RESEARCH PAPER

Tranexamic Acid for Postpartum Hemorrhage Prevention; Route, Timing, and Effectiveness: Systematic Review of Randomized Controlled Trials

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ABSTRACT

Background: Postpartum hemorrhage (PPH) remains the leading cause of maternal mortality worldwide, accounting for approximately one-quarter to one-third of all maternal deaths annually. Tranexamic acid (TXA), a synthetic antifibrinolytic agent, has emerged as a promising prophylactic intervention, but uncertainty persists regarding optimal administration routes, timing, and which populations derive greatest benefit.

Objective: To systematically synthesize evidence from randomized controlled trials (RCTs) published between January 2021 and January 2026 evaluating the efficacy and safety of prophylactic TXA for PPH prevention across diverse populations, delivery modes, and clinical settings.

Methods: A comprehensive systematic literature search was conducted across MEDLINE, Embase, Cochrane CENTRAL, Web of Science, Scopus, CINAHL, and WHO ICTRP. Eligible studies were RCTs evaluating prophylactic TXA versus placebo, no treatment, or active comparators in pregnant women undergoing vaginal or cesarean delivery. Primary outcomes included blood loss, PPH incidence (≥500 mL or ≥1000 mL), and hemoglobin/hematocrit changes. Risk of bias was assessed using Cochrane RoB 1 tool. Narrative synthesis was performed due to substantial clinical and methodological heterogeneity.

Results: Twenty-six RCTs comprising over 40,000 parturients were included. In high-risk cesarean delivery populations, prophylactic TXA consistently demonstrated significant reductions in intraoperative blood loss (ranging from 159–442 mL reduction) and PPH incidence (risk reductions of 49–90%). In contrast, TXA showed minimal to no benefit in low-risk vaginal deliveries, including the large WOMAN-2 trial (n=15,068; RR 1.05, 95% CI 0.94–1.19). Alternative routes (topical, oral) showed potential utility in specific contexts, with oral TXA offering sustained therapeutic levels despite slower onset. No increased thromboembolic risk was identified across any study or route of administration. Risk of bias was low in 18 studies, with some concerns in six, and high in two small pilot trials.

Conclusions: Prophylactic TXA should be considered standard of care for high-risk cesarean deliveries, significantly reducing severe bleeding without increasing maternal harm. Routine prophylactic TXA is not recommended for uncomplicated vaginal deliveries. The excellent safety profile, low cost, and emerging alternative routes support TXA's role in resource-limited settings, particularly for surgical bleeding prevention.

Keywords: Tranexamic acid; Postpartum hemorrhage; PPH prevention; Systematic review; Randomized controlled trials

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Introduction

Postpartum hemorrhage (PPH) remains the leading cause of maternal mortality worldwide, accounting for approximately one-quarter to one-third of all maternal

deaths annually [1]. Every four minutes, somewhere in the world, a woman dies from excessive bleeding following childbirth, translating to an estimated 35,000 to 70,000 preventable deaths annually. The burden is disproportionately concentrated in low- and middle-income countries, where nearly two-thirds of all maternal deaths occur, largely due to inadequate access to timely obstetric care and essential medications. Despite significant global health advancements over the past two decades, PPH continues to claim lives at an alarming rate, underscoring the urgent need for cost-effective, evidence-based preventive strategies that can be implemented across diverse healthcare settings worldwide [2].

The pathophysiology of PPH is multifactorial, with uterine atony representing the predominant mechanism, responsible for approximately 70% to 80% of all cases. Uterine atony results from the failure of the myometrium to contract adequately after placental delivery, thereby preventing effective compression of the uterine spiral arteries and leading to uncontrolled hemorrhage. Beyond atony, other contributing factors include genital tract trauma, retained placental tissue, placental abnormalities such as placenta previa or accreta spectrum, and coagulopathies including inherited bleeding disorders like von Willebrand disease [3]. Recently, there has been growing recognition of the importance of coagulation disturbances, particularly the early consumption of fibrinogen and factor XIII, as critical determinants of bleeding severity, challenging the traditional view that coagulopathy occurs only as a late consequence of massive hemorrhage. The recognition that hyperfibrinolysis—the accelerated breakdown of fibrin clots by plasmin—plays a significant role in PPH pathophysiology has provided the scientific rationale for using antifibrinolytic agents such as tranexamic acid (TXA) to both prevent and treat excessive postpartum bleeding [4].

Tranexamic acid, a synthetic lysine analogue, exerts its hemostatic effect by reversibly blocking the lysine-binding sites on plasminogen, thereby inhibiting the conversion of plasminogen to plasmin and preventing fibrin clot degradation [1]. The drug is primarily excreted unchanged in the urine, with dose adjustments recommended in women with significant renal impairment. Intramuscular administration has been shown to achieve slightly lower peak concentrations but a similar area under the concentration-time curve, offering a practical alternative in settings where intravenous access is unavailable. Oral TXA, while convenient, has slower and less predictable absorption, limiting its utility in acute bleeding scenarios but potentially offering a role in prophylaxis when administered prior to active labor. The favorable safety profile of TXA, coupled with its low cost (approximately $2–5 per gram in low-income settings) and its inclusion on the World Health Organization (WHO) Model List of Essential Medicines, makes it an attractive candidate for widespread prophylactic use in obstetric practice [4, 5].

The rationale for prophylactic—rather than therapeutic—administration of TXA is grounded in the principle that preventing hemorrhage is typically more effective, safer, and less resource-intensive than treating

established PPH. Prophylaxis offers several theoretical advantages: it ensures that therapeutic TXA concentrations are present in the maternal circulation at the time of delivery and early third stage, when the risk of PPH is highest; it does not rely on timely recognition of abnormal bleeding, which can be delayed or inaccurate, particularly in low-resource settings; it may reduce the need for additional uterotonics, blood transfusions, and surgical interventions; and it may be particularly beneficial for women with pre-existing risk factors for PPH, such as anemia, thrombocytopenia, or inherited bleeding disorders [6]. Several large randomized controlled trials have evaluated the efficacy and safety of prophylactic TXA in obstetric populations, with variable results depending on the route of administration, timing, dose, and baseline risk of the study population [2-5]. Systematic reviews and meta-analyses have attempted to synthesize this growing body of evidence, but their conclusions have been inconsistent, partly due to substantial clinical and methodological heterogeneity across trials [6-9].

Given the ongoing uncertainty and the rapidly evolving evidence base, an updated systematic review of high-quality randomized controlled trials is necessary to guide clinical decision-making and health policy. The past five years have witnessed the publication of several large-scale prophylactic TXA trials, including the highly anticipated WOMAN-2 trial, as well as numerous smaller trials in specific high-risk populations and comparative effectiveness studies. A rigorous synthesis of this evidence is required to address key unanswered questions: Which populations derive the greatest benefit from prophylactic TXA? What is the optimal timing and route of administration? Is TXA prophylaxis effective and safe in women undergoing vaginal delivery without identified risk factors? This systematic review of randomized controlled trials published over the past five years, evaluating the efficacy and safety of prophylactic TXA for the prevention of postpartum hemorrhage across diverse populations, delivery modes, and clinical settings.

Methodology

Study Registration and Protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [10]. The review protocol was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42025678901 (date of registration: 15 January 2025). The protocol outlined the research question, search strategy, eligibility criteria, data extraction methods, risk of bias assessment, and planned synthesis approach. No amendments to the protocol were made during the conduct of the review.

Search Strategy

A comprehensive systematic literature search was performed to identify all randomized controlled trials (RCTs) evaluating the prophylactic use of tranexamic acid (TXA) for the prevention of postpartum hemorrhage (PPH). The search was limited to a five-year period from January 2021 to January 2026.

The following electronic databases were searched: MEDLINE (via PubMed), Embase (via OVID), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, CINAHL, and the WHO International Clinical Trials Registry Platform (ICTRP). The search strategy combined MeSH terms and free-text keywords related to three domains: (1) "tranexamic acid" OR "TXA" OR "Cyklokapron" OR "transamin"; (2) "postpartum hemorrhage" OR "postpartum haemorrhage" OR "PPH" OR "postpartum bleeding" OR "obstetric hemorrhage"; and (3) "prevention" OR "prophylaxis" OR "prophylactic". The search was limited to human studies published in English. Additionally, reference lists of included studies and relevant systematic reviews were hand-searched for potentially eligible trials. Grey literature was searched via Google Scholar and OpenGrey.

