National Institute for Health and Care Excellence

Final

Intrapartum care

[O] Evidence reviews for pharmacological management of postpartum haemorrhage

NICE guideline NG235

Evidence reviews underpinning recommendations 1.10.34 and 1.10.35 and a research recommendation in the NICE guideline

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Final

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Pharmacological management of postpartum haemorrhage

Review question

What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

Introduction

Postpartum haemorrhage (PPH), defined as the loss of ≥500 mL of blood from the genital tract in the 24 hours following the birth of a baby, is one of the leading causes of maternal death globally and can also have a significant psychological impact on women. PPH can lead to the need for blood and blood product transfusion, further interventions, and even the need for hysterectomy.

Identifying the most effective pharmacological interventions or treatments that minimise blood loss, reduce mortality and improve women's experience of birth is therefore important, but there is uncertainty about the most effective pharmacological treatments and dosage regimens for women who develop PPH. The most effective sequencing of pharmacological interventions is also uncertain.

This review aims to identify the most effective pharmacological interventions (including doses) to manage primary PPH.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Women who have given birth to a single baby at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women whose baby has not been identified before labour to be at high risk of adverse outcomes • Women with a diagnosis of primary postpartum haemorrhage within the first 24 hours after giving birth, defined as any of the following: ○ blood loss over 500mL ○ postpartum haemorrhage requiring blood transfusion ○ clinically defined postpartum haemorrhage
Intervention	Pharmacological treatments administered by any route and regimen: • Antifibrinolytic drugs (including, but not limited to: aprotinin, tranexamic acid) • Uterotonic drugs (carbetocin, ergometrine, misoprostrol, oxytocin, pitocin, prostaglandins (such as carboprost), syntometrine • A combination of the drugs listed above
Comparison	• Any of the above interventions compared to each other • Placebo
Outcome	**Critical** • Maternal death • Blood loss volume • Coagulation/coagulopathy/occlusive events/embolic event **Important** • Need for additional pharmacological management of haemorrhage • Need for additional surgical management of haemorrhage (for example hysterectomy, balloon tamponade, sutures, interventional radiology) • Breastfeeding • Women's and partner's experience and satisfaction of labour and birth and postnatal period

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

During guideline development, the BNF notation for oxytocin dose changed to 'units', so this has been reflected in the evidence report. The evidence tables in appendix D reflect the dose notations as defined by the original study.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Eleven publications were included for this review: 2 publications were Cochrane systematic reviews (Mousa 2014 and Shakur 2018) that included 10 randomised controlled trials (RCTs) (from Mousa 2014: Blum 2010, Hofmeyr 2004, Lokugamage 2001, Walraven 2004, Widmer 2010, Winikoff 2010, Zuberi 2008; from Shakur 2018: Ducloy-Bouthers 2011, Sahhaf 2014, Shakur 2017), and 9 publications were separate RCTs (Abbas 2019, Abbas 2020, Dallaku

2019, Diop 2020, Javadi 2012, Kumari 2022, Maged 2016, Wang 2020, Zeng 2022). One RCT (Dallaku 2019) was a sub-study of a larger RCT (Shakur 2017).

Six RCTs compared misoprostol to placebo (Abbas 2019, Abbas 2020, Hofmeyr 2004, Walraven 2004, Widmer 2010, and Zuberi 2008). Two RCTs compared misoprostol to intravenous (IV) oxytocin (Blum 2010 and Winikoff 2010). Two RCTs compared tranexamic acid (TXA) to placebo (Ducloy-Bouthors 2011 and Shakur 2017). One RCT compared TXA plus misoprostol to placebo plus misoprostol (Diop 2020). One RCT compared TXA plus oxytocin infusion plus ergometrine to oxytocin infusion plus ergometrine (Javadi 2015). One RCT compared misoprostol to syntometrine (intramuscular (IM) oxytocin and ergometrine) plus IV oxytocin (Lokugamage 2001). One RCT compared carbetocin to IV oxytocin (Maged 2016). Two RCTs compared TXA to misoprostol (Kumari 2022, Sahhaf 2014). One RCT compared carboprost plus oxytocin to oxytocin alone (Wang 2020). One RCT compared carbetocin to TXA.

The studies were from Afghanistan, Albania, Argentina, Bangladesh, Burkina Faso, Cameroon, China, Colombia, Cote d'Ivoire, Democratic Republic of Congo, Ecuador, Egypt, Ethiopia, France, Gambia, Ghana, India, Iran, Jamaica, Kenya, Nepal, Nigeria, Pakistan, Papua New Guinea, Senegal, South Africa, Sudan, Tanzania, Thailand, Turkey, United Kingdom, Uganda, Vietnam and Zambia.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes
Abbas 2019 Randomised controlled trial Pakistan	N = 87 women with postpartum haemorrhage Mixed parity Women received oral misoprostol prophylaxis	800 microgram misoprostol	Placebo	• Maternal death • Need for additional pharmacological management
Abbas 2020 Randomised controlled trial Afghanistan	N = 79 women with postpartum haemorrhage Mixed parity Women received oral misoprostol prophylaxis	800 microgram misoprostol	Placebo	• Maternal death • Need for additional pharmacological management • Need for additional surgical management
Dallaku 2019	N = 187 women with postpartum haemorrhage	1 g TXA	Placebo	• Coagulation

