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REVIEW ARTICLE

Obstetrics

The cost-effectiveness of tranexamic acid for treatment of postpartum hemorrhage: A systematic review

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Abstract

Background: Postpartum hemorrhage (PPH) is responsible for nearly one quarter of maternal deaths. A 2017 multicountry trial found that incorporating tranexamic acid (TXA) into the PPH management package was effective in reducing maternal death due to bleeding.

Objective: To systematically review studies assessing the cost-effectiveness of tranexamic acid for PPH treatment.

Search strategy: Nine databases were searched using variations of keywords 'tranexamic acid', 'postpartum hemorrhage' and 'cost effectiveness'.

Selection criteria: Eligible studies were any type of economic or effectiveness evaluation studies on tranexamic acid for treating women with PPH.

Data collection and analysis: Two reviewers independently screened citations and extracted data on cost effectiveness measures. Quality was assessed using the Consensus on Health Economic Criteria list.

Main results: Four studies were included, of which two were abstracts. Three studies concluded that early administration of TXA was cost-saving or cost-effective. One abstract reported TXA was not cost-effective in the USA unless the probability of death due to hemorrhage is higher.

Conclusion: Available evidence (four studies in three countries) suggests that this life-saving intervention may be below willingness to pay thresholds (cost-effective) or cost saving. Further studies conducted in different populations and settings are needed to inform health policy decision-making to reduce PPH-associated morbidity and mortality.

KEYWORDS
cost effectiveness, postpartum hemorrhage, tranexamic acid

1 | INTRODUCTION

In the past 25 years, the global maternal mortality ratio has reduced by nearly 45%, from 385 deaths per 100 000 in 1990 to 216 per 100 000 in 2015.[1] However, an estimated 295 000 women continue to die each year due to pregnancy and related complications – an unacceptably high figure.[1] The majority of these deaths (around 94%) occurred in low- to middle-income countries (LMICs), and nearly all are from preventable causes.[2] Obstetric hemorrhage (27.1%) is the leading cause of maternal mortality, the majority of which are postpartum hemorrhage (PPH).[3]

Approximately 14 million women globally suffer from postpartum hemorrhage each year.[4] WHO has defined PPH as a loss of 500 ml or more blood from the genital tract in the first 24 h after birth.[5] Most PPH-related mortality and severe morbidity are preventable through routine administration of an effective uterotonic in the immediate postpartum period.[6] For those women experiencing PPH, the initial response comprises medications (uterotonics and tranexamic acid), intravenous resuscitation, and uterine massage.[7] If the PPH is not controlled by these measures, additional interventions such as uterine balloon tamponade, non-pneumatic anti-shock garment, compressive measures (bimanual uterine compression or aortic compression) can be used. Surgical procedures (compressive sutures, arterial ligation or hysterectomy) are recommended if hemorrhage continues.[7]

Tranexamic acid (TXA) is an antifibrinolytic drug that slows the breakdown of blood clots (fibrinolysis) and helps prevent prolonged bleeding.[8,9] The 2017 World Maternal Antifibrinolytic (WOMAN) trial was a randomized, double-blind, placebo-controlled trial conducted in 21 countries involving 20 060 women with clinically diagnosed PPH.[9,10] The WOMAN Trial demonstrated that the addition of TXA into standard PPH management packages was effective in reducing maternal death due to bleeding (risk ratio [RR] 0.81, 95% CI 0.65–1.00; P = 0.045).[10] A subsequent Cochrane review identified two trials (including the WOMAN Trial) and concluded that early TXA administration reduced mortality caused by bleeding in women with PPH.[11] Based on this evidence, WHO updated its guidelines to include intravenous TXA within 3 h of birth as part of standard PPH management, regardless of the cause of the bleeding.[12]

Cost-effectiveness analysis of health interventions can identify ways of reallocating finite resources, by identifying inexpensive and effective interventions.[13] In countries with limited resources, evidence on cost effectiveness of health interventions can support wider health service access and coverage.[13] Since the publication of the WOMAN trial, studies have been published exploring the cost effectiveness of TXA, however no study has systematically collated and compared available cost-effectiveness data. Therefore, the aim of this study was to address this knowledge gap and conduct a systematic review of studies of cost-effectiveness of TXA for the treatment of PPH.

2 | MATERIALS AND METHODS

This systematic review was conducted in accordance with PRISMA guidelines and was registered on PROSPERO (CRD42020179622).[14] As the review examined published literature, ethics approval was not required. The primary outcome of interest was the incremental cost effectiveness ratio (ICER) (the change in cost and effectiveness when an intervention is compared to alternative intervention) of TXA for PPH treatment, compared to PPH treatment without TXA. We also considered and extracted all available data pertaining to other measures of cost-effectiveness, including estimates of quality adjusted life years (QALYs) (years of life lived with perfect health), cost, cost savings and cost benefit.

2.1 | Literature search

The following databases were searched: Medline, Embase, Emcare, CINAHL, Business Source Complete, EconLit, NHSEED (NHS Economic Evaluation Database), Web of Science and Scopus, March 23, 2020 and April 05, 2020. Databases were searched using a predefined search strategy developed in consultation with a librarian (Appendix A). Eligible studies were economic evaluations (including full or partial economic evaluations, cost-benefit analyses, cost-effectiveness analyses or similar studies) or interventional studies (such as trials) that provided cost-effectiveness data. Systematic reviews and studies that examined the cost effectiveness of TXA for reasons other than PPH treatment were excluded.

All recovered citations were imported into the Covidence platform for screening.[15] Title and abstract of retrieved studies were screened for relevance against the inclusion criteria by two independent reviewers (SA, SR). Conflicts were resolved upon discussion between the two reviewers or in consultation with a third reviewer (JPV, NS) Full text review was undertaken, with studies assessed according to the aforementioned eligibility criteria. Any disagreements were resolved in consultation with a third reviewer. Reference lists of included studies were also screened for additional eligible studies. Conference abstracts that met the eligibility criteria were included, and we attempted to identify corresponding full texts via additional searching and contacting the study authors.

2.2 | Data extraction and quality assessment

Cochrane guidance for economic evaluation was adopted and followed for this review.[16] A data extraction form was adapted from a 2019 systematic review by Lawrie et al.,[17] which was based on the format and guidance abstracts of economic evaluations for inclusion in the NHS Economic Evaluation Database (NHS EED).[18] Two reviewers (SA, SR) independently extracted data from the included studies, with disagreements resolved through discussion or consulting a third author.