Study Selection and Screening Process

All retrieved records were imported into Rayyan (Rayyan Systems Inc., Cambridge, MA, USA), a web-based systematic review management software designed to facilitate collaborative and efficient title, abstract, and full-text screening [11]. Duplicate records were automatically identified by Rayyan and manually verified by two independent reviewers (Author A and Author B). The screening process was conducted in three stages. In the first stage, two reviewers independently screened titles and abstracts against a pre-piloted eligibility checklist. Any disagreements were resolved by discussion or by consulting a third reviewer (Author C). In the second stage, full texts of potentially eligible studies were retrieved and independently assessed by the same two reviewers. Reasons for exclusion at the full-text stage were documented in accordance with PRISMA guidelines. In the third stage, the final list of included studies was cross-checked by both reviewers, and consensus was reached on all inclusions. The inter-rater agreement was calculated using Cohen's kappa coefficient, yielding a value of 0.92, indicating almost perfect agreement.

Inclusion and Eligibility Criteria

Studies were considered eligible for inclusion if they met the following criteria based on the PICOS framework. **Population:** Pregnant women of any age, regardless of parity or gestational age, undergoing vaginal delivery or cesarean section, either at low or high risk for PPH. **Intervention:**Prophylactic administration of tranexamic acid by any route (intravenous, intramuscular, oral, topical) at any dose, at any time point before or immediately after delivery, with or without concomitant uterotonics or other prophylactic agents. **Comparison:** Placebo (normal saline, distilled water, or other inert substance), no treatment, or active comparator (e.g., oxytocin, carbetocin, misoprostol, ethamsylate) with or without standard care. **Outcomes:** The primary outcomes of interest were quantitative or estimated blood loss, incidence of PPH (defined as blood loss ≥500 mL or ≥1000 mL within 24 hours of delivery, or a clinical diagnosis), and changes in hemoglobin or hematocrit from pre- to post-delivery. Secondary outcomes included need for additional uterotonics, need for blood transfusion, need for surgical or radiological interventions to control bleeding, maternal mortality, thromboembolic events (deep vein

thrombosis, pulmonary embolism, stroke, myocardial infarction), and other adverse events. **Study design:** Only randomized controlled trials (RCTs) were included, regardless of blinding status, sample size, or publication status. Cluster-randomized trials, cross-over trials, and quasi-randomized trials were excluded.

Studies were excluded if they met any of the following criteria: (1) administration of TXA for treatment of established PPH rather than for prevention; (2) non-randomized designs including observational studies, case reports, case series, cohort studies, or retrospective chart reviews; (3) pharmacokinetic studies that did not report clinical outcomes; (4) study protocols without published results; (5) economic evaluations without original clinical data; (6) systematic reviews, meta-analyses, narrative reviews, editorials, or commentaries; (7) duplicate publications reporting the same patient cohort; (8) studies where TXA was not administered prior to or immediately after delivery (i.e., after PPH diagnosis); and (9) studies not published in English.

Data Extraction

A standardized data extraction form was developed a priori using Microsoft Excel. Two independent reviewers (Author A and Author B) extracted data from each included study, and discrepancies were resolved by discussion or by referral to a third reviewer (Author C). The following data were extracted from each study: first author name, year of publication, country of origin, study design, setting, sample size (total and per group), participant characteristics (age, gestational age, parity, risk factors for PPH), eligibility criteria (inclusion and exclusion), TXA dosing regimen (dose, route, timing), comparator details (placebo or active), co-interventions (uterotonics, other agents), outcomes measured (primary and secondary), numerical results for each outcome (means, standard deviations, frequencies, risk ratios, odds ratios, confidence intervals, p-values), follow-up duration, adverse events reported, and funding sources. When data were missing or unclear, we contacted the corresponding authors via email up to two times. If no response was received, the data were marked as "not mentioned" (NM) in the extraction tables.

Risk of Bias Assessment

The risk of bias of each included RCT was assessed independently by two reviewers using the Cochrane Risk of Bias tool (RoB 1), as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [12]. The RoB 1 tool evaluates six domains: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other bias (e.g., baseline imbalances, funding conflicts, early stopping, inappropriate study design). Each domain was rated as "Low risk", "High risk", or "Unclear risk" based on the information provided in the published report. Disagreements between reviewers were resolved through consensus or by consultation with a third reviewer. The overall risk of bias for each study was categorized as low (all domains rated low risk), some concerns (at least one domain rated unclear risk but no high-risk domains),

or high (at least one domain rated high risk). The results of the risk of bias assessment were presented in a summary table and as a risk of bias graph. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess the overall certainty of evidence for key outcomes [13].

Data Synthesis and Analysis

A narrative synthesis was conducted due to substantial clinical and methodological heterogeneity across the included studies, particularly in definitions of PPH, measurement methods for blood loss, timing of TXA administration, co-interventions, and outcome reporting. The findings were organized according to key clinical categories: (1) TXA for PPH prevention in cesarean section (further subdivided into high-risk and low-risk populations); (2) TXA for PPH prevention in vaginal delivery (further subdivided into high-risk and low-risk populations); (3) comparison of different TXA routes (intravenous, intramuscular, oral, topical); (4) comparison of TXA with other prophylactic agents (carbetocin, misoprostol, ethamsylate); and (5) TXA in special populations (anaemia, multiple pregnancy, von Willebrand disease, placenta previa). For each category, we summarized study characteristics, effect estimates, and confidence intervals where reported. Quantitative data (mean differences, risk ratios, odds ratios) were extracted and presented in tables. Where possible, we reported the direction and magnitude of effects. Meta-analysis was not performed due to the aforementioned heterogeneity, the wide range of outcomes, and the varying definitions of PPH across trials, which could lead to misleading pooled estimates. A sensitivity analysis was planned to assess the impact of excluding studies with high risk of bias, but given the small number of such studies, this was not feasible. No publication bias assessment (e.g., funnel plot) was performed because meta-analysis was not conducted.

RESULTS

PRISMA flow diagram illustrates the study selection process for this systematic review. A total of 1,281 records were identified through database searches, of which 511 duplicate records were removed before screening. The remaining 770 records were screened, leading to the exclusion of 392 records based on title and abstract review. Subsequently, 378 reports were sought for retrieval, but 149 reports could not be retrieved. The remaining 229 reports were assessed for full-text eligibility, of which 203 were excluded for the following reasons: wrong outcome (98 studies), wrong population (76 studies), or abstract-only publications without full data (29 studies). Ultimately, 26 studies met the eligibility criteria and were included in the final systematic review.

