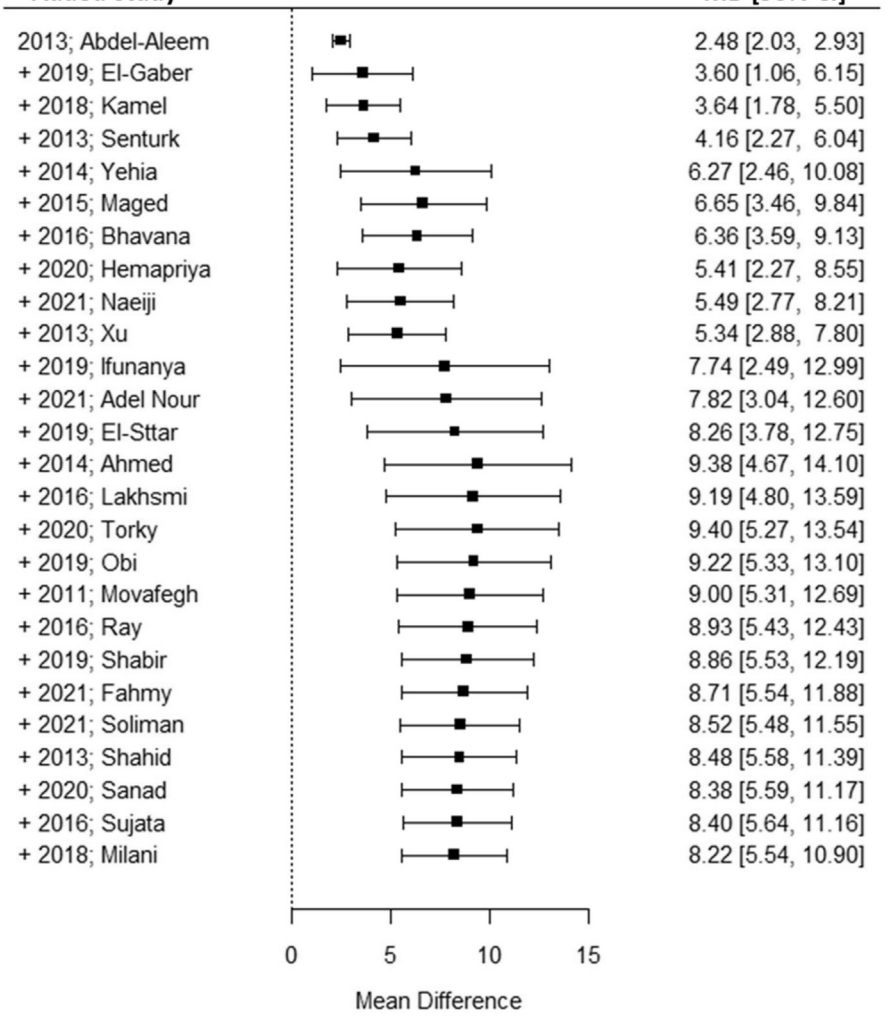
SUPPLEMENTAL FIGURE 7
Funnel plot of the hemoglobin percentage change outcome



No evident asymmetry was noted (P=.322).

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 8
Cumulative meta-analysis of the hemoglobin percentage change outcome