The methodological quality of included studies were assessed using the Consensus on Health Economic Criteria (CHEC) list for assessment of methodological quality of economic evaluations,[19] as recommended by the Cochrane handbook.[20] We adopted three quality categories for the CHEC score (a maximum score of 19) as used by van Eeden et al.[21]: - high (over 15), moderate (9–14) and low (<8). Two reviewers independently assessed the quality using CHEC, with assessments compared and disagreements resolved by discussion or consultation with a third reviewer (JPV, NS).

2.3 | Data synthesis

Data were extracted from included studies and summarized using tables. Descriptive summaries comparing different costing methods was undertaken for each study outcome. The currency and year

applicable to measure the outcome, cost or ICER for each study were reported, along with the time horizon. Available data on other relevant health outcomes (e.g. number of deaths, laparotomies averted) were also extracted. Costs were reported as they appeared in the evidence source, with no conversion used. We originally planned to compare findings between high-income and low- to middle-income countries but given the limited number of eligible studies in few countries, we opted to report results narratively.

3 | RESULTS

3.1 | Characteristics of included studies

A total of 1414 citations were identified. Duplicates were removed using Covidence,[15] with 1219 citations remaining (Figure 1). Title and abstract screening based on the eligibility criteria excluded 1200 citations, resulting in 19 citations for full text review. On full text review, seven citations were excluded as they did not provide cost-effectiveness data, two did not relate to TXA use, two assessed TXA cost effectiveness for prevention of PPH (rather than treatment), two involved drugs other than TXA, two were news articles associated with the WOMAN trial and two citations were duplicates of an included study.[22] The remaining four citations met the eligibility criteria and were included,[22-25] two of which were conference abstracts.[24,25] We attempted to contact the abstract authors, but no additional data were identified.

All four studies aimed to analyze the cost effectiveness of TXA for treatment of PPH and were published between 2018 and 2019 (Table 1). The studies by Sudhof et al. and Wong et al. were undertaken in the USA,[22,25] the study by Li et al. was based on data from the WOMAN trial in Nigeria and Pakistan[23] and the study by Howard et al. did not state which country (though the study authors were from the USA).[24] All studies used a decision tree model (using TreeAge software) and included univariate sensitivity analysis on cost and effectiveness inputs and multivariate probabilistic sensitivity analysis. The conference abstracts did not include information of model structure. The Sudhof et al. decision tree model included sequential branches/parameters for TXA use (none, any, ideal), laparotomy (yes, no), brace sutures (yes, no) and death from PPH (yes, no). The Li et al. decision tree model included sequential branches/parameters for TXA use (yes, no) and death (no death, death from bleeding, death from other causes). Sudhof et al.

