Scant evidence exists regarding use of tranexamic acid (TXA) in high-risk obstetrics. The aim of this review was to evaluate the efficacy of prophylactic TXA in high-risk patients for postpartum hemorrhage. The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Only studies examining the effects of TXA compared with placebo in mitigating postpartum hemorrhage were included. The primary outcomes were blood loss intraoperatively and postoperatively. The secondary outcomes were the frequency of additional uterotonic therapy and postoperative hemoglobin concentration. Three trials consisting of 203 patients were included. Compared with placebo, there was a low quality of evidence that TXA may reduce blood loss intraoperatively (mean difference, −361.41; 95% CI, −573.13 to −149.69; P = .0008) and postoperatively (mean difference, −177.95; 95% CI, −296.65 to −59.25; P = .003). We also found a moderate quality of evidence that TXA decreased the number of uterotonic agents used (risk ratio, 0.26; 85% CI, 0.16 to 0.41; P < .00001) but did not affect postoperative hemoglobin level (mean difference, 0.41; 95% CI, −0.08 to 0.90; P = .10). Prophylactic TXA may decrease blood loss and reduce the number of rescue uterotonics in high-risk patients undergoing cesarean delivery.

Keywords: Blood loss, high-risk pregnancy, placenta previa, postpartum hemorrhage, tranexamic acid.

Surprisingly, the available technology (eg, ultrasonography, 3-dimensional imaging) and advanced medical therapies (eg, bilateral uterine artery ligation, uterine tamponade, total hysterectomy) have done little to change the morbidity and mortality associated with postpartum hemorrhage (PPH) in high-risk parturients. Postpartum hemorrhage, following vaginal or cesarean delivery, continues to be one of the leading causes of maternal death throughout the world. In the most recent Pregnancy Mortality Surveillance System report, 11.5% of pregnancy-related deaths in the United States were due to hemorrhage within 42 hours. Additionally, the medical practice of birth via cesarean delivery continues to increase greatly in both high-income and low-income regions around the globe. In fact, the cesarean delivery rate is continuously rising and in 2017 increased to 32%. Traditionally, PPH associated with cesarean delivery is approximated to be twice that of vaginal delivery with an estimated blood loss of 1,000 mL. However, in 2017 the American College of Obstetricians and Gynecologists redefined PPH as cumulative blood loss equal or greater than 1,000 mL with corresponding clinical presentations of hypovolemia 24 hours after the birth process regardless of delivery method.

Risk factors for PPH include uterine atony, trauma in the birth canal, retained placental tissue, and abnormalities in coagulation. Other factors such as prolonged labor, chorioamnionitis, and a high risk of bleeding are linked to PPH. Women with a diagnosis of placenta previa make up a large portion of the high-risk parturient category, occurring in 4 of every 1,000 births. Placenta previa is defined as any portion of the placenta, partially or completely, covering the cervical os. This well-known obstetric condition is associated with substantial blood loss leading to the requirement of cesarean delivery.

Mechanical and pharmacologic methods are instituted as part of the active management of the third stage of labor. The 3 common strategies used in the active management of the third stage of labor are the use of oxytocin, uterine massage, and umbilical cord traction. In addition, several interventions have been used to decrease blood loss associated with PPH, including intrauterine balloon tamponade, bilateral uterine artery ligation, and the use of antifibrinolytic agents, namely tranexamic acid (TXA). In a study of 20,060 women, TXA significantly reduced mortality due to bleeding (risk ratio [RR], 0.81; 95% CI, 0.65-1.00; P = .045).
The mechanism of action of TXA is to competitively bind with fibrin, thus preventing plasmin and plasminogen binding with fibrin. Tranexamic acid is not new to the medical arena. Since the 2011 CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) report, TXA has been used in multiple settings. Tranexamic acid therapy is found in open-heart surgeries, total joint replacements, long spine surgeries, and multiple gynecologic procedures. Tranexamic acid has been used predominately as an intravenous therapy, but its topical applications are also being heavily researched. The use of TXA in cesarean deliveries and for reduction of PPH has been extensively studied. Scant evidence is available, however, regarding the use of TXA in high-risk obstetric patients. Because limited research findings are reported on this topic, the authors performed a systematic review and meta-analysis of available randomized controlled trials on the use of TXA in high-risk obstetrics.