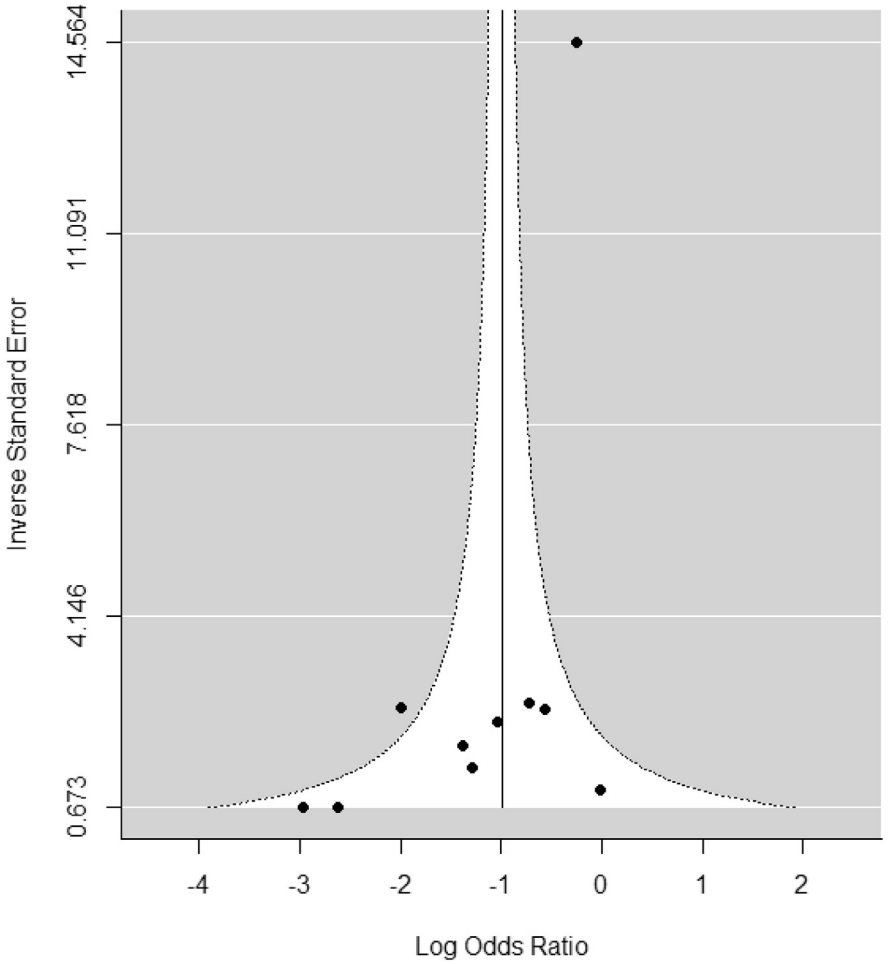


CI, confidence intervals; *MD*, mean difference.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

4.2. Blood loss>1000 milliliter

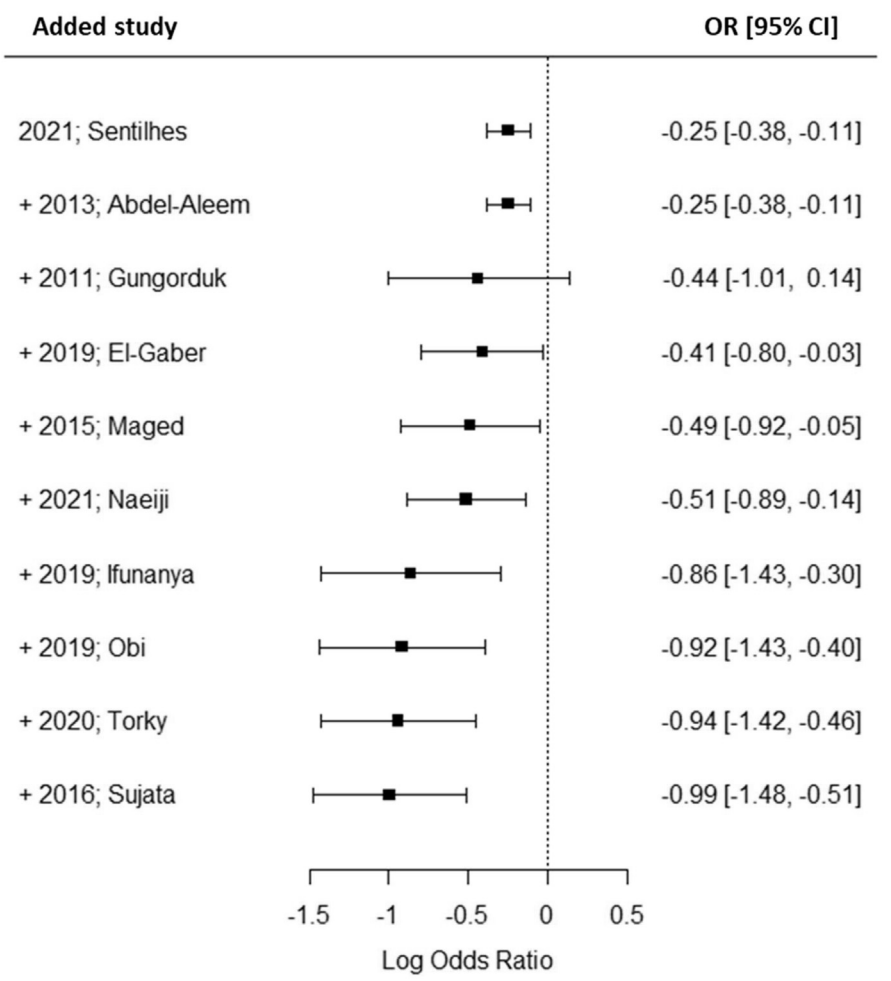
SUPPLEMENTAL FIGURE 9
Funnel plot of the postpartum hemorrhage outcome