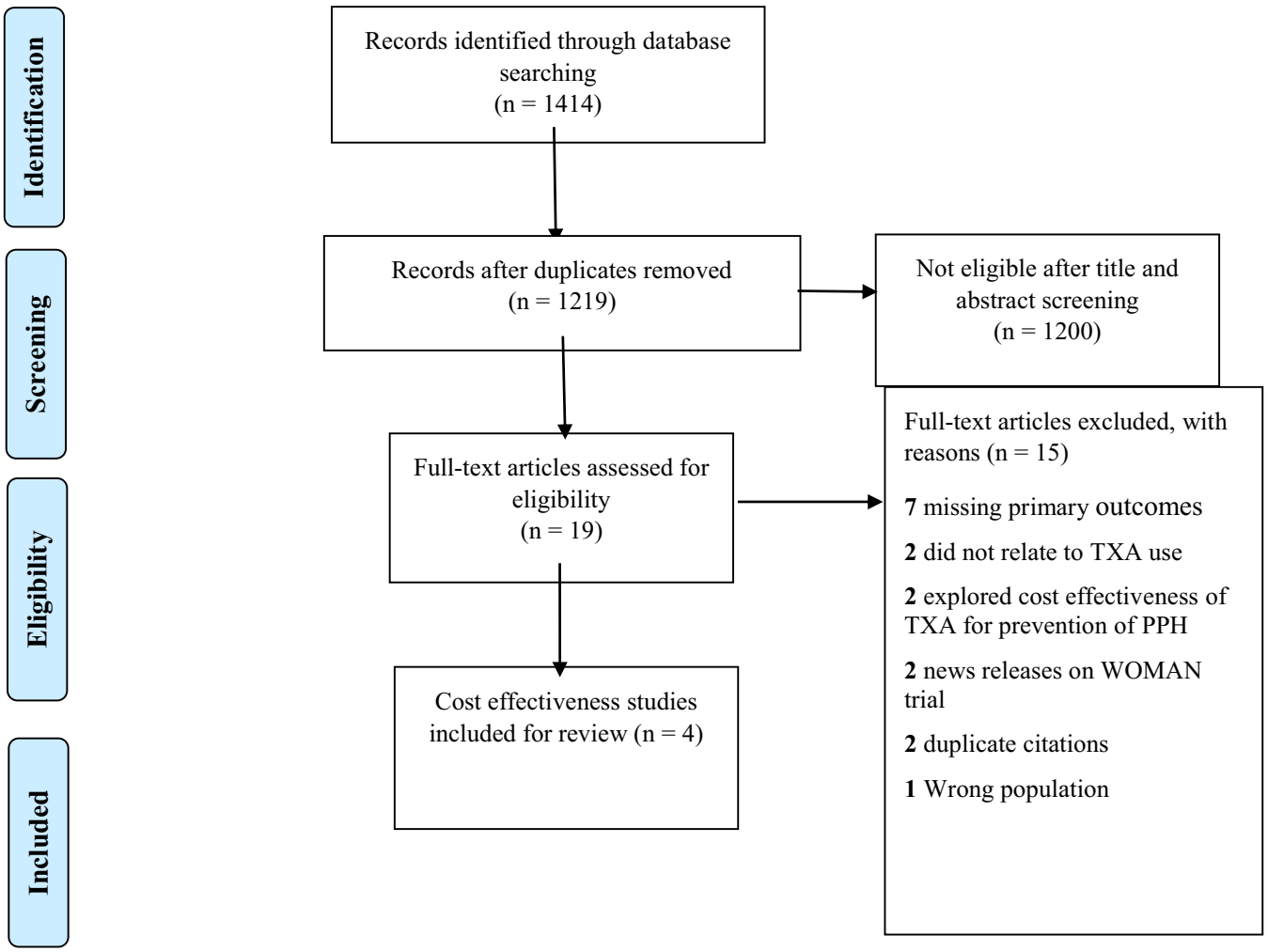

FIGURE 1 PRISMA flowchart for study identification and selection

TABLE 1 Characteristics of included studies

Study	Country	Aim	Design/analytic approach	Year of cost estimates	Study perspective	Types of evaluation (main outcomes)	Discounted rate (per year)	Time horizon (for effects)
Sudhof etal.(2019)[22] Primary Outcome	United States	Demonstrate the cost-effectiveness of routine TXA administration in the treatment of PPH	Decision tree model	2018	Health care system perspective	Incremental cost, PPH-related death avoided, and laparotomies avoided under each strategy	3%	1 year for costs, lifetime for effects
Sudhof et al. (2019)[22] Secondary Outcome			Decision tree model		Societal perspective	QALY and cost per QALY (i.e. incremental cost effectiveness ratio for each strategy)		1 year for costs, lifetime for effects
Li et al. (2018)[23]	Nigeria and Pakistan	Assess the cost-effectiveness of early administration of TXA for treatment of PPH.	Decision tree model	2016	Health care provider perspective	Costs, life-years, and QALYs with and without tranexamic acid, calculated incremental cost-effectiveness ratios (ICERs)	3%	Costs: time horizon as per WOMAN trial (42 days); lifetime for effects
Howard et al. (2018)[24]	Country not stated	Determine whether the routine use of TXA in the setting of PPH is cost-effective	Decision tree model	Not specified	Not specified	Cost savings, QALYs, number of death and laparotomy prevented	Not specified	Not specified
Wong, et al. (2019)[25]	United States	Identify whether TXA is cost effective when applied to a contemporary US population.	Decision tree model	2016	Not specified	ICER per QALY	Not specified	Not specified

Abbreviations: ICER, incremental cost-effectiveness ratio; PPH, postpartum hemorrhage; QALY, quality adjusted life year; TXA, tranexamic acid.

calculated cost for three probable treatment strategies (No TXA; TXA given at any time; TXA given within 3 h of birth).[22] Li et al. compared and estimated cost for no TXA with TXA given within 3 h of birth.[23] The study by Howard et al. estimated cost for TXA given at any time and within 3 h[24] and the Wong study did not specify the timing when TXA was given.[25] Li et al. estimated the cost of 1 g of TXA as US$29.84 for Nigeria and US$5.60 for Pakistan[23] while Sudhof et al. estimated US$37.8.[22] The study by Howard et al. assumed the cost of TXA as US$50.40 per administration[24] and Wong conducted the sensitivity analysis considering the cost of TXA constant at US$187,[25] however the study did not specify whether the estimation was for any specific dosage of TXA or per administration (Table 2).

Methodological quality varied between studies (Table 3). The study by Li et al.[23] was assessed as high quality (18/19) and Sudhof et al.[22]

TABLE 2 Treatment options and estimated outcomes of included studies – tranexamic acid administered at any time for the treatment of postpartum hemorrhage

Study	Country	Cost of TXA (USD)	Cost-effectiveness measures	Deaths averted	Laparotomy averted
Sudhof et al. (2019)[22]	United States	$37.80 per 1 g	$13.7 per QALY	9 per year	334 per year
Li et al. (2018)[23]	Nigeria	$29.84 per 1 g	Not reported	-	-
	Pakistan	$5.60 per 1 g	Not reported	-	-
Howard et al. (2018)[24]	Country not specified	$50.40 per administration	$54,182 per QALY	403 per 100,000 women	457 per 100,000 women
Wong et al. (2019)[25]	United States	$187[a]	$2.3 million per life year gained	9 per 120,000 cases of PPH per year	-

Abbreviations: PPH, postpartum hemorrhage; QALY, quality adjusted life year.

[a]Cost per dose/administration not specified

TABLE 3 Quality assessment of included studies using Consensus on Health Economic Criteria (CHEC)-list

	CHEC-List Items	Sudhof et al. (2019)	Li et al. (2018)	Howard et al. (2018)	Wong et al. (2019)
1	Is the study population clearly described?	Yes	Yes	No	No
2	Are competing alternatives clearly described?	Yes	Yes	Yes	Yes
3	Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes
4	Is the economic study design appropriate to the stated objective?	Yes	Yes	Yes	Yes
5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Yes	No	unable to assess	unable to assess
6	Is the actual perspective chosen appropriate?	Yes	Yes	unable to assess	unable to assess
7	Are all important and relevant costs for each alternative identified?	Yes	Yes	unable to assess	unable to assess
8	Are all costs measured appropriately in physical units?	Unclear	Yes	unable to assess	unable to assess
9	Are costs valued appropriately?	Yes	Yes	unable to assess	Yes
10	Are all important and relevant outcomes for each alternative identified?	Yes	Yes	unable to assess	unable to assess
11	Are all outcomes measured appropriately?	Yes	Yes	Yes	Yes
12	Are outcomes valued appropriately?	Yes	Yes	unable to assess	Yes
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes	unable to assess	unable to assess
14	Are all future costs and outcomes discounted appropriately?	Yes	Yes	unable to assess	unable to assess
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes	Yes	Yes	Yes
16	Do the conclusions follow from the data reported?	Yes	Yes	unable to assess	Yes
17	Does the study discuss the generalizability of the results to other settings and patient/client groups?	No	Yes	unable to assess	unable to assess
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Yes	unable to assess	unable to assess
19	Are ethical and distributional issues discussed appropriately?	No	Yes	unable to assess	unable to assess
	Total Score	16	18	unable to assess	unable to assess
	Methodological Quality	Moderate	High	unable to assess	unable to assess

was moderate quality (16/19). We were unable to fully assess quality of the studies by Howard et al. and Wong et al. as only the abstracts were available.