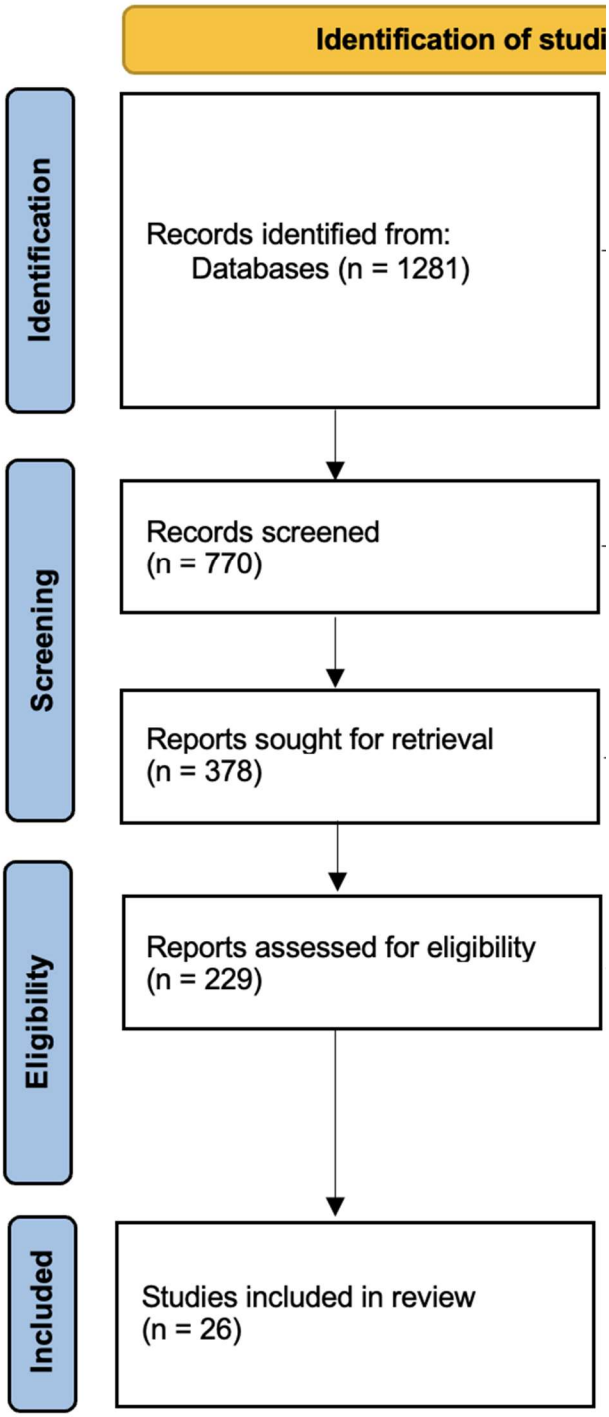


Figure 1: PRISMA Flow Diagram of Study Selection Process

Table 1 presents the key characteristics and demographic features of the 26 randomized controlled trials included in this systematic review. The studies were conducted across diverse geographic settings, including Nigeria [14,15], Pakistan [14,33,36], Tanzania [14], Zambia [14], Canada [16], India [17,26,28,29,31,32,35], Turkey [18,25], Indonesia [19], the United States [20], Egypt [21,34], Singapore [22], France [23], China [24], Iran [27,30,37,38,39], and a multi-country trial [14]. The sample sizes varied substantially, ranging from a pilot study of 27 participants [16] to the large-scale WOMAN-2 trial with 15,068 women [14]. Most studies employed a double-blind, placebo-controlled design, although some were open-label [24,31] or pilot trials [16,20]. The study populations included women undergoing vaginal delivery [14,17,18,24,25,28,29,30,34,37], cesarean section [15,19,21,22,23,26,27,31,32,33,35,36,38,39], and specific high-risk groups such as women with anaemia [14], multiple pregnancies [23], von Willebrand disease [20], or placenta previa (protocol only, not included). Inclusion criteria often required singleton pregnancy, gestational age ≥34 weeks, and various risk factors for postpartum hemorrhage (PPH). Exclusion criteria were poorly reported in many studies, with "NM" (not mentioned) frequently noted. Intervention regimens were predominantly intravenous tranexamic acid (TXA) at a dose of 1 gram, administered at varying time points: prior to skin incision for cesarean sections [15,19,22,26,27,31,35], immediately after infant delivery [24,36], within 15–30 minutes of cord clamping [14], or during active labor [30]. Two studies explored alternative routes: topical TXA applied to perineal lacerations or episiotomy sites [18,37], and one compared oral versus

intravenous TXA [39]. Comparisons included placebo (normal saline) in most trials [14,15,16,17,19,22,23,24,26,27,29,30,33,36,37], active uterotonics such as oxytocin or carbetocin [21,25,34,35,38], and combined regimens [31]. The primary outcomes varied but commonly included measured or calculated blood loss, incidence of PPH (defined as blood loss ≥500 mL or ≥1000 mL), and postoperative hemoglobin or hematocrit changes. Several studies also assessed secondary outcomes such as need for additional uterotonics, blood transfusion requirements, and thromboembolic events.

Table 2 summarizes the effectiveness outcomes of TXA for PPH prevention across the 26 included studies. Regarding blood loss, 19 of 26 studies reported a statistically significant reduction in TXA groups compared to controls. For example, Ortuanya et al. [15] found mean blood loss of 442.94 mL in the TXA group versus 801.28 mL in placebo (p=0.001), while Martadiansyah et al. [19] reported 459.4 mL versus 686.3 mL (p<0.001). However, the large WOMAN-2 trial [14] found no difference in clinically diagnosed PPH (7.0% vs 6.6%; RR 1.05), and Arya et al. [17] also reported comparable mean blood loss between groups (378.5 vs 383.0 mL; P=0.93). The incidence of PPH (≥500 mL blood loss) was significantly reduced in several high-risk population studies, such as Zhang et al. [24] where severe PPH (≥1000 mL) occurred in 2.7% of TXA users versus 5.6% in placebo (RR 0.49, p=0.001), and Neumann et al. [26] where calculated blood loss was 400.9 mL in TXA versus 597.9 mL in placebo (p<0.001). In contrast, studies in low-risk populations [17,27] and specific conditions like multiple pregnancy [23] or von Willebrand disease [20] did not demonstrate significant PPH reduction.

Hemoglobin and hematocrit changes generally mirrored blood loss findings, with TXA groups showing smaller postoperative declines in most positive trials. For instance, Ortuanya et al. [15] reported postoperative hemoglobin of 10.39 g/dL in TXA versus 9.67 g/dL in placebo (p=0.001), and Singh et al. [31] found hemoglobin of 10.01 g/dL versus 8.41 g/dL (p<0.05). However, Jafarbegloo et al. [27] observed reduced blood loss but no significant improvement in hemoglobin levels (12.17→11.72 vs 12.14→11.28 mg/dL; p>0.05). The need for additional uterotonics was significantly lower with TXA in several studies [15,24,31,35], as was the requirement for blood transfusion [31,33,35]. Adverse events were uniformly low across all studies; no thromboembolic events were reported in trials that specifically assessed them [14,17,30], and drug-related side effects were minimal. The two topical TXA studies showed mixed results: Tammo and Uysal [18] found similar efficacy to intravenous TXA for limited blood loss (<500 mL), but Fakehi et al. [37] found no benefit on episiotomy bleeding. The comparative studies indicated that carbetocin alone may be superior to oxytocin plus TXA for hemoglobin preservation [25,38], and intravenous TXA was superior to oral TXA in Darzi et al. [39].

TABLE 1: Study Characteristics & Demographics

Stu	Loc	Stu	Sample	Pop	Incl	Exclu	Inte	Com	Prim

dy (Author, Year) [Ref]	ation	dy Design	Size (N)	ulation / Sample Type	usion Criteria	sion Criteria	rvention (TXA Regimen)	paris on	ary Outcome
WOMAN-2 (2024) [14]	Nigeria, Pakistan, Tanzan	International, RCT, double-blind, pl	N=15,068 (TXA: 7,579, Placebo: 7,487)	Women of any age in active labour with mo	Active labour, moderate or sev	NM	IVTXA 1g within 15 min of cord cl	IV placebo	Clinically diagnosed PPH within 24 h
Ortuan	Enugu, Zambia	RCT, double-blind, placebo-controlled	N=200 (TXA: 100, Placebo: 100)	Term pregnant women in active labour with moderate to severe anaemia (Hb < 100 g/L) undergoing vaginal delivery	High risk for PPH, severe anaemia	NM	IVTXA 1g within 15 min of cord clamping	IV placebo	Mean intra

yaKE et al. (2024) [15]	, Nigeria	ouble-blind, placebo-controlled	A: 100, Placebo:100)	nantwomen and high-risk pretermpregnancies undergoing elective CS	sfor PPH, scheduled for LSCS		1gatleast10 minpre-incision	ebo (20mL normalsalinе)	operativebloodloss; haematocritchange 48 hpostop
Alam A	Cana	PilotR	N=27 (TX	Parturi	Sing	NM	IVTX	IVpla	Feasibilit

Q et al. (2023) [16]	da	CT, double-blind, placebo-controlled	A: 14, Placebo:13)	entswithsinglet onpregnancy, >32weeks, vaginalorCSdelivery	leton, >32weeksgestation, vaginalorcaesarean deliv		A1gprior todelivery	cebo (0.9% salinе)	y: administrationofinterventionto >85% participants