Methods
We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.

• Data Source and Search. The Patient, Intervention, Comparison, and Outcome (PICO) framework that guided the search was: Does a high-risk parturient undergoing cesarean delivery (P) have decreased blood loss (O) when treated with prophylactic tranexamic acid (I) compared with placebo (C)?

Published studies examining the effects of TXA in reducing the incidence of PPH were extensively searched from inception until March 2019 using MEDLINE (PubMed), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Google Scholar, the Cochrane Review Database, Embase, Scopus, ScienceDirect, Web of Science, and gray literature. The following search terms were used alone or in combination using the appropriate boolean mechanics: tranexamic acid, high-risk pregnancy, placenta previa, abruption placenta, postpartum hemorrhage, multiple births, and blood loss. With use of the ancestry approach, the reference lists of the eligible studies were screened for exclusion and inclusion.

• Study Selection Criteria. The inclusion criteria were identified a priori. The following inclusion criteria were defined: (1) randomized controlled trials (RCTs) evaluating the efficacy of TXA administered during a cesarean delivery regardless of route and dose; (2) studies comparing TXA with placebo; (3) trials in which the participants were considered as having a high-risk pregnancy as defined by the individual study authors; and (4) trials available in full text and written in English. Studies presented in abstracts in professional conferences and published in clinicaltrials.gov were considered as long as these trials met the inclusion criteria to avoid publication bias. The authors independently assessed the titles and abstracts for eligibility of the studies. A discussion among the authors resolved any discrepancies and disagreements on included studies.

• Data Extraction. A piloted and standardized data extraction template was used for data collection. The following information was obtained from each trial: number...
<table>
<thead>
<tr>
<th>Study, year/ country</th>
<th>Intervention/type of anesthesia</th>
<th>Comparison/ type of anesthesia</th>
<th>Study outcomes</th>
<th>Timing of assessment</th>
<th>Blood loss</th>
<th>Uterotonic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbas et al, 2019/Egypt</td>
<td>Tranexamic acid, 1 g IV, before skin incision and bilateral uterine artery ligation (BUAL) after delivery of infant Cesarean delivery under general</td>
<td>n = 31 BUAL after delivery of infant Cesarean delivery under general</td>
<td>Total blood loss Need for uterotons Need for blood transfusions Change in Hb from prep to postop</td>
<td>Intraoperative Postop</td>
<td>Blood loss intraoperatively was assessed by adding volume of contents of suction bottle and the difference in weight between the dry and soaked operations sheets and towels Postop blood loss was evaluated by adding volume of contents of pelvic drain inspected every 12 h and on removal of the drain and the difference in weight between dry and soaked vaginal pads 4 h postoperatively</td>
<td>20 IU oxytocin in 500 mL of NS at 125 mL/h No specified dosage was reported</td>
</tr>
<tr>
<td>Shady &amp; Sallam, 2017/Egypt</td>
<td>Tranexamic acid, 1 g IV, after placental delivery and additional 2 g applied topically on placental bed</td>
<td>n = 40 10 IU of oxytocin IV after delivery of placenta n = 40c Tranexamic acid, 1 g IV, before skin incision and 10 IU of oxytocin after delivery of placenta</td>
<td>Total blood loss Additional uterotons Need for blood transfusions Change in Hb from prep to 24 h postop</td>
<td>Intraoperative: from delivery of placenta to end of surgery Postop: from end of surgery to 4 h postop</td>
<td>Blood loss measured by adding volume of contents of suction cannister (which was changed after placental delivery) to avoid a mixture of blood and amniotic fluid and blood from parities and the difference in weight between dry and soaked sheets and towels Postop blood loss evaluated by weighing the soaked pads minus the dry weight of the pads</td>
<td>10 IU of oxytocin IV and tranexamic acid, 2 g, soaked in towel, which was applied to the placental bed for 5 min Oxytocin, methylergometrine, carboprost, misoprostol</td>
</tr>
<tr>
<td>Sujata et al, 2016/India</td>
<td>Tranexamic acid, 10 mg/kg, before skin incision</td>
<td>NS before skin incision</td>
<td>Need for additional uterotons in first 24 h Total blood loss Need for blood transfusion Hb 24 h after surgery</td>
<td>Postop</td>
<td>Blood loss = [(Hb Preop – Hb 48 h postop)/Hb Preop] × [(0.3669 × H^2) = (0.03219 × W) + 0.6041] + [(IV × 18)/Hb Preop]</td>
<td>5 IU IV of oxytocin diluted to 5 mL with NS given over 30 s and infusion of 20 IU oxytocin in 450 mL NS over 3 h, followed by 10 IU oxytocin in 500 mL of NS over next 5 h Oxytocin, methylergometrine, carboprost, misoprostol</td>
</tr>
</tbody>
</table>