3.2 | Outcome measures

The study by Howard et al was conducted on a theoretical cohort of 100 000 women receiving usual care for PPH (not otherwise specified).[24] Li et al. used data from WOMAN trial and assessed the cost effectiveness of TXA in usual care for treating women with PPH (blood loss of more than 500 ml after vaginal delivery or 1000 ml after caesarean section or any amount of blood loss that compromise the haemodynamic stability) for Nigeria and Pakistan.[23] The trial randomized a total of 5711 women from Nigeria and 5282 women from Pakistan.[23] Sudhof et al. conducted the analysis on women with PPH requiring second line uterotonics and Wong et al considered women with PPH (not specified otherwise), however the number of women selected for the studies was not specified and used the probability of death due to PPH for the analysis.[22,25] For three included studies, clinical outcomes included number of deaths and laparotomies prevented.[22,24,25] However, Li et al. considered three possible outcomes: death due to PPH, death from other causes, or whether women were alive when discharged.[23]

The study in USA (Sudhof et al.) assessed two outcomes.[22] The primary outcome was the estimated incremental cost per hemorrhage-related death or laparotomy averted, with costs estimated from a health care provider perspective for a one-year period. The secondary outcome was cost per QALY gained from a societal perspective, using a one-year time horizon for costs and a lifetime time horizon for QALYs gained due to deaths or laparotomies averted, which were discounted at 3% per annum.[22] The study in Nigeria and Pakistan (Li et al.[23]) used data from the WOMAN trial [10] to estimate the cost per QALY gained from the health care provider perspective.[23] The time-period for costs were the trial's follow up period (42 days), while a lifetime horizon for benefits was considered, with discounting at 3% per annum. Wong et al.[25] considered cost per life-year gained as the outcome measure, and Howard et al.[24] considered maternal deaths due to hemorrhage averted and laparotomies averted and cost per QALY gained, but additional details (abstracts only) were not available.

Sudhof et al. used cost-effectiveness threshold as 100 000$ per QALY while performing the threshold analysis, stating it as the commonly used threshold in USA, though they observed that there is currently no international consensus on the best cost effectiveness threshold for maternal death.[22] Wong et al. also used $100 000 per life-year threshold for cost-effectiveness estimation.[25] Li et al. reported the cost-effectiveness threshold range used for Nigeria was $446-$2880 per QALY and for Pakistan was $314-$2416 per QALY.[23] However, the study by Howard et al. did not describe a cost-effectiveness threshold.[24]

3.3 | Cost-effectiveness

One study (Sudhof et al.[22]) and one abstract (Howard et al.[24]) reported that TXA was cost saving, and one study (Li et al.[23]) found that TXA was cost effective for reducing maternal mortality and morbidity caused by PPH. However, the abstract by Wong et al. reported TXA was not cost effective compared to usual care in US women with PPH.[25] The authors reported that it may cost US$2.3 million per life-year gained, exceeding their assumed willingness to pay threshold of US$100,000. However, the authors stated that widespread use of TXA may be cost-effective in settings where the probability of death from PPH is higher (i.e. exceeds 7.2 deaths per 10,000 PPH events).[25]

Sudhof et al. estimated that if TXA were used throughout the USA, TXA given at any time could be cost-saving, leading to 9 maternal deaths and 334 laparotomies averted per annum, and save US$11.3 million per annum in healthcare costs (Table 2). If TXA were given to women with PPH within 3 h of birth, an additional 5 maternal deaths and 924 laparotomies could be averted, with a total of US$30.1 million per annum in healthcare cost savings[22] (Table 4). Howard et al. also found TXA to be cost saving – TXA administered at any time would avert 403 deaths and 457 laparotomies, leading to a gain in 11 000 QALYs per 100 000 women, and US $596 million in avoided healthcare costs (Table 2). If TXA were given within 3 h of birth, an additional 165 deaths and 178 laparotomies could be

TABLE 4 Treatment options and estimated outcomes of included studies – tranexamic acid administered within 3 h for the treatment of postpartum hemorrhage

Study	Country	Cost of TXA (USD$)	Cost-effectiveness measures (USD$)	Deaths averted	Laparotomy averted
Sudhof et al. (2019)[22]	United States	37.80 per 1 g	10.91 per QALY	14 per year	1258 per year
Li et al. (2018)[23]	Nigeria	29.84 per 1 g	208 per QALY	-	-
	Pakistan	5.60 per 1 g	83 per QALY	-	-
Howard et al. (2018)[24]	Country not specified	50.40 per administration	52 625 per QALY	568 per 100 000 women	635 per 100 000 women
Wong et al. (2019)[25]	United States	187[a]	-	-	-

Abbreviation: QALY, quality adjusted life year.

[a] Cost per dose/administration not specified.

averted; a total of 16 000 QALYs gained and US$842 million could be saved per 100 000 women with PPH[24] (Table 4). Li et al. estimated the ICER for TXA use in Nigeria and Pakistan to be US$208 and US$83 per QALY gained respectively (year of cost estimated, 2016), which were below the lower bounds of cost-effectiveness in these countries.[23]

All four studies conducted sensitivity analyses.[22-25] Sudhof et al.[22] performed a series of analyses to determine the cost effectiveness of TXA considering important predictive variables. The one-way analysis showed that TXA was cost-effective unless the relative risk reduction due to hemorrhage-related mortality with TXA was greater than 4.7% (the model was not sensitive to any other variables). The threshold analysis showed TXA was cost saving, unless the relative risk reduction of laparotomy with TXA was greater than 7%.They also performed a 2-way sensitivity analysis considering risk reduction of death due to TXA and probability of PPH-related death, confirming that TXA is cost saving.[22] Li et al.[23] performed a series of one-way sensitivity analyses to observe the effect of different parameters (discount rate, cost of TXA and the baseline probability of death due to PPH) on ICER and observed TXA was cost-effective for upper and lower bounds of each parameter for both the countries. They also undertook a multivariate probabilistic uncertainty analysis to determine the probability that TXA was cost-effective for different willingness-to-pay threshold.[23] Wong et al. conducted a one-way sensitivity analysis while keeping the cost of TXA constant at $187 and found that TXA was cost-effective if the probability of death from PPH exceeded 7.2 per 10 000.[25] Howard et al. performed sensitivity analysis considering a range of probabilities for maternal death due to bleeding and found TXA remained the dominant strategy.[24]

4 | DISCUSSION

Limited evidence is available regarding the cost-effectiveness of TXA for PPH treatment. Three of four articles included in this review reported that TXA administration (at any time, and particularly within 3 h of birth) is either cost-saving or cost-effective. One abstract based on a USA population concluded that TXA is not cost-effective unless the death rate due to PPH is more than 7.2 per 10 000. While further evidence is required, it seems likely that in settings where PPH and PPH-related maternal death is prevalent and TXA is available at low price, it is likely to be cost-effective.