Asymmetry was noted (P=.043).

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 10
Cumulative meta-analysis of the postpartum hemorrhage outcome

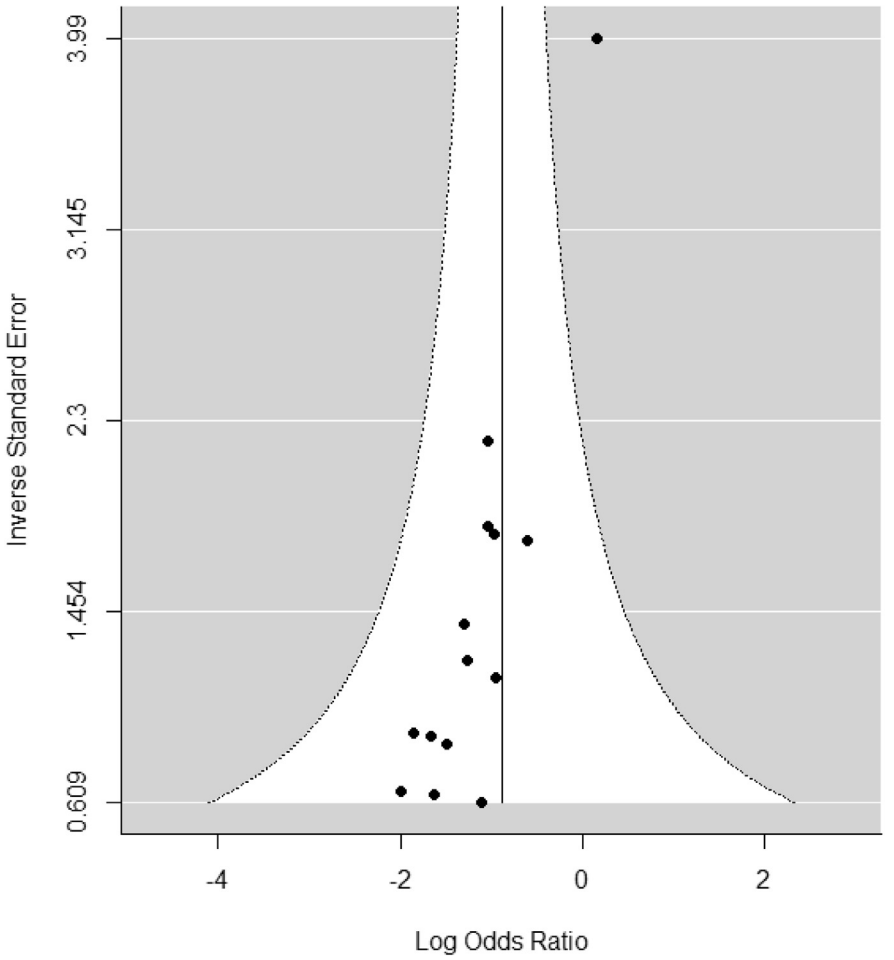


CI, confidence intervals; *OR*, odds ratio.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