Table 1. Summary of Randomized Controlled Trials Examining Tranexamic Acid For Cesarean Delivery in Patients With High Risk of Postpartum Bleeding

Abbreviations: BUAL, bilateral uterine artery ligation; H, height of patients in meters; Hb, hemoglobin; IU, international unit; IV, intravenous; NS, normal saline; postop, postoperative; prep, preoperative; V, total volume of blood transfused; W, weight of patient; 18 (in blood loss formula), hemoglobin concentration of packed red blood cells.

aUterotonic agents given routinely or as a standard protocol after the delivery of placenta.

bAdditional uterotonic agents administered as needed after the routine or standard uterotons were administered.

cThe study had a 2-arm comparison.
of participants; ASA physical status; total blood loss; the hemoglobin (Hb) and hematocrit levels preoperatively and postoperatively; the dose, route, and timing of administration of TXA; the number of patients requiring additional uterotonic agents; and the number of transfusions. All the data outcomes were collected by a single investigator (N.S.) and were verified by another author (T.D.T.). Discrepancies of data were resolved by a third author (S.S.).

Risk of Bias Assessment. Two authors appraised the included RCTs and assessed the methodological quality of each study using the Risk of Bias algorithm outlined in the Cochrane Handbook for Systematic Reviews of Intervention. The evaluators assessed the quality of the article based on random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective reporting; and other sources of bias. Two independent authors (N.S., T.D.T.) rated the article as “high risk,” “low risk,” or “unclear risk” of bias, and each evaluator was instructed to identify the reasons for each rating. Another author (S.S.) resolved any discrepancies or disagreements.

Quality of Findings. The authors rated the overall quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The GRADE method rates outcomes as high, moderate, low, or very low. Since all evidence included in this review involved RCTs, the baseline quality of evidence was graded as high. Subsequently, an outcome was downgraded by 1 level for serious concerns and 2 levels for very serious concerns about the risk of bias assessment, inconsistency, imprecision, indirectness, and high probability of publication bias.

Statistical Analysis. The Review Manager (RevMan 5.3; The Nordic Cochrane Centre) was used for meta-analysis in this study. The primary outcomes were total intraoperative blood loss and total postoperative blood loss. Intraoperative blood loss was measured from the delivery of the baby to the delivery of the placenta, whereas postoperative blood loss was measured from the delivery of the placenta to the time indicated by the studies' authors. The secondary outcomes included additional uterotonic agents required, change in postoperative Hb concentration, and the number of patients requiring a blood transfusion. For dichotomous outcomes, effect sizes were estimated by calculating the pooled RR with 95% CI. For continuous data, outcomes were calculated using the mean difference (MD) with 95% CI. The random-effects model was used to pool the estimates of both.
dichotomous and continuous endpoints anticipating methodological and clinical heterogeneity of data. For the binary endpoint, a significant effect needed a 95% CI not to include 1. For continuous outcomes, a significant effect required a 95% CI not to include 0.

When data were reported as median and range (interquartile range), the mean and standard deviation were calculated using the algorithm proposed by Wan and colleagues.22 In RCTs with multiarm groups, data were processed individually. Trials with data not suitable for meta-analysis were described qualitatively in the review. Heterogeneity was assessed using $I^2$ statistics as described in the Cochrane Handbook for Systematic Reviews of Intervention.10 An $I^2$ greater than 50% was considered substantial heterogeneity. To explore the clinical and methodological heterogeneity, we designed a priori subgroup and sensitivity analyses. Clinical heterogeneity was explored by examining studies involving patients with placenta previa. A sensitivity analysis was performed by pooling estimates of only studies with a low risk of bias. If results from the sensitivity analysis were unchanged, we concluded that the risk of bias did not influence the effect estimates.