The available data are broadly consistent with other cost-effectiveness analyses on the use of TXA for management of non-obstetric bleeding. The CRASH 2 trial in Tanzania, India and the United Kingdom evaluated the cost effectiveness of giving TXA in bleeding trauma patients.[26] The analysis of this trial found that early administration of TXA to a bleeding trauma patient is cost-effective in countries, irrespective of resource availability. The same authors conducted a separate economic evaluation of TXA for elective surgical patients in sub-Saharan Africa with bleeding, where they found that use of TXA reduced mortality and was cost-effective.[27]

Only one article by Wong et al. included in our review found that TXA was not cost effective.[25] Notably, the study was an abstract – hence we cannot fully evaluate methods and study quality – and the unit cost of tranexamic acid ($187) was significantly higher than other studies ($5.60 to $50.40) which may have affected the findings. The study used data from WOMAN trial, where most (91.6%) of the study participants were from Africa and Asia[28] with higher rates of maternal mortality and more limited health resources compare to the US context.

To the best of our knowledge this is the first systematic review to assess the cost effectiveness of TXA for the treatment of PPH. Although WHO has already incorporated and recommended the use of TXA (within 3 h of birth) as part of standard PPH management,[1] incorporation of TXA in routine PPH management varies between countries. High-income countries such as Australia have incorporated use of TXA for initial response to PPH management into clinical guidelines.[29] Some LMIC's have also adopted TXA into standard care – for example, the Kenyan Government recently listed TXA as an important commodity to treat PPH in their implementation plan for scaling up maternal and newborn health interventions.[30] However, few LMICs have formally adopted TXA into standard PPH guidelines.

Cost effectiveness analyses can assist health service providers and policy makers by providing robust evidence of intervention effectiveness. Though few studies are available, the findings can help allocate public and private fund allocation for health system that may lead to wider adoption of TXA into management packages. Strengths of this study include a broad search strategy and duplicate screening, extraction and quality assessment, in line with best practices.[20] Nine databases were searched to minimize the possibility of missing relevant studies. Despite the extensive search, we identified a limited number of studies that met the eligibility criteria. Moreover, two of the studies were abstracts, where methodology detail was not available; contacting study authors did not yield further information. A further limitation is that two studies were based on the US population, where health resources are generally higher, and maternal deaths due to PPH is relatively lower than many LMICs.[22,25] There is not yet sufficient evidence on the cost-effectiveness of TXA in LMICs, where the majority of the world's births occur. Further studies in different settings (and different healthcare system arrangements) are therefore needed. Ideally, such studies should focus on estimating cost per QALY gained to facilitate comparison between studies. When further evidence becomes available, we plan to update this review to inform maternal health policy and programme decision-making, and help reduce PPH-associated morbidity and mortality.

5 | CONCLUSION

There is limited available evidence to evaluate the cost-effectiveness of tranexamic acid for the treatment of PPH in different settings, however available evidence (4 studies in three countries) suggest that this life-saving intervention may be below willingness to pay thresholds (cost-effective) or cost saving.

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CONFLICTS OF INTEREST

JPV and CH were involved in the development of WHO guidelines on the prevention and treatment of postpartum hemorrhage. The authors have no other interests to declare.

AUTHOR CONTRIBUTIONS

Concept for this article was conceived by JPV and SA. Protocol drafted by SA and JPV, with input from all authors. Literature screening, data extraction and quality assessment performed by SA, SR, JPV and NS. All authors contributed to the analysis, interpretation and write up. This article represents the views of the named authors only, and not the views of their institutions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX A

Search strategy for studies of cost-effectiveness of tranexamic acid for the treatment of postpartum hemorrhage

Database: Ovid MEDLINE(R) 1946 to March 25, 2020		
#	**Searches**	**Results**
1	Tranexamic Acid/	3419
2	(tranexamic acid* or txa).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5910
3	(Anti fibrinolytic or antifibrinolytic or antifibrinolysin or anti-fibrinolysin or antiplasmin or anti-plasmin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	12 309
4	(4 amino methylcyclohexane carboxylate or 4 aminomethylcyclohexanecarbonic acid or 4 aminomethylcyclohexanecarboxylic acid or amca or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anexan or antivoff or anvitoff or t-AMCHA).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	480
5	(Caprilon or cis 4 aminomethylcyclohexanecarboxylic acid or cis aminomethyl or cyclohexanecarboxylic acid or cl 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or fibrinon or frenolyse or hemostan or hexacapron or hexakapron or kalnex or lysteda or micranex or para aminomethylcyclohexane carboxylic acid or rikaparin or ronex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	296
6	(Theranex or tramic or tranex or tranexam or tranexanic acid or tranexic or trans 1 aminomethylcyclohexane 4 carboxylic acid or trans 4 aminomethylcyclohexane 1 carboxylic acid or trans 4 aminomethylcyclohexane carboxylic acid or trans 4 aminomethylcyclohexanecarboxylic acid or trans achma or trans amcha or trans aminomethyl cyclohexane carboxylic acid or trans aminomethylcyclohexane carboxylic acid or trans aminomethylcyclohexanecarboxylic acid or transamin or tranol or transaminomethylcyclohexane carboxylic acid transexamic acid or traxamic or trenaxin or ugurol or KABI 2161 or spotof or zataranax).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	87
7	1 or 2 or 3 or 4 or 5 or 6	15 989
8	Postpartum Hemorrhage/	6973
9	((post partum or postpartum or postpartal or postnatal or post natal or puerperal or after childbirth or after birth or after giving birth or after delivery or after the delivery or following childbirth) adj3 (h?em?or?hag* or bleed* or bled or blood loss)).mp.	10 703
10	((atonia or atonic or atony) adj3 (uterus or uterine or myometrium)).mp.	901
11	(obstetric* or birth or pregnan* or labor).mp.	1 247 373
12	8 or 9 or 10 or 11	1 248 408
13	(Cost* or expenditure* or economic* or budget* or finan* or saving or savings).mp.	1 256 066
14	7 and 12 and 13	35

(Continues)

APPENDIX A (Continued)