4.3. Red blood cell transfusion

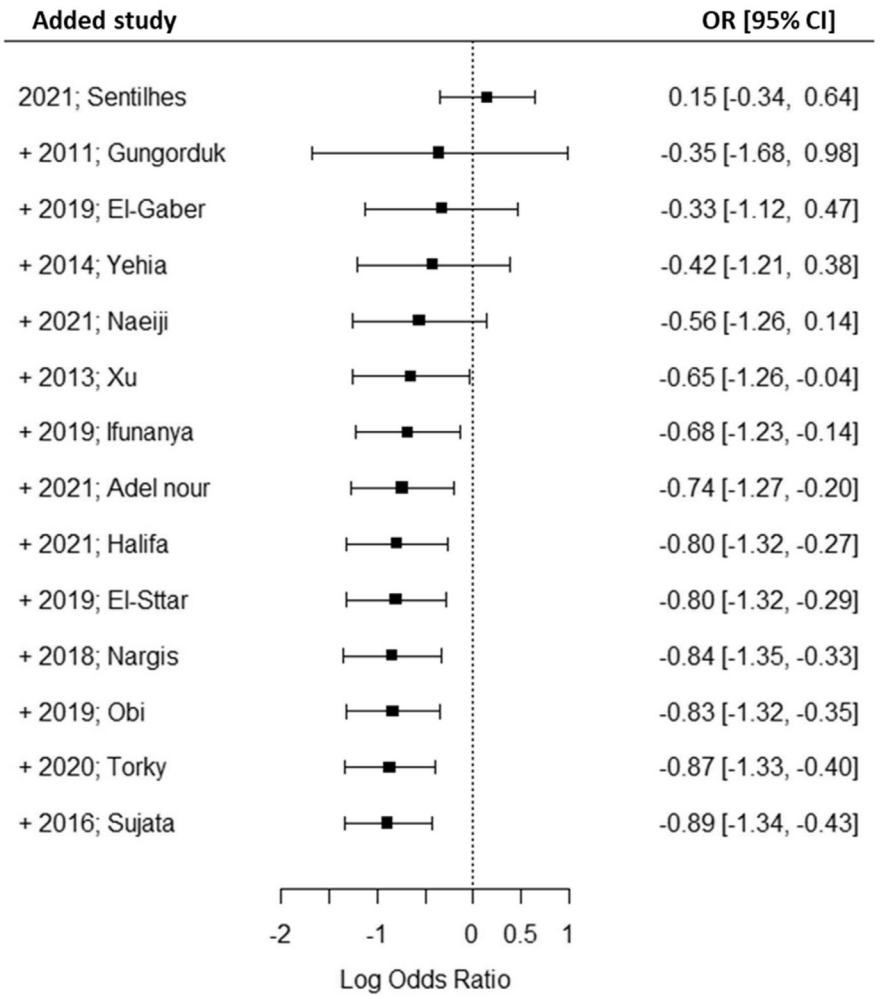
SUPPLEMENTAL FIGURE 11
Funnel plot of the red blood cell transfusion outcome



Asymmetry was noted (*P*=.002).

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 12
Cumulative meta-analysis of the red blood cell transfusion outcome

