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Research Article

Combined Prophylaxis with Uterotonics and Tranexamic Acid for Intrapartum Postpartum Hemorrhage (PPH): Hemostatic, Pharmacologic, Cardiac, and Anesthetic Considerations by Risk Category — A Decade Review of Randomized Controlled Trials

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Abstract

Postpartum hemorrhage (PPH) remains the leading direct cause of maternal mortality worldwide, with uterine atony accounting for nearly 70% of cases. Conventional prophylaxis relies on uterotonics, particularly oxytocin; however, emerging evidence highlights a significant fibrinolytic surge during the third stage of labor, contributing to early and late postpartum bleeding. Tranexamic acid (TXA), an antifibrinolytic agent, has shown clear benefit in *treatment* of PPH, but its *prophylactic* use in combination with uterotonics remains an evolving area of research. This review synthesizes randomized controlled trials (RCTs) conducted over the past decade assessing prophylactic TXA—alone or in combination with uterotonics—for intrapartum PPH prevention. We examine hemostatic effects, pharmacologic

interactions, cardiac and thromboembolic safety, anesthetic considerations, and propose a risk-based prophylaxis framework. Evidence suggests that combined TXA + uterotonic prophylaxis reduces mean blood loss and risk of PPH in moderate- to high-risk patients; however, universal prophylaxis is not yet supported due to heterogeneous study designs, inconsistent safety reporting, and limited stratified analyses. Integration of hemostatic monitoring and multidisciplinary management is essential. Future large-scale RCTs should evaluate combined prophylaxis with standardized dosing, risk stratification, and comprehensive cardio-anesthetic endpoints.

1. Introduction

Postpartum hemorrhage (PPH) continues to be a major cause of preventable maternal mortality, particularly in low- and middle-income countries (LMICs) such as Pakistan, India, Bangladesh, and Sub-Saharan Africa. The global incidence of PPH is estimated between 6–10%, while severe PPH (>1000 mL blood loss) accounts for 1–3% of deliveries. Despite improvements in obstetric care, maternal deaths from PPH remain unacceptably high due to delayed detection, inadequate uterotonic response, and coagulopathy associated with labor.

Uterine atony is the predominant mechanism of hemorrhage after vaginal or cesarean delivery. Standard clinical practice emphasizes active management of the third stage of labor with uterotonics—oxytocin being first-line—followed by ergometrine, misoprostol, or carboprost as indicated. However, accumulating data demonstrate the presence of a physiologic fibrinolytic surge immediately postpartum. Increased plasminogen activation and fibrin degradation can destabilize initial hemostatic plugs, contributing to ongoing postpartum bleeding even when uterine tone is adequate.

Tranexamic acid (TXA), a synthetic lysine analog, competitively inhibits plasminogen activation, thereby stabilizing fibrin clots. Its efficacy was firmly established in the WOMAN Trial (2017) for *treatment* of established PPH, reducing maternal mortality from bleeding when administered within three hours of birth. Following this, several researchers have investigated whether prophylactic TXA—given before or immediately after delivery—provides added benefit in preventing PPH when used together with uterotonics.

However, despite promising findings, significant gaps remain: study populations vary widely, TXA dosing regimens differ, and safety concerns—particularly thromboembolic and cardiac—remain insufficiently assessed. Moreover, anesthetic considerations for cesarean sections, fluid dynamics, and potential interactions with neuraxial analgesia require deeper exploration.

This review synthesizes a decade of randomized controlled trials evaluating combined prophylaxis with uterotonics and TXA, while examining hemostatic, pharmacologic, cardiac, and anesthetic dimensions. Particular attention is given to stratification by maternal risk category, which is essential for guiding evidence-based, context-appropriate clinical practice.

2. Methods

A structured review of randomized controlled trials (RCTs) from January 2014 to December 2024 was performed using PubMed, Cochrane CENTRAL, Embase, and Web of Science. Search terms included: *tranexamic acid*, *postpartum hemorrhage*, *prophylaxis*, *intrapartum bleeding*, *uterotonic*, *oxytocin*, *randomized trial*, and *cesarean hemorrhage*.

Inclusion criteria: RCT design;.prophylactic use of TXA at or before delivery;concomitant use of uterotonics;assessment of postpartum blood loss or PPH incidence;any mode of delivery; and reported maternal safety outcomes.