Database: Embase Classic+Embase 1947 to 2020 March 23		
#	**Searches**	**Results**
1	Tranexamic Acid/	13 045
2	(tranexamic acid* or txa).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	13 923
3	(Anti fibrinolytic or antifibrinolytic or antifibrinolysin or anti-fibrinolysin or antiplasmin or anti-plasmin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	13 641
4	(4 amino methylcyclohexane carboxylate or 4 aminomethylcyclohexanecarbonic acid or 4 aminomethylcyclohexanecarboxylic acid or amca or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anexan or antivoff or anvitoff or t-AMCHA).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	811
5	(Caprilon or cis 4 aminomethylcyclohexanecarboxylic acid or cis aminomethyl or cyclohexanecarboxylic acid or cl 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or fibrinon or frenolyse or hemostan or hexacapron or hexakapron or kalnex or lysteda or micranex or para aminomethylcyclohexane carboxylic acid or rikaparin or ronex).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2767
6	(Theranex or tramic or tranex or tranexam or tranexanic acid or tranexic or trans 1 aminomethylcyclohexane 4 carboxylic acid or trans 4 aminomethylcyclohexane 1 carboxylic acid or trans 4 aminomethylcyclohexane carboxylic acid or trans 4 aminomethylcyclohexanecarboxylic acid or trans achma or trans amcha or trans aminomethyl cyclohexane carboxylic acid or trans aminomethylcyclohexane carboxylic acid or trans aminomethylcyclohexanecarboxylic acid or transamin or tranol or transaminomethylcyclohexane carboxylic acid transexamic acid or traxamic or trenaxin or ugurol or KABI 2161 or spotof or zataranax).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	306
7	1 or 2 or 3 or 4 or 5 or 6	26 585
8	Postpartum Hemorrhage/	14 508
9	((post partum or postpartum or postpartal or postnatal or post natal or puerperal or after childbirth or after birth or after giving birth or after delivery or after the delivery or following childbirth) adj3 (h?em?or?hag* or bleed* or bled or blood loss)).mp.	17 610
10	((atonia or atonic or atony) adj3 (uterus or uterine or myometrium)).mp.	2374
11	(obstetric* or birth or pregnan* or labor).mp.	1 493 216
12	8 or 9 or 10 or 11	1 496 684
13	(Cost* or expenditure* or economic* or budget* or finan* or saving or savings).mp.	1 769 590
14	7 and 12 and 13	158
Database: CINAHL		
	Thursday, March 26, 2020 7:27:46 PM	
#	**Query**	**Results**
S13	(S7 AND S11 AND S12)	196
S12	Cost* or expenditure* or economic* or budget* or finan* or saving or savings	506 967
S11	(S8 OR S9 OR S10)	165 529
S10	((atonia or atonic or atony) N2 (uterus or uterine or myometrium))	294
S9	post partum or postpartum or postpartal or postnatal or post natal or puerperal or after childbirth or after birth or after giving birth or after delivery or after the delivery or following childbirth) N2 (hemorrhage or hemorrhage or bleed* or bled or blood loss	165 507
S8	(MH "Postpartum Hemorrhage")	3567
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	2913

(Continues)

APPENDIX A (Continued)

Database: CINAHL

Thursday, March 26, 2020 7:27:46 PM

#	Query	Results
S6	Theranex or tramic or tranex or tranexam or tranexanic acid or tranexic or trans 1 aminomethylcyclohexane 4 carboxylic acid or trans 4 aminomethylcyclohexane 1 carboxylic acid or trans 4 aminomethylcyclohexane carboxylic acid or trans 4 aminomethylcyclohexanecarboxylic acid or trans achma or trans amcha or trans aminomethyl cyclohexane carboxylic acid or trans aminomethylcyclohexane carboxylic acid or trans aminomethylcyclohexanecarboxylic acid or transamin or tranol or transaminomethylcyclohexane carboxylic acid transexamic acid or traxamic or trenaxin or ugurol or KABI 2161 or spotof or zataranax	801
S5	Caprilon or cis 4 aminomethylcyclohexanecarboxylic acid or cis aminomethyl or cyclohexanecarboxylic acid or cl 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or fibrinon or frenolyse or hemostan or hexacapron or hexakapron or kalnex or lysteda or micranex or para aminomethylcyclohexane carboxylic acid or rikaparin or ronex	826
S4	4 amino methylcyclohexane carboxylate or 4 aminomethylcyclohexanecarbonic acid or 4 aminomethylcyclohexanecarboxylic acid or amca or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anexan or antivoff or anvitoff or t-AMCHA	819
S3	Anti fibrinolytic or antifibrinolytic or antifibrinolysin or anti-fibrinolysin or antiplasmin or anti-plasmin	1857
S2	tranexamic acid* or txa	1958
S1	(MM "Tranexamic Acid")	799

Database(s): Ovid Emcare 1995 to 2020 week 12

Search Strategy:

#	Searches	Results
1	Tranexamic Acid/	4014
2	(tranexamic acid* or txa).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4122
3	(Anti fibrinolytic or antifibrinolytic or antifibrinolysin or anti-fibrinolysin or antiplasmin or anti-plasmin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2043
4	(4 amino methylcyclohexane carboxylate or 4 aminomethylcyclohexanecarbonic acid or 4 aminomethylcyclohexanecarboxylic acid or amca or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anexan or antivoff or anvitoff or t-AMCHA).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	46
5	(Caprilon or cis 4 aminomethylcyclohexanecarboxylic acid or cis aminomethyl or cyclohexanecarboxylic acid or cl 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or fibrinon or frenolyse or hemostan or hexacapron or hexakapron or kalnex or lysteda or micranex or para aminomethylcyclohexane carboxylic acid or rikaparin or ronex).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	277
6	(Theranex or tramic or tranex or tranexam or tranexanic acid or tranexic or trans 1 aminomethylcyclohexane 4 carboxylic acid or trans 4 aminomethylcyclohexane 1 carboxylic acid or trans 4 aminomethylcyclohexane carboxylic acid or trans 4 aminomethylcyclohexanecarboxylic acid or trans achma or trans amcha or trans aminomethyl cyclohexane carboxylic acid or trans aminomethylcyclohexane carboxylic acid or trans aminomethylcyclohexanecarboxylic acid or transamin or tranol or transaminomethylcyclohexane carboxylic acid transexamic acid or traxamic or trenaxin or ugurol or KABI 2161 or spotof or zataranax).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	43
7	1 or 2 or 3 or 4 or 5 or 6	5420
8	Postpartum Hemorrhage/	4305