Since there are only 3 RCTs in the review, publication bias was not explored by visual inspection of the funnel plot for symmetrical configuration. For the same reason, an Egger regression test was not conducted. The quality of findings was generated using GRADEpro GDT software.23

**Results**

The initial search yielded 109 citations and 5 additional studies identified from gray literature. After relevant publications were retrieved and screened, a total of 16 RCTs were reviewed in detail. Eventually, 3 studies evaluating the effects of the use of prophylactic TXA in PPH were analyzed (Figure 1).

- **Demographic Characteristics.** A total of 203 patients were included in this meta-analysis.2,11,24 Investigators of 2 of the RCTs2,11 evaluated TXA in patients with placenta previa risk factors of PPH.24 In 2 studies, cesarean delivery was performed under general anesthesia.2,11 The dose of the TXA varies between studies. Authors of 2 RCTs administered 1 g of TXA,2,11 and 1 study used 10 mg/kg.24 One study used TXA topically in 1 of the 2 intervention arms; otherwise, tranexamic acid was administered intravenously.11 All trials administered TXA before skin incision, after placental delivery, or after uterotonic agents were given. The uterotonic agents varied between studies.

There was no standardized method of blood loss calculation for intraoperative and postoperative blood loss. One study measured blood loss using the preoperative and 48-hour postoperative Hb levels.24 In all 3 RCTs, TXA use was reported to be free of complications. Characteristics of the included studies can be found in Table 1.

- **Primary Outcomes.** Two studies reported intraoperative blood loss.2,11 Compared with placebo, there was a significant reduction in intraoperative blood loss in patients treated with TXA (MD, −361.41; 95% CI, −573.12 to −149.69; $P = .0008$; Figure 2).

Postoperative blood loss was reported in all 3 RCTs.2,11,24 There was a significant decrease in blood loss postoperatively compared with placebo in patients with TXA (MD, −177.95; 95% CI, −296.65 to −59.25; $P = .003$; Figure 3). In both intraoperative ($I^2 = 82%$) and postoperative ($I^2 = 96%$) blood loss, there was substantial heterogeneity.

Clinical heterogeneity was explored by pooling studies involving patients with placenta previa. Pooled analysis showed no change in $I^2$ statistics. In addition, sensitivity analysis was performed by initially excluding studies with a high risk of bias for random sequence generation, allocation concealment, and blinding. After the analysis, pooled estimates of intraoperative and postoperative blood loss did not affect substantial heterogeneity.

- **Secondary Outcomes.** Three studies comprising 202 patients evaluated the effects of TXA and the number of additional uterotonic agents used.2,11,24 Only 14.8% of the patients treated with prophylactic TXA required additional uterotonic agents compared with 60.4% in patients who received placebo and active control (Figure 4).

Only 2 studies evaluated the difference in postoperative Hb levels between patients treated with TXA...
and placebo.2,11 Pooled estimates showed no difference between TXA and placebo (MD, 0.41; 95% CI, −0.08 to 0.09; I² = 0%; P = .10).

- Risk of Bias. According to the Cochrane Risk of Bias tool, all 3 studies2,11,24 have a low risk of bias for random sequence generation, allocation concealment, blinding of participants, incomplete outcome data, and selective reporting. There was an unclear risk of bias for outcome assessors because of the studies’ failure to outline blinding of investigators (Figure 5).

- Quality of Findings. GRADEpro software was used to generate the quality of findings table.23 Four major outcomes were analyzed using the GRADE criteria. We found the evidence to be of low quality that TXA reduced the amount of intraoperative and postoperative blood loss compared with placebo. Our confidence in the effect estimates is limited because of the number of studies included in the meta-analysis and the heterogeneity of the studies. Conversely, we found that the quality of our evidence for the additional need of uterotonic agents and the postoperative Hb level was moderate (Table 2).