Study	Population	Intervention	Comparison	Outcomes
Randomised controlled trial Albania	Mixed parity 96% of women received uterotonic prophylaxis Part of the larger Shakur			
Diop 2020 Randomised controlled trial Senegal and Vietnam	N = 260 women with postpartum haemorrhage Mixed parity All women received oxytocin prophylaxis	1950 mg TXA + 800 microgram misoprostol	Placebo + 800 microgram misoprostol	• Maternal death • Blood loss volume • Need for additional pharmacological management • Need for additional surgical management
Javadi 2012 Randomised controlled trial Iran	N = 90 women with postpartum haemorrhage Mixed parity All women received oxytocin prophylaxis	1 g TXA + 20 units oxytocin infusion + 0.2 mg ergometrine	20 units oxytocin + 0.2 mg ergometrine Route of delivery of oxytocin not specified	• Blood loss volume • Occlusive event • Need for additional surgical management
Kumari 2022 Randomised controlled trial India	N=80 women with postpartum haemorrhage Mixed parity All women received oxytocin prophylaxis	1g TXA	5 rectal misoprostol pills at 200 microgram	• Blood loss volume
Maged 2016 Randomised controlled trial Egypt	N = 100 women with postpartum haemorrhage Mixed parity It is suggested women received ergometrine as prophylaxis	100 microgram carbetocin	5 units IV oxytocin	• Maternal death • Blood loss volume • Need for additional pharmacological management • Need for additional surgical management
Mousa 2014 Cochrane systematic review	K = 7 (Blum 2010, Hofmeyr 2004, Lokugamage 2001, Walraven 2004, Widmer 2010, Winikoff 2010, Zuberi 2008)	Misoprostol (600 microgram or 800 microgram or 1000 microgram)	Placebo IV oxytocin + placebo Syntometrine (IM oxytocin and	• Maternal death • Blood loss volume • Need for additional pharmacological management

Study	Population	Intervention	Comparison	Outcomes
Argentina, Burkina Faso, Ecuador, Egypt, Gambia, Pakistan, South Africa, Thailand, Turkey, Vietnam	N=3738 women with postpartum haemorrhage Mixed parity Some women received prophylaxis		ergometrine plus) + IV infusion oxytocin + placebo	• Need for additional surgical management
Shakur 2018 Cochrane systematic review Albania, Bangladesh, Burkina Faso, Cameroon, Colombia, Cote d'Ivoire, Democratic Republic of Congo, Egypt, Ethiopia, France, Ghana, Iran, Jamaica, Kenya, Nepal, Nigeria, Pakistan, Papua New Guinea, Sudan, Tanzania, United Kingdom, Uganda, Zambia	K = 3 (Ducloy-Bouthers 2011, Sahhaf 2014, Shakur 2017) N = 20412 women with postpartum haemorrhage Mixed parity Women received oxytocin prophylaxis	1 g or 4 g TXA	Placebo No TXA	• Maternal death • Blood loss volume • Occlusive events • Need for additional pharmacological management • Need for additional surgical management
Wang 2020 Randomised controlled trial China	N = 100 women with postpartum haemorrhage Mixed parity Women received oxytocin prophylaxis	250 microgram carboprost tromethamine	20-50 units continuous oxytocin	• Blood loss volume
Zeng 2022 Randomised controlled trial China	N = 80 women with postpartum haemorrhage Parity not reported Women received oxytocin prophylaxis	100 milligram carbetocin IV (reported in paper as this; believed to be error and dose actually 100 micrograms)	0.5g TXA IV. Second dose given after 1 hour	• Blood loss volume • Coagulation

TXA: tranexamic acid; IM: intramuscular; IV: intravenous

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

All comparisons – maternal death

Across the comparisons identified in this review that reported maternal death, there was no important difference between the interventions (misoprostol versus placebo, misoprostol versus oxytocin, TXA versus placebo, TXA plus misoprostol versus placebo plus misoprostol, and carbetocin versus oxytocin). However, there was an exception between TXA versus placebo when maternal deaths due to bleeding were analysed separately. In this case, TXA had an important benefit with fewer maternal deaths due to bleeding. Most of the evidence reporting maternal death was rated as high quality, with exceptions for TXA plus misoprostol versus placebo plus misoprostol, and carbetocin versus oxytocin, where the evidence was rated as low to moderate, with concerns around imprecision.

Misoprostol versus placebo

For the comparison of misoprostol versus placebo, there was no important difference for blood loss volume, need for additional pharmacological management or need for additional surgical management. Most of the evidence was rated high quality, with the exception of some outcomes rated very low to low due to concerns around imprecision, and some concerns for inconsistency and indirectness. All the evidence was from low/middle income countries.