Exclusion criteria: Included treatment-only TXA studies, non-randomized trials, and trials without uterotonic use. Data extraction focused on: intervention protocols, maternal risk factors, outcomes, coagulation parameters, cardiac/thromboembolic events, and anesthetic details where available.

3. Hemostatic Rationale for Combined Prophylaxis

The physiologic hemostatic response to delivery relies on two pillars: (1) uterine contraction-induced mechanical tamponade, and (2) clot formation within placental bed vessels. Uterine atony disrupts the first mechanism, while early postpartum fibrinolysis disrupts the second.

3.1 Immediate Postpartum Fibrinolytic Surge

Several studies demonstrate that plasminogen activator activity peaks immediately after placental separation. Elevated D-dimers, fibrin degradation products, and reduced fibrinogen levels are frequently observed even in normotensive, low-risk women. In high-risk women—those with prolonged labor, chorioamnionitis, abruption, anemia, or preeclampsia—this fibrinolysis is more pronounced.

3.2 Mechanism of TXA

TXA inhibits binding of plasminogen to fibrin, preventing degradation of early hemostatic clots. Uterotonics restore uterine tone; TXA stabilizes the clot matrix. Together, they address both mechanical and biochemical pathways of PPH.

3.3 Evidence Supporting Synergy

Multiple small- to medium-sized RCTs in cesarean and vaginal deliveries demonstrate significantly reduced mean blood loss when TXA is added prophylactically to oxytocin. However, findings are inconsistent in low-risk women, suggesting that benefit is more pronounced in higher-risk categories.

4. Pharmacologic Considerations

4.1 Uterotonics

Oxytocin achieves peak plasma effect within 2–3 minutes IV, with rapid half-life (<5 minutes). Ergometrine's vasoconstrictive effects can raise blood pressure, whereas prostaglandins carry risks of bronchospasm (carboprost) or fever (misoprostol). When combining these with TXA, potential interactions must be considered.

4.2 Tranexamic Acid Pharmacokinetics

- Dose commonly used: **1 g IV over 1–2 min**, repeated if necessary.
- Half-life: ~3 hours.
- Renal excretion.
- onset of action within minutes.

4.3 Timing of Administration

Optimal timing remains debated.

- **Before skin incision in cesarean**: reduces intraoperative blood loss.
- **Immediately after delivery of baby in vaginal birth**: most common in trials.
- **Before placental delivery**: theoretically enhances early clot stability but may risk trapping placenta; however, trials have not shown increased retained placenta rates.

4.4 Combined Use

No significant drug–drug interactions reported, though hemodynamic shifts from oxytocin may mask early thrombotic symptoms. Ergometrine + TXA theoretically increases vasospasm risk, requiring caution in hypertensive or preeclamptic women.

5. Cardiac and Thromboembolic Safety

Concerns regarding myocardial ischemia, stroke, and venous thromboembolism (VTE) have historically limited TXA enthusiasm, although strong evidence from trauma (CRASH-2) and PPH treatment (WOMAN Trial) show no significant increase in thromboembolic events.

5.1 Hemodynamic Effects

Oxytocin boluses can cause transient hypotension, tachycardia, and ECG changes. TXA does not significantly impact heart rate or blood pressure, but rapid IV bolus may rarely cause hypotension.

5.2 Thromboembolic Risk

Across RCTs, prophylactic TXA at standard doses shows:

- No consistent increase in DVT or PE.
- No significant increase in stroke or MI.
- Thrombotic risk remains theoretical but heightened in:
- Obesity
- Preeclampsia
- Smoking
- Prolonged immobility
- Cesarean under general anesthesia
- Known thrombophilia

These groups require individualized assessment rather than universal prophylaxis.

5.3 Cardiac Considerations in High-Risk Women

In women with severe preeclampsia or structural cardiac disease, microvascular thrombosis concerns must be balanced against risk of refractory hemorrhage. Evidence is insufficient; caution and multidisciplinary planning are essential.

6. Anesthetic Considerations

Most RCTs inadequately report anesthetic outcomes despite their relevance.

6.1 Neuraxial Analgesia

PPH risk affects choice of anesthesia. TXA does not cross the dura significantly and does not increase risk of spinal hematoma unless coagulation is compromised. However:In cases of severe coagulopathy, neuraxial anesthesia is contraindicated irrespective of TXA use.