(Continues)

APPENDIX A (Continued)

Database(s): Ovid Emcare 1995 to 2020 week 12

Search Strategy:

#	Searches	Results
9	((post partum or postpartum or postpartal or postnatal or post natal or puerperal or after childbirth or after birth or after giving birth or after delivery or after the delivery or following childbirth) adj3 (h?em?or?hag* or bleed* or bled or blood loss)).mp.	4806
10	((atonia or atonic or atony) adj3 (uterus or uterine or myometrium)).mp.	738
11	(obstetric* or birth or pregnan* or labor).mp.	283 711
12	8 or 9 or 10 or 11	284 822
13	(Cost* or expenditure* or economic* or budget* or finan* or saving or savings).mp.	478 358
14	7 and 12 and 13	68

Database(s): EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016

#	Searches	Results
1	Tranexamic Acid/	14
2	(tranexamic acid* or txa).mp. [mp=title, text, subject heading word]	18
3	(Anti fibrinolytic or antifibrinolytic or antifibrinolysin or anti-fibrinolysin or antiplasmin or anti-plasmin).mp. [mp=title, text, subject heading word]	15
4	(4 amino methylcyclohexane carboxylate or 4 aminomethylcyclohexanecarbonic acid or 4 aminomethylcyclohexanecarboxylic acid or amca or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anexan or antivoff or anvitoff or t-AMCHA).mp. [mp=title, text, subject heading word]	0
5	(Caprilon or cis 4 aminomethylcyclohexanecarboxylic acid or cis aminomethyl or cyclohexanecarboxylic acid or cl 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or fibrinon or frenolyse or hemostan or hexacapron or hexakapron or kalnex or lysteda or micranex or para aminomethylcyclohexane carboxylic acid or rikaparin or ronex).mp. [mp=title, text, subject heading word]	0
6	(Theranex or tramic or tranex or tranexam or tranexanic acid or tranexic or trans 1 aminomethylcyclohexane 4 carboxylic acid or trans 4 aminomethylcyclohexane 1 carboxylic acid or trans 4 aminomethylcyclohexane carboxylic acid or trans 4 aminomethylcyclohexanecarboxylic acid or trans achma or trans amcha or trans aminomethyl cyclohexane carboxylic acid or trans aminomethylcyclohexane carboxylic acid or trans aminomethylcyclohexanecarboxylic acid or transamin or tranol or transaminomethylcyclohexane carboxylic acid transexamic acid or traxamic or trenaxin or ugurol or KABI 2161 or spotof or zataranax).mp. [mp=title, text, subject heading word]	0
7	1 or 2 or 3 or 4 or 5 or 6	24

Database: Business Source Complete, Econlit

#	Searches	Results
S13	(S7 AND S11 AND S12)	6
S12	Cost* or expenditure* or economic* or budget* or finan* or saving or savings	7 349 532
S11	(S8 OR S9 OR S10)	11 388
S10	((atonia or atonic or atony) N2 (uterus or uterine or myometrium))	2
S9	post partum or postpartum or postpartal or postnatal or post natal or puerperal or after childbirth or after birth or after giving birth or after delivery or after the delivery or following childbirth) N2 (hemorrhage or hemorrhage or bleed* or bled or blood loss	11 388
S8	(MH "Postpartum Hemorrhage")	2
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	292
S6	Theranex or tramic or tranex or tranexam or tranexanic acid or tranexic or trans 1 aminomethylcyclohexane 4 carboxylic acid or trans 4 aminomethylcyclohexane 1 carboxylic acid or trans 4 aminomethylcyclohexane carboxylic acid or trans 4 aminomethylcyclohexanecarboxylic acid or trans achma or trans amcha or trans aminomethyl cyclohexane carboxylic acid or trans aminomethylcyclohexane carboxylic acid or trans aminomethylcyclohexanecarboxylic acid or transamin or tranol or transaminomethylcyclohexane carboxylic acid transexamic acid or traxamic or trenaxin or ugurol or KABI 2161 or spotof or zataranax	21

(Continues)

APPENDIX A (Continued)