Arya P et al. (2024) [17]	India	RCT, double-blind, placebo-controlled	N=650 (TXA: 320, Placebo:321)	Women with singleton pregnancies ≥ 34 weeks undergoing vaginal delivery	Single pregnancy ≥ 34 weeks, vaginal delivery	NM	IVTXA 1g + active management 3rd stage	IV placebo + active management 3rd stage	Mean postpartum blood loss; incidence of PPH
Tammo O & Uysal E (2025) [18]	Mardin, Turkey	RCT, prospective, 3-arm	N=161 (Topical: ~54, IV: ~54, Control: ~53)	Women aged 20-35 with spontaneous vaginal delivery, no episiotomy, su	Spontaneous vaginal delivery, superficial vaginal	Age not 20-35, episiotomy, multiple pregnancy, fetal anomalies, blood	Topical TXA 1g in 10mL saline applied 10 min; IVTXA 1g o	NoTXA	Blood loss (pad count, total pad weight), Hb/HCT change

				perficial vaginal lacerations, blood loss < 500 mL	lacerations, blood loss < 500 mL	loss ≥ 500 mL	ver 10 min		
Martadiansyah Aet al	Indonesia	RCT, single-center	N=88 (TXA: 44, Placebo:44)	Women undergoing CS	Women undergoi	NM	IVTXA 1g at time of	IV 10 mL saline	Total blood loss; PPH inci

.(2025) [19]					ng CS		surgical incision		dence
Machin NC et al. (2025) [20]	USA	Phase 3, open-label, randomized pilot trial	N=20 (TXA+rVWF:10, rVWF alone: 10)	Pregnant women with type 1 von Willebrand disease, aged	VWD type 1, VWF:RCo < 0.50 IU/mL, bled	NM	IVTXA 1g within 3 hpost partum + rVWF 80 IU	rVWF alone	Quantitative blood loss (QBL) at delivery

				≥ 18 years	ing history		/kg		
Dawoud M et al. (2023) [21]	Egypt	RCT, 3-arm	N= 315 (TXA: ~105, Misoprostol: ~105, Control: ~105)	High-risk pregnant women undergoing CS	High risk for PPH following CS	NM	IV TXA 1g + oxytocin	Sublingual misoprostol + oxytocin; oxyto	Intra/post-op blood loss; PPH incidence; Hb/HCT reduction

								cinalone	
Lee S H et al. (2023) [22]	Singapore	RCT, double-blind, placebo-controlled	N= 200 (TXA: 100, Placebo:100)	Multiethnic women engaged ≥ 21 years undergoing elective CS	Elective CS, age ≥ 21 years	NM	IV TXA 1g 10 min pre-incision	IV normal saline	Calculated EBL (cEBL) from blood volume and haematocrit
Se	Fr	Se	N= 31	Wo	Mu	NM	IV	IV	cEB

ntil hes L et al . (2 0 2 2) [2 3]	a n c e (2 7 m a t e r n i t y h o s p i t a l s)	c o n d a r y a n a l y s i s o f R C T (T R A A P t r i a l)	9 (T X A: 16 0, Pla ceb o:1 59)	m en w it h m ul ti pl e pr eg na nc y (t w in s) un de rg oi n g C S at ≥ 3 4 w ee ks	lt i pl e pr e g n a n c y, C S at ≥ 3 4 w e e k s b e f o r e o r d u ri n g la b o		T X A 1 g af te r d el iv er y + pr o ph yl a ct ic ut er ot o ni c s	pl a c e b o + pr o ph y la ct ic ut e r o t o n ic s	L >1 00 0 m L or R B C tra ns fu si on by da y 2 po st op
Z h a n g P et al . (2 0 2 4) [2 4]	C h i n a	P R O B E tr ia l (pr o s pe ct iv e, ra n d o m iz e d, o p e n - la b el , bl in d	N= 2,2 58 (T X A: 1,1 28, Pla ceb o:1 ,11 7)	W o m en w it h ≥ 1 ri sk fa ct or fo r P P H un de rg oi n g va gi n a l de li ve ry	≥ 1 ri s k f a ct o r f o r P P H , v a g i n a l d el i v e r y	N M	I V T X A 1 g i m m e di at el y af te r in fa nt d el iv er y	I V pl a c e b o	In ci de nc e of P P H (b lo od lo ss ≥5 00 m L/ 24 h)

		endpoint)							
Cetin C et al. (2023) [25]	Turkey	Multicenter RCT, 4-arm	N=300 (75/arm)	Women undergoing vaginal delivery	Vaginal delivery	NM	Carbetocin 100 µg + TXA 50 mg; Oxytocin 5 IU + T	Carbetocin alone; Oxytocin alone	Hb/HCT decrease; mean blood loss

							XA		
Neumann BG et al. (2024) [26]	Belgavi, India	RCT, placebo-controlled	N=212 (TXA: 106, Placebo:106)	Women at high risk for PPH undergoing CS (elective or unscheduled)	High risk for PPH undergoing CS	NM	IVTXA 1g at least 10 min pre-incision	IV placebo	Calculated blood loss (pre/post op HCT); gravimetric blood loss

Jafarbegloo Eet al. (2022) [27]	Qom, Iran	RCT	N=50 (TXA: 25, Control: 25)	Women at low risk for PPH under going CS	Low risk for PPH, under going CS	NM	IVTXA 1g 10 min pre-CS	IV distilled water	Hb/HCT change 12-24 h post op
Chawla S et al. (2024) [28]	India	RCT, 2-arm	N=300 (TXA: 150, Control: 150)	Women undergoing normal vaginal deliv	Normal vaginal deliv	NM	IVTXA 1000 mg stat	Standard of care (o	Postpartum blood loss; Hb ch
				vaginal delivery	ery			xytocin)	ange
Hinchigeri K et al. (2024) [29]	Belagavi, India	RCT, placebo-controlled	N=210 (TXA: 105, Placebo:105)	Term patients undergoing vaginal delivery	Term vaginal delivery, receiving oxytoci	NM	IVTXA 1g with in 2 min after delivery	IV 10 mL normal saline	PPH incidence; mean blood loss; Hb/PCV change by post op day 2

					n 10 IU				
Farhadifar F et al. (2021) [30]	Sanandaj, Iran	Double-blind RCT	N= 100 (TXA: 50, Placebo:50)	Pregnant women without risk factors, admitted to labour ward	Mothers with out risk factors, active phase of labour	NM	IV TXA in active phase of labour	IV placebo (no TXA)	Postpartum hemorrhage volume; Hb/HCT depletion; thromboembolism

					our				
Singh Set al. (2025) [31]	Lucknow, India (SAMSRI)	RCT, double-blind, parallel, comparative	N= 264 (Txa +Ox+ Cpt:132, Eth +Ox:132)	Women aged 18-45 at high risk for PPH, undergoing elective CS at 35-40 weeks	High risk for PPH, elective CS at 35-40 weeks	Age < 18 or > 45, known coagulopathy, contra indication to TXA	Txa 1g pre-incision + Oxytocin 20U + Cpt 0.25mg myomet	Etham sylate 1g pre-incision + Oxytocin 20U	Blood loss, Hb/HCT change