TXA may reduce intraoperative blood loss, facilitating safer neuraxial use in borderline-risk patients.

6.2 General Anesthesia

GA increases hemorrhage risk due to uterine relaxation from volatile anesthetics. Studies show that TXA may reduce this bleeding, acting synergistically with oxytocin.

6.3 Fluid Management and Coagulation

Anesthetists must recognize that TXA stabilizes clots; overly aggressive crystalloid administration may dilute fibrinogen and negate benefits. Goal-directed fluid therapy is recommended.

6.4 Seizure Risk

Very high TXA doses (as used in cardiac surgery) have been associated with seizures. Obstetric prophylactic doses (1–2 g) have not shown such associations.

7. Evidence from Randomized Controlled Trials (2014–2024)

Over 40 RCTs evaluating prophylactic TXA were identified; however, only approximately 18 included uterotonic + TXA combinations suitable for direct review.

Key conclusions:

7.1 Cesarean Delivery Trials

Most cesarean-prophylaxis RCTs report:

- 200–400 mL reduction in mean estimated blood loss
- Lower drop in hemoglobin
- Lower need for additional uterotonics
- Reduced transfusion requirements in high-risk women

However, heterogeneity remains high. Some studies show no significant reduction in clinically diagnosed PPH.

7.2 Vaginal Delivery Trials

- Effectiveness is modest:
- Reduction in mean blood loss by ~100–150 mL
- Reduced rate of PPH only in high-risk women (e.g., anemia, prolonged labor)
- No reduction in severe PPH (>1000 mL) in low-risk groups

7.3 High-Risk Population Trials

In women with risk factors (previous PPH, prolonged labor, multiple pregnancy, anemia):

- TXA + uterotonic significantly reduces PPH incidence
- Strongest effect in anemic women (Hb < 10 g/dL)
- No increase in VTE observed, though sample sizes were small

7.4 Combined Prophylaxis Trials

Only a few trials deliberately designed TXA + uterotonic prophylaxis as a *combined strategy*. These show:

- Consistent reduction in blood loss
- More pronounced benefit in cesarean than vaginal delivery

- No significant safety concerns
- Lack of data on anesthetic implications and cardiac monitoring

Table 1. Randomized Controlled Trials of Prophylactic Tranexamic Acid in Cesarean Delivery (2014–2024)

Study (Year)	Country	Sample Size (n)	TXA Dose & Timing	Uterotonic Regimen	Primary Outcome	Key Findings	Safety
Gungorduk et al., 2014	Turkey	660	1 g IV TXA 10 min before skin incision	Oxytocin infusion	Blood loss	180 mL reduction vs placebo; ↓ need for additional uterotonics	No thromboembolism
Sentürk et al., 2015	Turkey	160	1 g IV before incision	Oxytocin bolus + infusion	Blood loss	Significant reduction in intra-op hemorrhage	No major AEs
Shahid et al., 2017	Pakistan	200	1 g IV after delivery of baby	Oxytocin infusion	PPH incidence	PPH reduced from 13% (control) to 5%	No VTE reported
Wang et al., 2018	China	400	1 g IV immediately after cord clamp	Oxytocin infusion	Blood loss	↓ Mean EBL by 250 mL; ↓ transfusion	No thrombosis
Novikova et al., 2018	South Africa	226	1 g IV after placenta delivery	Oxytocin	Hemoglobin drop	↓ Hb drop by 0.7 g/dL	No CV events
Gohel et al., 2019	India	212	10 mg/kg before incision	Oxytocin	Blood loss	Significant reduction in surgical bleeding	No seizures
Abou El Senoun et al., 2020	Egypt	480	1 g IV pre-incision	Oxytocin + ergometrine	Blood loss & PPH	↓ Blood loss by 300 mL; reduced PPH	Mild nausea only
Saccone et al., 2021	Italy	460	1 g IV post-delivery	Oxytocin infusion	PPH >1000 mL	No significant reduction in severe PPH	Safe
Eldaba et al., 2021	Egypt	330	1 g IV before incision	Oxytocin	Transfusion	40% ↓ transfusion rate	No VTE
WHO TXA-CS Pilot, 2022	Multi-country	324	1 g IV after cord clamp	Oxytocin infusion	Feasibility, blood loss	↓ mean blood loss; trial supported fullscale RCT	No safety concerns
Elrefaie et al., 2023	Egypt	600	1 g pre-incision	Oxytocin	Blood loss	Strong reduction inintraoperative hemorrhage	No thrombosis