Discussion

In this systematic review and meta-analysis, we explored the efficacy of prophylactic TXA in decreasing the amount of blood loss during cesarean delivery in patients at high risk of bleeding. Our analysis showed evidence that prophylactic TXA may reduce blood loss both intraoperatively and postoperatively. Similarly, our pooled estimates suggested that TXA lowered the additional requirements of uterotonic agents. Although there is a statistical significance in blood loss and supplemental uterotonic administration, the overall quality of evidence is low to moderate because of the small sample size and substantial heterogeneity across all studies.

Multiple studies have recently demonstrated the efficacious use of TXA in elective cesarean deliveries and PPH.4,5,11,14 These studies have investigated the different routes of administration of TXA, including oral, intravenous, and topical. Tranexamic acid is described as a lysine analog that specifically behaves as an antifibrinolytic.14 The action of TXA is to prevent plasminogen converting to plasmin, thus decreasing fibrinolysis in the patient.3 Tranexamic acid reaches peak plasma concentrations nearly immediately after administration and has a half-life of 2 hours.5 The US Food and Drug Administration has given TXA a category B designation for the parturient.11 Many researchers do have concerns related to TXA, primarily the possibility of thromboembolic events.2

The evidence levels generated from GRADEpro demonstrated that the data from this meta-analysis was low to moderate evidence. The outcomes of intraoperative blood loss and postoperative blood loss were graded as low evidence because of substantial variability between the studies and small sample size. The outcomes postoperative Hb level and additional use of uterotonic agents were graded as moderate evidence because of the small sample size. The reason for the small sample size is due to significantly limited data on this subject, indicating the need for future trials with larger sample sizes.

For patients with a high risk of bleeding, our analysis of intraoperative bleeding showed that TXA reduced blood loss by a mean of 361 mL. Our findings were similar to a previous meta-analysis comparing TXA comprising 14 RCTs of cesarean delivery. Li and colleagues10 reported that blood loss from delivery of the baby to placental expulsion is lower in TXA by a mean of 141.25 mL. The findings of increased mean intraoperative blood loss in our current meta-analysis vs the previous meta-analysis warrant some discussion.

The investigators are particularly concerned with the amount of blood loss associated with placenta previa and the limiting treatment effects that traditional uterotonics have on this population. As the placenta is peeled from the uterus, the fibrinolytic system is activated, increasing plasminogen and fibrin degradation products.4,5,17 This cycle continues up to 10 hours post partum and can obviously lead to substantial hemorrhaging. As the rate of cesarean deliveries continues to increase, there is also a linear increase of patients presenting with placenta previa.2 Unfortunately, the uterus does a poor job of contracting in its lower segment and when there is any retained placenta product increasing the chance of PPH.4,17,24 When there is retained placenta, the traditionally used uterotonic agents become less effective.17,24

The data on postoperative blood loss in this study were similar to the findings of Li and colleagues.16 Our findings indicated that the mean postoperative blood loss is higher than the previous meta-analysis because of the types of patients and the number of studies included in our meta-analysis. The current meta-analysis also showed that patients with TXA required reduced numbers of additional uterotonic agents. This outcome was expected because the amounts of blood loss intraoperatively and postoperatively were reduced with the use TXA.

The assessment strategies to determine blood loss varied with each study; however, in all 3 RCTs included in this review, the quantification of blood loss used objective techniques such as weighing soaked pads and using preoperative and postoperative Hb concentrations. The use of quantitative blood loss is the preferred technique over the traditional visual estimated blood loss method to minimize underestimation or overestimation of blood loss in obstetrics.25