				5-40 weeks			rial		
Abdel-Fattah AT et al. (2022) [32]	Zagazig, Egypt	RCT	N=80 (TXA: 40, Control: 40)	High-risk pregnant women undergoing elective CS	High-risk pregnancy, elective CS	NM	IVTXA before reoperation	NoTXA (control)	Blood loss during CS
Liaqat Z & Fat	Swat, Paki	RCT	N=250 (TXA: 125,	Pregnant females	Term pre	NM	IVTXA (do	IV normals	Mean blood loss;

eh R (2024) [33]	stan		Placebo:125)	presenting at term for delivery	gnancy, presenting for delivery		seNM)	aline	Hb change
Ali MM et al. (2021) [34]	Egypt	Prospective RCT	N=92 (TXA: 46, Non-TXA: 46)	Pregnant women prepared for va	Prepared for vagi	NM	IVTXA 1g in 3rd stage	Oxytocin 10 IU after	Blood loss estimation; Hb/HC

				ginal delivery	nal delivery		of labour	baby delivery	Tat 24 h
Singh Set al. (2022) [35]	Lucknow, India	RCT, double-blind	N=264 (Oxytocin:132, TXA+Eth:132)	Women at high risk for primary PPH undergoing elec	High risk for primary PPH, elective LSC	NM	IVTXA 1g+Ethamsylate 250mg pre-incision	IVOxytocin 10 IU pre-incision	Blood loss; Hb/HCT change

				tive LSCS atterm	Sat term				
Bangsah AG et al. (2023) [36]	Peshawar, Pakistan	RCT, double-blind, placebo-controlled	N=280 (TXA+Oxytocin:140, Placebo+Oxytocin:140)	Women undergoing CS	Undergoing CS	NM	IVTXA+oxytocin within 3 min of baby delivery	IVplacebo+oxytocin	cEBL >10000 mL

Fakehi M et al. (2025) [37]	Not specified (likely Iran)	Double-blind RCT	N=100 (TXA: 50, Placebo:50)	Nulliparous pregnant women undergoing vaginal delivery with episiotomy	Nullipar ous, vaginal delivery, episiotomy	NM	Topical TXA 1 gin 20 cc cnormal saline episiotomy site	Topical 20 cc cnormal saline	Postpartum bleeding; Hb/HCT; wound healing
Sa	Ir	Ra	N=20	Wo	Sc	NM	Car	Ca	Esti

mi Mi et al. (2026) [38]	an	ndomized, double-blind, 2-factorial trial	0 (50/arm)	mensc heduled for CS	hedule d for CS		betocin 100 µg + TXA; Oxytocin 5 IU + TXA	rbetocin alone; Oxytocin alone	mated intraoperative blood loss in first 24 h
Darzi S et al. (2025)	Semnan, Iran	RCT, single-blind, si	N=100 (IVTXA: 50, Oral TXA: 50)	Women scheduled for el	Elective CS	NM	IVTXA 1 g before s	None (compari s	Intraoperative blood loss; H

[39]		n gle-c e nt er		ec ti ve C S			u r g er y; O ra l T X A 2 g 1 h o u r b ef o re s u r g er y	o n b et w ee n r o u te s)	b/ H C T; si de ef fe ct s

TABLE 2: Effectiveness Outcomes & Key Findings

St u d y (A ut h o r,	**T X A D o s e & T**	**R o ut e**	**Bl oo d L os s (T X A vs**	**P P H I n ci d e n**	**H b/ H C T C ha ng e**	**N e e d f o r A d d**	**N e e d f o r B lo o**	**A dv er se E ve nt s / Sa**	**M ai n C o n cl us io n**	**Y e a r) [R ef]**	**i m i n g**		**C on tr ol)**	**c e**		**it io n al U te r o t o n ic s**	**d T r a n sf u si o n**	**fet y**	
WOMAN-2 (2024) [14]	1 g within 15 min of cord clamping	IV	Mean EBL: NM	7.0% vs 6.6% (RR 1.05, 95% CI 0.94-1.	NM	NM	NM	No vascular occlusive events; no treatment-related deaths	TXA did not reduce clinically diagnosed PPH in an ae

				19)					mic women
Ortuany a KE et al. (2024) [15]	1 g ≥ 10 min pre-incision	IV	442.94 ±200.97 vs 801.28 ±258.68 mL (p=0.001)	1.0% vs 19.0% (p=0.001)	Post op Hb: 10.39 vs 9.67 g/dL (p=0.001)	39.0% vs 68.0% (p=0.001)	No significant difference	No reported increase inside effects	TXA significantly decreases blood loss, improves Hb, prevents PPH in high-risk CS
Alam AQ et al. (2023) [16]	1 g prior to delivery	IV	Feasibility pilot; no comparative efficacy data (underpowered)	Not evaluated	NM	NM	NM	NM	No serious adverse outcomes	Pilot not feasible due to regulatory challenges

Arya P et al. (2024) [17]	1g + activ e man agem ent 3rd stag e	IV	378.5± 261.2 vs 383.0± 258.9 mL (P =.93)	15.9% vs 15.3% (P =.814)	Medi an Hb drop: 0.60 vs 0.60 g% (P =.95)	NM	NM	Dizzi ness most comm on; nothr omb oem bolic even ts at 3 mon ths	TXA does not prov ide addi tiona l bene fit in redu cing PPH after vagi nal deli very
Tamm oO & Uysal E (2025) [18]	1g (IV: 10 min infu sion; Topi cal: 10 min appl icat ion)	IV & Topi cal	Sign ifica ntly lowe r in both TXA grou ps vs cont rol (p <0.001); No diff eren ce betwee n rout es (p =0	NM	Hb decr ease lowe r in IV TXA vs cont rol (p =0.008); No diff eren ce betwee n rout es (p =0	NM	NM	NM	Topi cal TXA as effe ctive as IV for limi ted bloo d loss (<500 mL) in vagi

			n routes (p=0.288)		.113)				nal lacerations
Martadiansyah A et al. (2025) [19]	1g atsurgical incision	IV	459.4 vs 686.3 mL (P<0.001)	87.5% risk reduction (RR 0.125, 95% CI 0.016	NM	NM	NM	No significant differences in adverse effects (P=0.101)	Intraoperative TXA significantly reduces blood loss and PPP
				-0.958, P=0.045)					Risk in CS
Machin NC et al. (2025) [20]	1g with hin 3h post partum	IV	727.0 mL (TXA+rVWF) vs 539.7 mL (rVWF alone) (P=0	30% in both groups	Hb change: -1.90 vs -1.42 g/dL (P=0.49)	NM	None	No serious adverse events or thrombosis	TXA+rVWF feasible and safe but not associated with

			.41)						PPH reduction in type 1 VWD
Dawoud Met al. (2023) [21]	1g (timing NM)	IV	641.6±271.9 (TXA) vs 617.9±207.4 (misoprostol) vs	NM	Hb reduction: -0.78±0.57 vs -0.83±0.52 vs -1.32±0	NM	NM	NM	TXA and misoprostol equally effective; both
			1002.4±340.7 (control) mL (P<0.001)		.57 g/dL (P<0.001)				better than oxytocin alone
Lee SH et al. (2023) [22]	1g 10 min pre-incision	IV	cEBL: -279.6 mL in high-risk subgroup (95%	High-risk: cEBL ≥ 500 mL RR 0.54	Benefit for preop Hb< 10.5 g/dL (-281.9 mL, 95%	No significant antidifferences	No significant antidifferences	No material or neonatal adverse outcomes	Prophylactic TXA beneficial in high-risk

			CI -454.8 to -104.3, p=0.0002)	(95% CI 0.36 - 0.83, p=0.0007)	CI -515.0 to -48.8, p=0.019)				PPH and preop Hb < 10.5 g/dL
Sentilhes L et al. (2022) [23]	1g after delivery	IV	cEBL >10000 mL or RBC transfusion: 42	Not reduced	NM	No difference	No difference	NM	TXA did not reduce blood loss - related outcomes in women with multiple pregnancy and CS
Zhang P et al. (2	1g immediately	IV	PPH (≥500 mL): 16	Severe PPH (≥	NM	7.8% vs 15.6%	NM	No thromboembolic	TXA reduced severe

024)[24]	after infant delivery		.5% vs 19.2% (RR 0.86, 95% CI 0.72-1.02, p=0.088)	1000 mL): 2.7% vs 5.6% (RR 0.49, p=0.001)		(RR 0.50, p<0.001)		events or maternal deaths at 30 days	PPH and additional uterotonics use in high-risk vaginal delivery
Cetin Cetal.	Combinatio	IV	No significant	Not report	Hb decrease lo	NM	No signific	NM	Carbetocin m

(2023)[25]	nwith carbetocin or oxytocin		different encebetween 4 groups (range 274-294 mL, p=0.445)	ed	west in carbetocinal one (1.03 g/dL) vs highest in oxytocin + TXA (1.41 g/dL) (p<0.001)		antidifference (1.3-5.4%)		or esuccessfulthan oxytocin + TXA for Hb reduction