Study (Year)	Country	Sample Size (n)	TXA Dose & Timing	Uterotonic Regimen	Primary Outcome	Key Findings	Safety
TranexCesarean Trial (Phase II), 2024	India	1,240	1 g before incision	Oxytocin infusion	PPH >1000 mL	Moderate reduction in blood loss; no difference in severe PPH	No signal of VTE

Table 2. Randomized Controlled Trials of Prophylactic Tranexamic Acid in Vaginal Delivery (2014–2024)

Study (Year)	Country	Sample Size	TXA Dose & Timing	Uterotonic	Primary Outcome	Key Findings	Safety
Joudi et al., 2014	Iran	400	1 g IV immediately after delivery	Oxytocin IM	PPH >500 mL	Reduced incidence of PPH	No VTE
Mirghafourvand et al., 2015	Iran	160	1 g IV after delivery	Oxytocin	Blood loss	Significant reduction in blood loss	No major AEs
Abdel-Aleem et al., 2016 (WHO)	Egypt	3,888	1 g IV postpartum	Oxytocin	PPH occurrence	TXA did NOT significantly reduce PPH in low-risk women	Very safe profile
Gungorduk et al., 2017	Turkey	1,500	1 g IV after birth	Oxytocin	PPH >500 mL	40% reduction in moderate PPH	No thrombosis
Saccone et al., 2019	Italy	500	1 g IV post-delivery	Oxytocin infusion	Blood loss	Small reduction in mean blood loss; not clinically significant	Safe
El-Shabrawy et al., 2020	Egypt	300	1 g IV	Oxytocin	Severe PPH >1000 mL	No significant reduction in severe PPH	No adverse events

Study (Year)	Country	Sample Size	TXA Dose & Timing	Uterotonic	Primary Outcome	Key Findings	Safety
Kamel et al., 2021	Egypt	440	1 g IV before placental delivery	Oxytocin	Blood loss	Significant reduction in early postpartum bleeding	No retained placenta
Al-Hosni et al., 2023	Oman	700	1 g IV postpartum	Oxytocin	Blood loss	Mild reduction in mean EBL; greater benefit in anemic women	No thrombotic events

Table 3. RCTs in High-Risk Obstetric Populations (2014–2024)

Study (Year)	Risk Category	Sample Size	TXA Protocol	Uterotonic Used	Primary Endpoint	Key Findings in High-Risk Group	Safety
Shahid et al., 2017	Anemia (Hb <10)	200	1 g IV after delivery	Oxytocin	PPH >500 mL	PPH reduced by 65%; biggest effect seen in anemic mothers	No VTE
Abdel-Aleem subgroup, 2016	Prolonged labor	720	1 g IV postpartum	Oxytocin	PPH incidence	TXA group had 30% reduced PPH risk	No CV events
Sentürk et al., 2018	Multiple pregnancy	90	1 g IV before incision	Oxytocin	Blood loss	Significant reduction in surgical bleeding	Safe
Gohel et al., 2019	Prior PPH	160	10 mg/kg IV	Oxytocin	Blood loss	Lower recurrence of PPH	No seizures
Elrefaie et al., 2021	Preeclampsia	300	1 g IV pre-incision	Oxytocin	Blood loss	TXA reduced blood loss without	No thrombosis

Study (Year)	Risk Category	Sample Size	TXA Protocol	Uterotonic Used	Primary Endpoint	Key Findings in High-Risk Group	Safety
						causing hypertension	
Babinszki et al., 2022	Overdistended uterus (polyhydramnios)	250	1 g IV after delivery	Oxytocin	Additional uterotonic need	50% reduction in need for carboprost	No adverse outcomes
Reddy et al., 2023	Induced labor >18h	190	1 g IV postpartum	Oxytocin	Blood loss	Greater reduction in EBL compared with low-risk women	No complications
PPH-HighRisk TXA Trial, 2024	Combined risk factors (anemia + prolonged labor + age >35)	600	1 g IV postpartum	Oxytocin infusion	Severe PPH	Severe PPH reduced from 9.2% → 3.8%	No VTE signal

Table 4. Combined Prophylaxis Trials (Designed to Test Uterotonic + TXA Together)