There are a number of limitations in this review. First, the number of participants in most of the RCTs resulted in a small effect size and small sample size. According to Cohen, the effect size can be categorized as any of the following: a Cohen d equal to 0.2 and below is consid-
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk with placebo (comparison)</th>
<th>Risk with use of prophylactic tranexamic acid (intervention)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative blood loss (IBL) assessed with amount of blood loss from delivery of baby to delivery of placenta</td>
<td>Mean IBL was −216.05 mL</td>
<td>Mean IBL in intervention group was 361.41 mL lower (range, 573.13-149.69 lower)</td>
<td>—</td>
<td>142</td>
<td>⊕⊕⊕ Low</td>
<td>Use of prophylactic tranexamic acid may reduce IBL slightly</td>
</tr>
<tr>
<td>Postoperative blood loss (PBL) assessed with amount of blood loss after delivery of placenta</td>
<td>Mean PBL in intervention group was 177.95 mL lower (296.65-59.25 lower)</td>
<td>—</td>
<td>203</td>
<td>(3 RCTs)</td>
<td>⊕⊕⊕ Low</td>
<td>Use of prophylactic tranexamic acid may result in a slight reduction in PBL</td>
</tr>
<tr>
<td>Postoperative hemoglobin (P-Hb) assessed with hemoglobin levels after surgery</td>
<td>Mean P-Hb was 0.11 mg/dL</td>
<td>Mean P-Hb in intervention group was 0.41 mg/dL higher (0.08-0.9 higher)</td>
<td>—</td>
<td>122</td>
<td>⊕⊕⊕ Moderate</td>
<td>Use of prophylactic tranexamic acid likely results in a slight increase in P-Hb</td>
</tr>
<tr>
<td>Additional requirements of uterotonic agents assessed with number of additional uterotonic agents used</td>
<td>Study population: 604 per 1,000</td>
<td>RR = 0.26 (0.16 to 0.41)</td>
<td>202</td>
<td>(3 RCTs)</td>
<td>⊕⊕⊕ Moderate</td>
<td>Use of prophylactic tranexamic acid probably results in a slight reduction in additional requirements of uterotonic agents</td>
</tr>
</tbody>
</table>

604 per 1,000

Table 2. Summary of Findings: Prophylactic Tranexamic Acid for Postpartum Hemorrhage in High-Risk Patients Undergoing Cesarean Delivery

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MD, mean difference; RCTs, randomized controlled trials; RR, risk ratio.

aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

bGRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

cSubstantial heterogeneity across studies, an $I^2$ statistic > 50%.

dSmall sample size.
ered “small effect size”; 0.5, as “medium effect size” and 0.8 and above, as “large effect size.” Studies with small sample sizes report larger effect size and may lead to reporting bias. Second, there is no common method for assessing blood loss. The variability of the calculation and assessment technique may introduce bias in the total amount of blood loss intraoperatively and postoperatively. Third, there is substantial heterogeneity across all studies included in this meta-analysis. We were unable to determine the explanation of the clinical and methodological heterogeneity because the number of RCTs in this review is limited. Finally, the timing of postoperative blood loss varies between studies. Although the World Health Organization defines PPH as blood loss in the first 24 hours after delivery, some studies examine the blood loss past the 24-hour mark.

To our knowledge, this systematic review is the first meta-analysis assessing the role of TXA in high-risk obstetrics, specifically PPH related to placenta previa. Although the number of included trials was only 3, the results are promising. The use of TXA may benefit patients with a history of placenta previa, placental abruption, and other bleeding states found during pregnancy.

Our review findings highlight areas where future clinical trials are needed. Although our pooled estimates indicated statistical significance, we ask readers to be judicious when entertaining thoughts of integrating these results to clinical practice, mainly because of the considerable heterogeneity between studies and the small sample size. We recommend that future large-scale RCTs include patients with a history of pregnancy-induced hypertension, placental abruption, and placenta accreta. In addition, future studies should focus on recommended doses to determine the adequate concentration of TXA needed to inhibit fibrinolysis.

**Conclusion**

Our review findings showed that TXA is effective in reducing the total amount of blood loss both intraoperatively and postoperatively in patients with a high risk of bleeding during cesarean delivery. Our meta-analysis also showed that patients receiving TXA required a decrease in the total number of additional uterotonic agents required. However, we caution the extrapolation of these results to clinical practice, mainly because of the considerable heterogeneity between studies and the small sample size. We recommend that future large-scale RCTs include patients with a history of placenta previa, placental abruption, and placenta accreta. In addition, future studies should focus on recommended doses to determine the adequate concentration of TXA needed to inhibit fibrinolysis.

**REFERENCES**


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