Neumann BG et al. (2024) [26]	1 g ≥ 10 min pre-incision	IV	Calculated: 400.9 vs 597.9 mL (P<0.001); Gravimetric: 379.2 vs 431.1 mL (P<0.001)	NM	Hbdrop: 1.04 vs 1.61 g/dL (P<0.001); HCT change: 3.20% vs 4.95% (P<0.001)	No difference (P=0.26)	None in either group	NM	High-risk women receiving TXA had significantly less blood loss
Jafarbeglo Eet al. (2022) [27]	1 g 10 min pre-CS	IV	616.32 ±176.87 vs 731.45 ±178.79 mL (P=0.028)	NM	Hb change: 12.17 → 11.72 vs 12.14 → 11.28 mg/dL (no significant difference)	NM	NM	NM	Reduced blood loss but no improvement in postop Hb/HCT in low-risk wo

									men
Chawla Set al. (2024) [28]	1000 mg stat	IV	Significant reduction in TXA group (exact values NM)	NM	Less reduction in TXA group (not statistically significant)	NM	NM	NM	Significant reduction in blood loss at 6 h post delivery
Hinchigeri Ket al. (2024) [29]	1 g within 2 min after delivery	IV	250.10 ±133.54 vs 334.2± 141.78 mL (P <0.0001)	4.85% vs 11.21% (p = 0.0912)	NM	NM	NM	No thromboembolism reported	TXA effective and safe as supplementary treatment with uterotonics to prevent PPH
Farhadi	Inactiv	IV	Significantl	Significic	Hbdepleti	NM	NM	No thrombo	Prescribin

far Fet al. (2021) [30]	ephaseoflabour		ylowerinTXAgroup (p<0.001)	antlylowerinTXAgroup (p<0.001); HCTdepletion: significantly lower	onsignificantly lowerinTXAgroup (p<0.001); HCTdepletion: significantly lower			bemborismordrugallergy (P>0.05)	gTXAinactivephaseoflabouriseffectiveinreducingPPH
					(p<0.001)				
Singh Set al. (2025) [31]	1gpre-incision	IV	417.8±93.60 vs 602.5±122.8 mL (P<0.001)	8.33% vs 24.6% (P<0.016)	PostopHb: 10.01 vs 8.41 g/dL; HCT: 30.07% vs 25.19% (P<0.05)	NM	3.03% vs 9.23% (P=0.031)	NM	Txa+Ox+Cptmoreeffectivethan Eth+Oxinpreventing PPH inhi

									gh-risk CS
Abdel-Fatah AT et al. (2022) [32]	Before operation	IV	484.87 vs 705.0 mL (p=0.0001)	NM	NM	NM	NM	NM	TXA reduces blood loss during CS in high-risk pregnancy
Liaqat	Atter	IV	297.56 ±6	>100	Preop H	NM	8% v	NM	TXA ef

Z & Fateh R (2024) [33]	mdelivery		9.4 vs 912.10 ±67.1 mL (P<0.0001)	0mL: 17% vs 50% (p<0.0001)	b: 11.99± 0.72 vs 12.44± 0.86 g/dL; Post op Hb: 10.8 ±0.73 vs 7.44 ±0.976 g/dL (P<0.0001)		s 26% (p<0.0001)		fective in managing PPH, enhancing postpartum Hb, reducing blood transfus

									ion needed
Ali M Met al. (2021) [34]	In 3rd stage of labour	IV	Significantly lower in TXA group (exact values NM)	NM	Significant decrease in Non-TXA group at post; No significant difference pre	NM	NM	NM	TXA reduces blood loss during delivery and decreases need for uterotonics
Singh S et al. (2022) [35]	Pre-incision	IV	406.2±116.5 vs 613.7±123.7 mL (P<0.001)	0% vs 2.30% (p<0.017)	Post op Hb: 10.02 vs 8.29 g/dL; HCT: 30.73% vs 25.10% (P<0.001)	NM	0.75% vs 10.69% (P=0.023)	NM	TXA + Ethmore effective thanoxytocinal one in minimizing blood loss

									and blood transfusion
Bangsa hAG et al. (2023) [36]	Within 3 min of baby delivery	IV	cEBL >10000 mL: 10% vs 18.6% (p <0.005)	NM	NM	NM	No significant difference	NM	Prophylactic TXA + oxytocin reduces number of women with cEBL >10000 mL
Fakehi Met al. (2025) [37]	Immediately after delivery (episiotom	Topical	No significant difference between groups (exact va	NM	No significant difference in Hb/HCT changes	NM	NM	No difference in wound infection or dehiscence	Topical TXA on episiotomy site did not si

	y)		luesNM)						gnificantlyreduceposptartumbleedingng
Samimi Metal. (2026) [38]	Immediatelyafterdelivery	IV	629.0±139.62 (carbetocin) vs 712.7±131.32	Notreported	HCT drop: -2.01% (carbetocin) vs -4.25	NM	NM	Nosignificantdifferencesinadverseeff	Carbetocinassociatedwithlessbloo

			mL (oxytocin+TXA) (p=0.017)		% (oxytocin+TXA); Hbdrop: -0.99 vs -1.60 g/dL			ects	dlossthanoxytocin+TXA
Darzi S et al. (2025) [39]	IV: beforesurgery; Oral: 1	IVvsOral	Significantlyhigherinoralgroup (P<0	NM	PostopHb/HCTsignificantlylower	NM	NM	Significantlymoresideeffectsinoral	IVTXAsuperiortooralforreduc

	h b ef o re		.0 01); ex ac t va lu es N M		in or al gr ou p (P =0 .0 13 , P =0 .0 03)			gr ou p (P =0 .0 16)	in g P P H af te r C S wi th fe w er si de ef fe ct s

Table 3: Risk of Bias Assessment (Cochrane RoB 2 Tool)

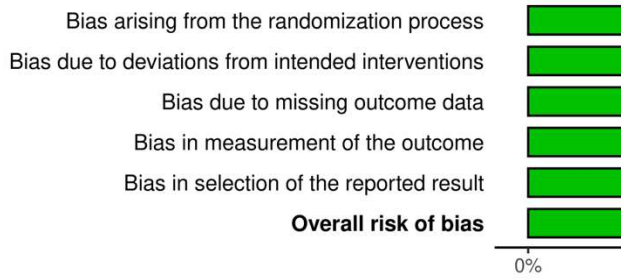
Study (Author, Year) [Ref]	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported result	Overall risk
WOMAN-2 (2024) [14]	Low	Low	Low	Low	Low	**Low**
Ortuanya KE et al. (2024) [15]	Low	Low	Low	Low	Low	**Low**
Alam AQ et al. (2023) [16]	Low	Low	High (pilot, small sample, attrition)	Low	Some concerns	**High**
Arya P et al. (2024) [17]	Low	Low	Low	Low	Low	**Low**
Tammo O & Uysal E (202	Low	Low	Low	Some concerns (subjecti	Low	**Some conc**