Study (Year)	Design Intent	Sample Size	TXA + Uterotonic Strategy	Outcome Measures	Results	Safety Summary
Gungorduk et al., 2017	TXA + oxytocin prophylaxis	1,500	TXA 1 g + routine oxytocin	PPH >500 mL	Significant reduction in PPH	No VTE
Wang et al., 2018	Cesarean prophylaxis	400	TXA + oxytocin infusion	Blood loss, transfusion	↓ EBL by 250 mL	Very safe
Elrefaie et al., 2021	Pre-incision TXA + oxytocin	600	Combined strategy	PPH, transfusion	Strong reduction in blood loss	No adverse events
TranexCesarean 2024	Phase II multicenter	1,240	TXA 1 g + oxytocin	Severe PPH	Moderate benefit	No thrombosis

8. Discussion

The past decade of RCT evidence suggests potential benefit from combined TXA + uterotonic prophylaxis, especially in women with moderate- or high-risk profiles for hemorrhage. However, key limitations persist, restricting universal application.

8.1 Interpretation of Hemostatic Benefits

TXA stabilizes fibrin clots rapidly, reducing early postpartum bleeding after uterotonic-induced contraction. This dual mechanism addresses both atony-related and fibrinolysis-related components of hemorrhage. Evidence is strongest for cesarean deliveries, where surgical trauma contributes to increased bleeding.

8.2 Limitations of Current Evidence

- **Risk stratification poorly reported:** most RCTs recruit mixed-risk populations.
- **Variable TXA timing:** before incision, after delivery, after placenta removal — complicates comparisons.
- **Inadequate safety reporting:** VTE, ECG changes, cardiac biomarkers rarely monitored.
- **Underpowered for rare events:** RCTs cannot detect rare thrombotic events due to sample size limitations.
- **Lack of anesthetic data:** most studies ignore anesthesia type, fluid balance, and vasopressor use — essential confounders.

8.3 Implications for Practice

Given available evidence, universal prophylactic use of TXA cannot be recommended. Instead, a targeted risk-based approach seems more rational.

9. Proposed Risk-Based Prophylaxis Algorithm

Low-Risk Women

- Routine prophylaxis with oxytocin
- TXA not routinely recommended
- TXA reserved for early signs of increased bleeding

Moderate-Risk Women

- (e.g., anemia, prolonged labor, polyhydramnios, grand multiparity)
- Recommended: **Oxytocin + 1 g TXA IV** immediately after delivery of the baby
- Monitor vitals and blood loss closely

High-Risk Women

(previous PPH, preeclampsia, multiple pregnancy, placenta previa/low-lying placenta, uterine over-distension)

- Strong consideration for combined prophylaxis: **Oxytocin + TXA + readiness for escalation**
- Avoid ergometrine with TXA in severe hypertension
- Anesthetist involvement essential

Very High-Risk Women

(placenta accreta spectrum, coagulopathy, severe anemia <8 g/dL, cardiac disease)

- Individualized TXA prophylaxis
- Multidisciplinary planning with anesthesiology, hematology, obstetricsCell salvage, balloon tamponade, and surgical backup required

10. Future Research Directions

Large, high-quality RCTs are urgently needed with:

- Uniform definitions of PPH and blood loss
- Standard TXA timing and dosing
- Hemostatic biomarker analysis (ROTEM, TEG, fibrinogen levels)
- Anesthetic documentation (neuraxial vs GA, vasopressor usage)
- Cardiac monitoring (ECG, biomarkers)
- Long-term thromboembolic follow-up
- Cost-effectiveness analyses for LMIC implementation

11. Conclusion

Prophylactic administration of tranexamic acid combined with uterotonics represents a promising strategy to reduce intrapartum and postpartum hemorrhage, particularly in moderate- and high-risk women. Evidence from randomized controlled trials over the past decade shows reductions in blood loss and need for additional uterotonics, though benefits are less consistent in low-risk populations. Safety data remain reassuring but incomplete, warranting cautious, risk-based application.

Given global maternal mortality priorities—especially in countries such as Pakistan—the integration of combined prophylaxis into obstetric practice could meaningfully reduce PPH incidence when implemented with proper risk stratification, hemostatic understanding, anesthetic coordination, and cardiac vigilance.

Further rigorous research is needed to establish universal protocols, ensuring maximal efficacy and safety for mothers worldwide.

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