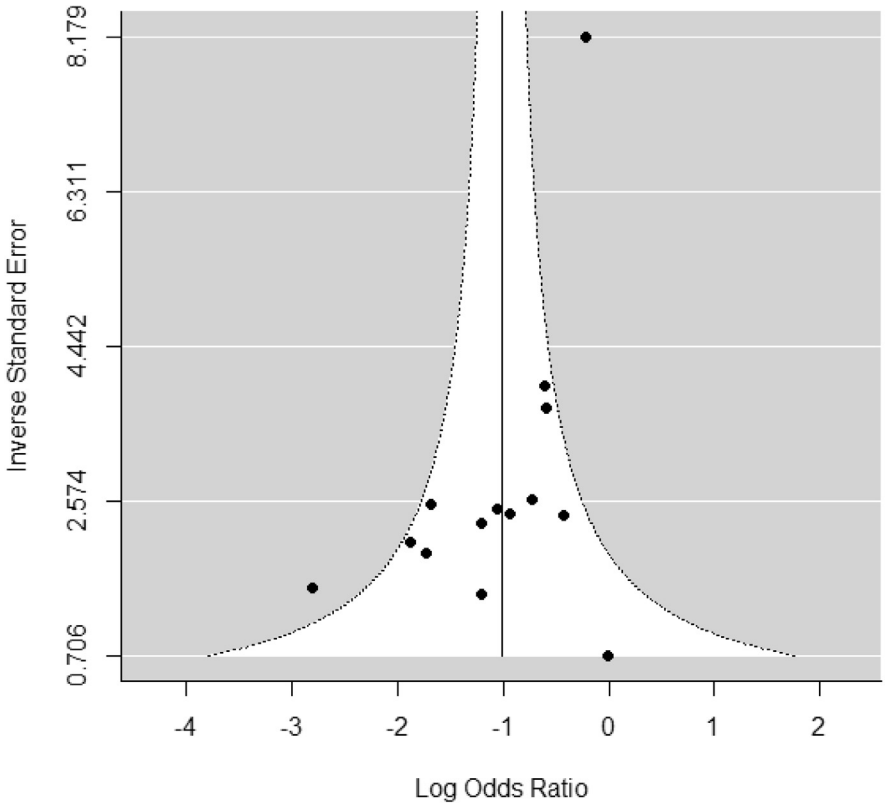


CI, confidence intervals; *OR*, odds ratio.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

4.4. Additional uterotonic agents

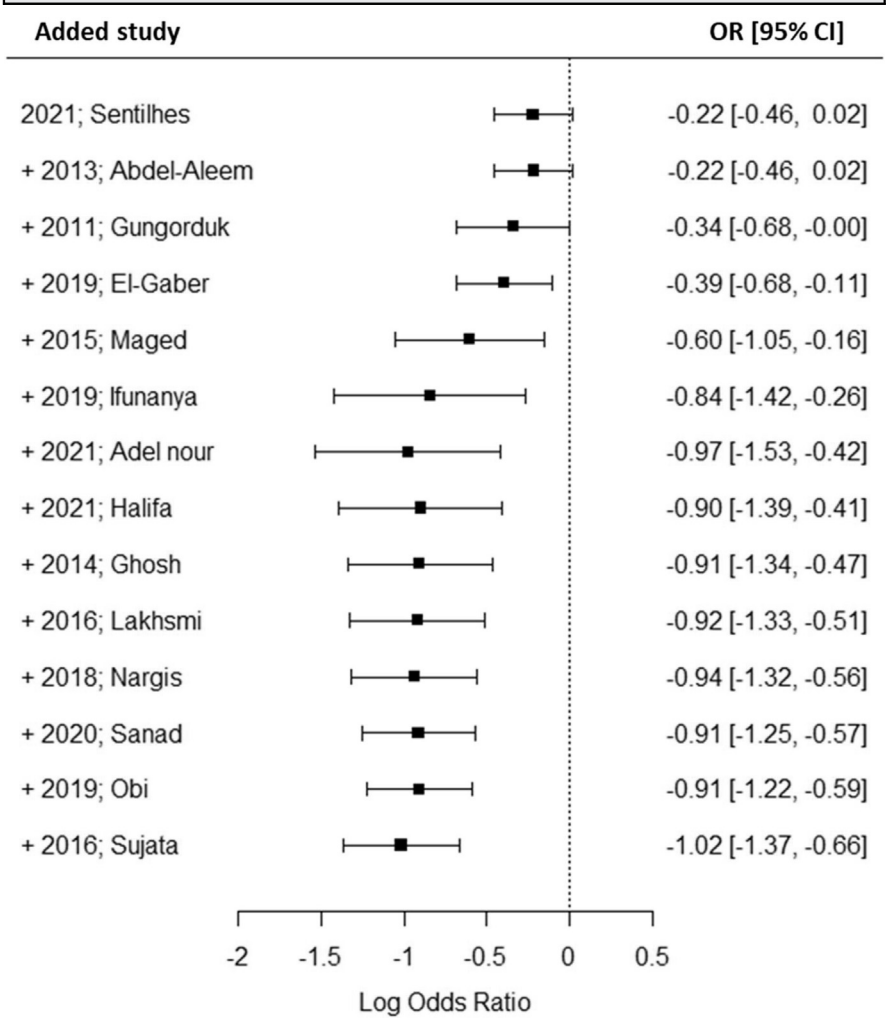
SUPPLEMENTAL FIGURE 13
Funnel plot of the need of uterotonic agents outcome



Asymmetry was noted ($P<.001$).

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 14
Cumulative meta-analysis of the need of uterotonic agents outcome



CI, confidence intervals; *OR*, odds ratio.

Bellos. Prophylactic tranexamic acid in cesarean delivery. Am J Obstet Gynecol 2022.