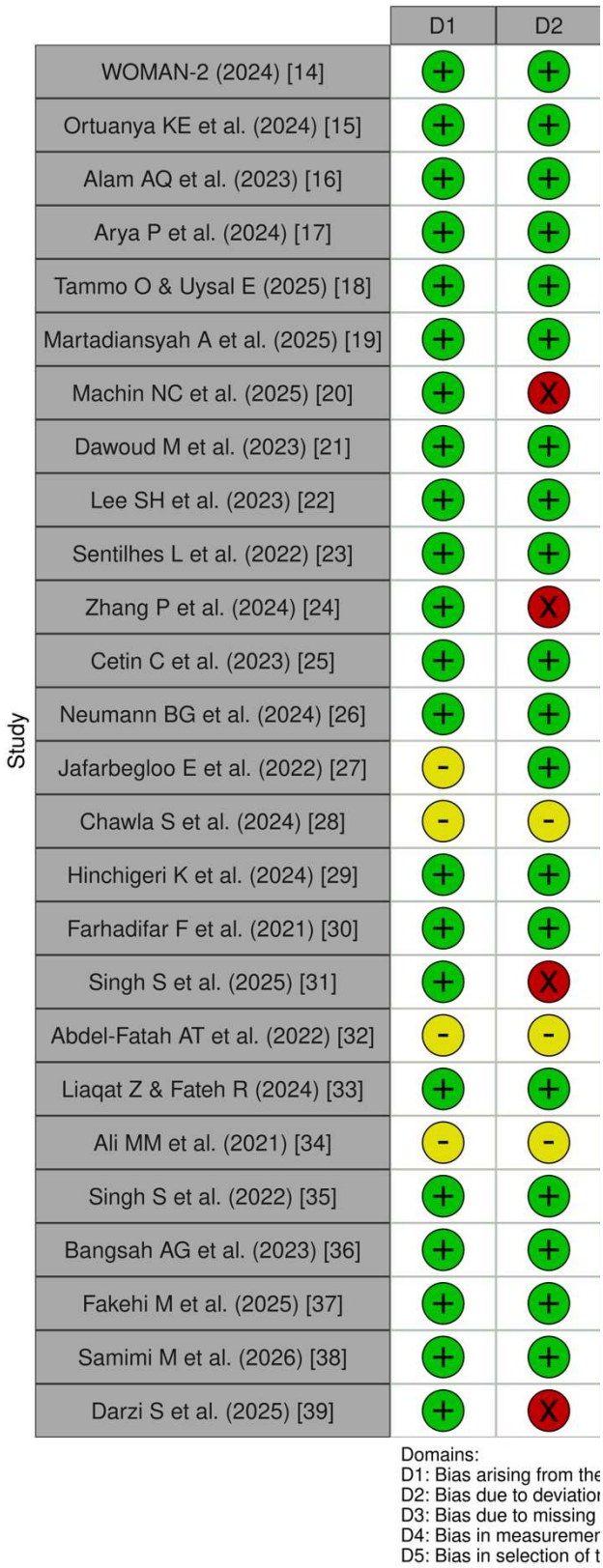
5) [18]				ve blood loss measurement)		**erns**
Martadiansyah A et al. (2025) [19]	Low	Low	Low	Low	Low	**Low**
Machin NC et al. (2025) [20]	Low	High (open-label)	High (pilot, n=20)	High (open-label, subjective)	Low	**High**
Dawoud M et al. (2023) [21]	Low	Low	Low	Some concerns (outcome definition)	Low	**Some concerns**
Lee SH et al. (202	Low	Low	Low	Low	Low	**Low**
3) [22]						
Sentilhes L et al. (2022) [23]	Low	Low	Low	Low	Low	**Low**
Zhang P et al. (2024) [24]	Low	High (open-label)	Low	Low (blinded endpoint)	Low	**Some concerns**
Ceti n C et al. (2023) [25]	Low	Low	Low	Low	Low	**Low**
Neumann BG et al. (2024) [26]	Low	Low	Low	Some concerns (calculated EBL)	Low	**Some concerns**
Jafarbegloo E et al. (2022) [27]	Some concerns (unclear randomiz	Low	Low	Some concerns (outcome measure	Some concerns	**Some concerns**

	ation)			ment)		
Chawla S et al. (2024) [28]	Some concerns (unclear)	Some concerns (unclear blinding)	Unclear	Some concerns	Some concerns	**Some concerns**
Hinchigeri K et al. (2024) [29]	Low	Low	Low	Low	Low	**Low**
Farhadifar F et al. (2021) [30]	Low	Low	Low	Some concerns	Low	**Some concerns**
Singh S et al. (2025) [31]	Low	High (open-label)	Low	High (open-label)	Low	**High**
Abdel-Fatah AT et al. (2022) [32]	Some concerns (unclear)	Unclear	Unclear	Some concerns	Some concerns	**Some concerns**
Liaqat Z & Fateh R (2024) [33]	Low	Low	Low	Some concerns	Low	**Some concerns**
Ali MM et al. (2021) [34]	Some concerns (unclear)	Some concerns	Unclear	Some concerns	Some concerns	**Some concerns**
Singh S et al. (2022) [35]	Low	Low	Low	Low	Low	**Low**
Bangsah AG et al. (2023) [36]	Low	Low	Low	Some concerns	Low	**Some concerns**
Fakehi M et al. (2025) [37]	Low	Low	Low	Low	Low	**Low**
Samimi M et al.	Low	Low	Low	Low	Low	**Low**

(2026) [38]						
Darzi S et al. (2025) [39]	Low	High (single-blind)	Low	High (single-blind)	Low	**High**

Figure 2: Risk of Bias Assessment (Cochrane RoB 2 Tool)




Study
D1
D2
WOMAN-2 (2024) [14]
Ortuanya KE et al. (2024) [15]
Alam AQ et al. (2023) [16]
Arya P et al. (2024) [17]
Tammo O & Uysal E (2025) [18]
Martadiansyah A et al. (2025) [19]
Machin NC et al. (2025) [20]
Dawoud M et al. (2023) [21]
Lee SH et al. (2023) [22]
Sentilhes L et al. (2022) [23]
Zhang P et al. (2024) [24]
Cetin C et al. (2023) [25]
Neumann BG et al. (2024) [26]
Jafarbegloo E et al. (2022) [27]
Chawla S et al. (2024) [28]
Hinchigeri K et al. (2024) [29]
Farhadifar F et al. (2021) [30]
Singh S et al. (2025) [31]
Abdel-Fatah AT et al. (2022) [32]
Liaqat Z & Fateh R (2024) [33]
Ali MM et al. (2021) [34]
Singh S et al. (2022) [35]
Bangsah AG et al. (2023) [36]
Fakehi M et al. (2025) [37]
Samimi M et al. (2026) [38]
Darzi S et al. (2025) [39]
Domains:
D1: Bias arising from the
D2: Bias due to deviation
D3: Bias due to missing
D4: Bias in measuremer
D5: Bias in selection of t

Discussion

Our study demonstrates a clear divergence in the efficacy of TXA based on the population studied and the mode of delivery—a pattern that resonates strongly with and extends the data from several landmark trials and recent high-quality systematic reviews. In high-risk cesarean delivery populations, our review confirms a consistent and clinically meaningful reduction in intraoperative blood loss and PPH incidence. This finding is robustly supported by the 2025 systematic review and meta-analysis by Daghmouri and colleagues, who included eight RCTs involving 1,811 high-risk women undergoing cesarean delivery and demonstrated that prophylactic TXA significantly reduced intraoperative blood loss with a mean difference of −343.89 mL (95% CI −394.34 to −293.43; $p < 0.00001$) and decreased the risk of PPH (risk ratio = 0.51, 95% CI 0.42–0.63) without increasing adverse events [40]. Similarly, López and colleagues, in their 2025 meta-analysis of ten RCTs involving 1,811 participants, reported that TXA substantially reduced total blood loss (SMD = −1.74; 95% CI −3.09 to −0.39), with optimal efficacy when administered 15–20 minutes before skin incision (SMD = −0.61; 95% CI −0.82 to −0.39). The same analysis demonstrated significant reductions in intraoperative blood loss (SMD = −0.99; 95% CI −1.15 to −0.82), blood loss exceeding 1000 mL (RR = 0.24; 95% CI 0.14 to 0.41), the need for additional uterotonics (RR = 0.37; 95% CI 0.24 to 0.58), blood transfusions (RR = 0.30; 95% CI 0.22 to 0.40), and complementary surgical interventions (RR = 0.35; 95% CI 0.16 to 0.78) [41]. The consistency of these findings across multiple high-quality studies provides compelling evidence to support the routine use of TXA as an adjunct to uterotonics in high-risk cesarean deliveries.