#	Searches	Results
Database: Business Source Complete, Econlit		
S5	Caprilon or cis 4 aminomethylcyclohexanecarboxylic acid or cis aminomethyl or cyclohexanecarboxylic acid or cl 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or fibrinon or frenolyse or hemostan or hexacapron or hexakapron or kalnex or lysteda or micranex or para aminomethylcyclohexane carboxylic acid or rikaparin or ronex	27
S4	4 amino methylcyclohexane carboxylate or 4 aminomethylcyclohexanecarbonic acid or 4 aminomethylcyclohexanecarboxylic acid or amca or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anexan or antivoff or anvitoff or t-AMCHA	228
S3	Anti fibrinolytic or antifibrinolytic or antifibrinolysin or anti-fibrinolysin or antiplasmin or anti-plasmin	35
S2	tranexamic acid* or txa	65
S1	(MM "Tranexamic Acid")	57
Database: Web of Science		
1.	((TS=(("post partum" OR "postpartum" OR "postpartal" OR "postnatal" OR "post natal" OR "puerperal" OR "after childbirth" OR "after birth" OR "after giving birth" OR "after delivery" OR "after the delivery" OR "following childbirth") near/3 ("hemorrhage" OR "hemorrhage" OR bleed* OR "bled" OR "blood loss"))))	7059
2	((TS=(("atonia"OR"atonic"OR"atony")near/3("uterus"OR"uterine"OR"myometrium"))))	733
3	((TS= (obstetric* OR "birth" OR pregnan* OR "labor")))	922 954
4	#3 OR #2 OR #1	925 276
5	((TS=("Tranexamic acid" OR "txa" OR "Anti fibrinolytic" OR "antifibrinolytic" OR "antifibrinolysin" OR " anti-fibrinolysin" OR "antiplasmin" OR "anti-plasmin" OR "4 amino methylcyclohexane carboxylate" OR "4 aminomethylcyclohexanecarbonic acid" OR "4 aminomethylcyclohexanecarboxylic acid" OR "amca" OR "AMCHA" OR "amchafibrin" OR "amikapron" OR "aminomethyl cyclohexane carboxylic acid" OR "aminomethyl cyclohexanecarboxylic acid" OR "aminomethylcyclohexane carbonic acid" OR "aminomethylcyclohexane carboxylic acid" OR "aminomethylcyclohexanecarbonic acid" OR "aminomethylcyclohexanecarboxylic acid" OR "aminomethylcyclohexanocarboxylic acid" OR "aminomethylcyclohexanoic acid" OR "amstat" OR "anexan" OR "antivoff" OR "anvitoff" OR "t-AMCHA" OR "Caprilon" OR "cis 4 aminomethylcyclohexanecarboxylic acid" OR "cis aminomethyl" OR "cyclohexanecarboxylic acid" OR "cl 65336" OR "cl65336" OR "cyclocapron" OR "cyclokapron" OR "cyklocapron" OR "cyklokapron" OR "exacyl" OR "fibrinon" OR "frenolyse" OR "hemostan" OR "hexacapron" OR "hexakapron" OR "kalnex" OR "lysteda" OR "micranex" OR "para aminomethylcyclohexane carboxylic acid" OR "rikaparin" OR "ronex" OR "Theranex" OR "tramic" OR "tranex" OR "tranexam" OR "tranexamic acid" OR "tranexic" OR "trans 1 aminomethylcyclohexane 4 carboxylic acid" OR "trans 4 aminomethylcyclohexane 1 carboxylic acid" OR "trans 4 aminomethylcyclohexane carboxylic acid" OR "trans 4 aminomethylcyclohexanecarboxylic acid" OR "trans achma" OR "trans amcha" OR "trans aminomethyl cyclohexane carboxylic acid" OR "trans aminomethylcyclohexane carboxylic acid" OR "trans aminomethylcyclohexanecarboxylic acid" OR "transamin" OR "tranol or transaminomethylcyclohexane carboxylic acid transexamic acid" OR "traxamic" OR "trenaxin" OR "ugurol" OR "KABI 2161" OR "spotof" OR "zataranax"))) *AND* **LANGUAGE:** (English)	12 057
6	((TS=(cost* OR expenditure* OR economic* OR budget* OR finan* OR "saving" OR "savings")))	3 036 930
7	#6 AND #5 AND #4	40

(Continues)

APPENDIX A (Continued)

Database: Scopus		
1	((("post partum" OR "postpartum" OR "postpartal" OR "postnatal" OR "post natal" OR "puerperal" OR "after childbirth" OR "after birth" OR "after giving birth" OR "after delivery" OR "after the delivery" OR "following childbirth") W/3 ("hemorrhage" OR "hemorrhage" OR bleed* OR "bled" OR "blood loss")) OR (("atonia" OR "atonic" OR "atony") W/3 ("uterus" OR "uterine" OR "myometrium")) OR (TITLE-ABS-KEY (obstetric* OR childbirth OR pregnan*))) AND ("Tranexamic acid" OR "txa" OR "Anti-fibrinolytic" OR "antifibrinolytic" OR "antifibrinolysin" OR " anti-fibrinolysin" OR "antiplasmin" OR "anti-plasmin" OR "4 amino methylcyclohexane carboxylate" OR "4 aminomethylcyclohexanecarbonic acid" OR "4 aminomethylcyclohexanecarboxylic acid" OR "amca" OR "AMCHA" OR "amchafibrin" OR "amikapron" OR "aminomethyl cyclohexane carboxylic acid" OR "aminomethyl cyclohexanecarboxylic acid" OR "aminomethylcyclohexane carbonic acid" OR "aminomethylcyclohexane carboxylic acid" OR "aminomethylcyclohexanecarbonic acid" OR "aminomethylcyclohexanecarboxylic acid" OR "aminomethylcyclohexanocarboxylic acid" OR "aminomethylcyclohexanoic acid" OR "amstat" OR "anexan" OR "antivoff" OR "anvitoff" OR "t-AMCHA" OR "Caprilon" OR "cis 4 aminomethylcyclohexanecarboxylic acid" OR "cis aminomethyl" OR "cyclohexanecarboxylic acid" OR "cl 65336" OR "cl65336" OR "cyclocapron" OR "cyclokapron" OR "cyklocapron" OR "cyklokapron" OR "exacyl" OR "fibrinon" OR "frenolyse" OR "hemostan" OR "hexacapron" OR "hexakapron" OR "kalnex" OR "lysteda" OR "micranex" OR "para aminomethylcyclohexane carboxylic acid" OR "rikaparin" OR "ronex" OR "Theranex" OR "tramic" OR "tranex" OR "tranexam" OR "tranexamic acid" OR "tranexic" OR "trans 1 aminomethylcyclohexane 4 carboxylic acid" OR "trans 4 aminomethylcyclohexane 1 carboxylic acid" OR "trans 4 aminomethylcyclohexane carboxylic acid" OR "trans 4 aminomethylcyclohexanecarboxylic acid" OR "trans achma" OR "trans amcha" OR "trans aminomethyl cyclohexane carboxylic acid" OR "trans aminomethylcyclohexane carboxylic acid" OR "trans aminomethylcyclohexanecarboxylic acid" OR "transamin" OR "tranol or transaminomethylcyclohexane carboxylic acid transexamic acid" OR "traxamic" OR "trenaxin" OR "ugurol" OR "KABI 2161" OR "spotof" OR "zataranax") AND (cost* OR expenditure* OR economic* OR budget* OR finan* OR "saving" OR "savings") AND (EXCLUDE (DOCTYPE,"ed") OR EXCLUDE (DOCTYPE,"no") OR EXCLUDE (DOCTYPE,"le") OR EXCLUDE (DOCTYPE,"sh")) AND (EXCLUDE (SUBJAREA,"AGRI") OR EXCLUDE (SUBJAREA,"DECI") OR EXCLUDE (SUBJAREA,"DENT") OR EXCLUDE (SUBJAREA,"ENGI") OR EXCLUDE (SUBJAREA,"COMP") OR EXCLUDE (SUBJAREA,"ARTS") OR EXCLUDE (SUBJAREA,"CHEM") OR EXCLUDE (SUBJAREA,"EART") OR EXCLUDE (SUBJAREA,"MATE") OR EXCLUDE (SUBJAREA,"VETE") OR EXCLUDE (SUBJAREA,"CENG")) AND (LIMIT-TO (LANGUAGE,"English"))	977