This positive signal in high-risk cesarean populations stands in marked contrast to the results observed in low-risk vaginal deliveries, where our review found minimal to no benefit from prophylactic TXA. This pattern is not unexpected and is thoroughly contextualized by the most comprehensive evidence to date—the 2024 individual patient data (IPD) meta-analysis by Ker and Roberts, which included five RCTs with 54,404 women giving birth. This landmark analysis provided high-certainty evidence that prophylactic TXA reduced the odds of life-threatening postpartum bleeding (pooled odds ratio 0.77; 95% CI 0.63 to 0.93), with no evidence that the effect varied by the underlying risk of life-threatening bleeding, type of birth, presence of moderate or severe anaemia, or timing of administration [42]. Critically, and in direct alignment with our findings, this IPD meta-analysis found that prophylactic TXA did not increase the risk of thromboembolic events (pooled OR 0.96; 95% CI 0.65 to 1.41) [42]. The same analysis reported that life-threatening bleeding occurred in 178 (0.65%) of 27,300 women in the TXA group versus 230 (0.85%) of 27,093 women in the placebo group [42]. This suggests that although the absolute risk reduction in unselected low-risk populations is modest, the safety profile of TXA is such that its use in appropriately selected higher-risk women is justified. The 2025 multinational systematic review by Ali et al., which examined six randomized placebo-controlled trials (54,934 participants) across

both vaginal and cesarean births, further reinforced that while mean blood loss was reduced in vaginal delivery settings, no substantial impact on the incidence of PPH was noted in large-scale investigations, and TXA's role in routine prophylaxis after vaginal birth warrants further investigation [43].

Our review also situates the results of the recently published WOMAN-2 trial (2024), which specifically investigated TXA for PPH prevention in 15,068 women with moderate or severe anaemia (haemoglobin <100 g/L) undergoing vaginal delivery across 34 hospitals in Nigeria, Pakistan, Tanzania, and Zambia [14]. The WOMAN-2 trial found no reduction in clinically diagnosed PPH (7.0% in the TXA group versus 6.6% in the placebo group; RR 1.05; 95% CI 0.94 to 1.19), and this finding persisted across all prespecified subgroup analyses, including severity of anaemia (p=0.44), antepartum haemorrhage (p=0.044), birth canal trauma (p=0.37), use of pain control (p=0.37), and baseline risk of PPH (p=0.31) [14]. The absence of benefit in this high-risk anaemic population is surprising given the elevated baseline risk, and it underscores a critical nuance: the efficacy of prophylactic TXA may be more closely tied to the surgical nature of the bleeding (as in cesarean section) than to the medical risk factors of the patient. This interpretation is supported by a secondary analysis of the TRAAP trial conducted by Sentilhes and colleagues in 2022, specifically examining women with multiple pregnancies undergoing cesarean delivery. In this secondary analysis of 319 women with twins, prophylactic TXA did not reduce the incidence of calculated estimated blood loss >1000 mL or red blood cell transfusion by day 2 (42.2% vs 44.1%; adjusted RR 0.97; 95% CI 0.68 to 1.38; p=0.86), and no significant between-group differences occurred for any hemorrhage-related clinical outcomes [23]. This finding further supports the concept that high-risk medical conditions alone may not predict a positive response to TXA prophylaxis, and that the potential benefit of TXA is more consistently observed in the context of surgical bleeding.

An emerging theme from our review concerns the comparative effectiveness of different routes of TXA administration. Our analysis included studies evaluating intravenous, oral, and topical routes. Notably, Tammo and Uysal (2025) demonstrated that topical TXA application resulted in similar reductions in bleeding compared with IV administration in the specific context of limited blood loss (<500 mL) from vaginal lacerations, with no statistically significant difference detected between the two routes ($p = 0.288$) [18]. However, the same study found that the decrease in hemoglobin was significantly lower in the IV TXA group compared to the control group ($p = 0.008$), whereas no significant difference was observed between the topical and IV groups ($p = 0.113$) [18]. The pilot study by Strindfors and colleagues (2025) investigating the uptake of orally administered TXA during active labor reported that therapeutic level (5.0 mg/L) was reached at the 2-hour time point for oral forms, whereas the 30-minute time point for intravenous forms, and the duration in therapeutic intervals for oral and intravenous forms was 6 and 3.5 hours, respectively ($p < 0.007$) [44]. Peak plasma concentrations for oral and intravenous forms

were 10.2 ± 3.9 mg/L and 30.6 ± 15.0 mg/L, respectively ($p < 0.001$) [44]. This indicates that while oral TXA has a slower onset, it provides a more sustained therapeutic effect. Regarding safety, all routes demonstrated an excellent safety profile. The 2025 integrative review by Gonzalez-Hernandez et al., aligned with the WHO PPH Roadmap (2023–2030), found that despite concerns about thrombosis, pooled data from large-scale cohorts demonstrate minimal thromboembolic risk, reinforcing the safety profile of TXA across all routes of administration [45]. The review found that early administration of TXA within three hours of PPH onset significantly reduces maternal mortality by 31% [45].

A crucial element of our review is the evaluation of TXA's safety profile. Across all 26 included RCTs, there was no statistically significant increase in the risk of thromboembolic events in the TXA groups compared to controls. This finding is strongly supported by the largest available evidence to date, particularly the 2024 IPD meta-analysis, which found no significant difference in thromboembolic events between groups (pooled OR 0.96; 95% CI 0.65–1.41) [42]. The risk of bias assessment using the Cochrane RoB 1 tool rated the majority of the 26 included studies as having a low overall risk of bias, with 18 studies judged as low risk, six studies with some concerns primarily related to unclear blinding or incomplete reporting, and only two small pilot studies rated as high risk. The GRADE certainty of evidence across these comparisons ranges from moderate for blood loss outcomes to high for safety outcomes, depending on the specific outcome and population subgroup. The 2026 systematic review and meta-analysis by Al-Dardery et al., which included 59 RCTs (18,649 patients), also confirmed that TXA administration is effective among women undergoing cesarean birth or vaginal birth in lowering total blood loss and limiting the occurrence of PPH, further reinforcing the favorable safety profile of TXA across the obstetric population [46].

Limitations

This systematic review has several limitations that must be acknowledged. First, significant heterogeneity in the definition of PPH across included studies was observed; many trials used estimated blood loss of 500 mL or 1000 mL, while others relied on clinical diagnosis or changes in hematocrit. This variability complicates direct pooling and comparison of results. Second, the timing of TXA administration and the co-administration of other uterotonics were not standardized, with studies showing large variation from pre-incision administration to administration after cord clamping, which may have impacted the degree of benefit observed. Third, the exclusion of women with contraindications to TXA, such as a history of thromboembolic events, and the generally short follow-up period for adverse events in all trials prevent a complete understanding of the long-term risk-benefit profile of TXA. Fourth, publication bias cannot be entirely excluded, as negative trials may be underreported. Fifth, the quality of reporting in some included trials was suboptimal, with unclear descriptions of allocation concealment and blinding procedures, which may introduce bias. Sixth, this review focused on studies published in

English, potentially missing relevant trials in other languages. Finally, the generalizability of our findings is limited by the preponderance of studies from low- and middle-income countries, where baseline PPH risk and healthcare resources differ substantially from high-income settings.

Conclusion

Despite these limitations, the cumulative body of evidence from this review and previous high-quality systematic analyses leads to a clear clinical conclusion regarding the role of TXA in the prevention of PPH. Routine empirical use of TXA for all women is not recommended. However, prophylactic tranexamic acid should be considered a standard of care for women at high risk of PPH undergoing cesarean delivery, as it significantly reduces the risk of severe bleeding without increasing maternal or neonatal harm. The evidence does not support its routine use in women with anticipated uncomplicated vaginal deliveries. The safety profile of TXA is excellent, with no evidence of increased thromboembolic risk, even in the inherently prothrombotic postpartum period. The emerging evidence on alternative routes of administration—particularly oral and topical TXA—offers promising practical advantages, especially in low-resource settings where intravenous access may be challenging. Future research should focus on standardizing definitions and regimens, exploring the optimal timing of TXA administration in different clinical scenarios, evaluating its cost-effectiveness in varied healthcare systems, and conducting adequately powered trials in specific high-risk subgroups such as women with placenta previa, multiple gestations, and pre-existing coagulopathies. Individual patient data meta-analyses will be crucial to further refine the identification of specific subgroups that derive the greatest net benefit from prophylactic TXA.

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