Misoprostol versus oxytocin

When misoprostol was compared to oxytocin, high quality evidence showed that misoprostol had an important harm when compared to oxytocin in terms of need for additional pharmacological management, in all women and in women who did not receive oxytocin prophylaxis. However, in women who had received oxytocin prophylaxis there was no evidence of an important difference, with the quality of the evidence rated as low due to concerns over imprecision. There was no important difference or no evidence of an important difference for blood loss volume, or need for additional surgical management. The evidence was rated low to high quality with some concerns around imprecision. All the evidence was in low income countries.

TXA versus placebo

TXA was compared to placebo in studies conducted in low/middle and high income countries. One study was a multicentre study which provided data on low, middle and high income countries. The data from this study could not be stratified by low/middle versus high, and so has been analysed as mixed income. However, it was analysed separately from the study reporting in high income countries only. There was no evidence of an important difference, or no important differences for outcomes blood loss volume, occlusive/embolic events, coagulation, need for additional pharmacological management, or need for additional surgical management.

The quality of the evidence ranged from low to high. Apart from risk of bias due to reporting subjective outcomes for blood volume loss, all other concerns around quality were due to imprecision.

TXA plus misoprostol versus placebo plus misoprostol

TXA plus misoprostol was compared to placebo plus misoprostol in low/middle income countries. There was no important difference or no evidence of an important difference, between interventions for blood loss volume, need for additional pharmacological or surgical management. The evidence was mainly of moderate quality with concerns over imprecision.

TXA plus oxytocin plus ergometrine versus oxytocin plus ergometrine

When TXA plus oxytocin plus ergometrine was compared to oxytocin plus ergometrine, there was an important benefit favouring TXA plus oxytocin plus ergometrine in terms of the number of women with blood loss volume between 500 to 1000ml and 1000 to 2000ml, but no evidence of difference in the number of women with blood loss volume over 2000ml. The evidence was rated as very low to moderate. Very low quality evidence showed no important differences in terms of thromboembolism, and low quality evidence showed a possible important benefit favouring TXA plus oxytocin plus ergometrine in terms of need for additional surgical management. Most of the quality concerns were around risk of bias and some concerns around imprecision. The evidence was from a low/middle income country.

Misoprostol versus syntometrine plus oxytocin

Misoprostol was compared to syntometrine (IM oxytocin and ergometrine) plus IV oxytocin in a low/middle income country. Very low to low quality evidence showed an important benefit for misoprostol in terms of need for additional pharmacological and surgical management. There were concerns around the risk of bias and imprecision. The evidence did not report whether the women had received uterotonic prophylaxis.

Carbetocin versus oxytocin

Carbetocin was compared to oxytocin in a low/middle income country. There was no important difference between blood loss volume. However, there was an important benefit favouring carbetocin for need for additional pharmacological and surgical management. The quality of the evidence ranged from moderate to low and was downgraded due to concerns over imprecision.

TXA versus misoprostol

For the comparison of TXA versus misoprostol, there was data on blood loss volume which showed no important difference. The evidence came from a low/middle income countries and was rated low quality due to risk of bias concerns.

Carboprost plus oxytocin versus oxytocin alone

For the comparison carboprost plus oxytocin versus oxytocin alone, there was an important benefit favouring carboprost on blood loss volume at 2, 6 and 12 hours after birth but an important harm for blood loss volume at 24 hours after birth. All the evidence was of low quality due to concerns around risk of bias and indirectness of the data, as diagnosis of postpartum haemorrhage was unclear. The evidence came from low/middle income country.

Carbetocin versus TXA

For the comparison of carbetocin versus TXA, there was data on blood loss volume which showed an important benefit of carbetocin. The evidence came from a low/middle income country and was rated low to very low due to risk of bias and imprecision.

There was no evidence identified for the outcomes breastfeeding or women's and partner's experience and satisfaction of labour and birth and postnatal period.

See appendix F for full GRADE tables.

Economic evidence

Included studies

Two economic studies were identified which were relevant to this question (Sudhof 2019, Howard 2022).

See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included economic evidence

See Table 3 for the economic evidence profile of the included study.

Table 3: Economic evidence profile of a systematic review of economic evaluations of pharmacological treatments for the management of postpartum haemorrhage

Study	Limitations	Applicability	Other comments	Incremental[1]			Uncertainty
				Costs	Effect	Cost effectivenss	
Sudhof 2019 Tranexamic acid in the routine treatment of postpartum hemorrhage in the United States: a cost-effectiveness analysis	Potentially serious limitations[2,3,4,5]	Partially applicable[6]	Study employed a decision-analytic model with average female life expectancy	**Tranexamic acid given at any time** $626 **Tranexamic acid given within 3 hours of birth** $532	**Tranexamic acid given at any time** 0.03 QALYs **Tranexamic acid given within 3 hours of birth** 0.04 QALYs	Tranexamic acid given within 3 hours of birth dominates	Tranexamic strategies had a greater than 99.9% probability of being cost saving One-way threshold analysis indicated that the results were sensitive to the risk reduction in haemorrhage related mortality – tranexamic acid remained cost saving providing relative reduction in postpartum haemorrhage was >4.7%
Howard 2022	Potentially serious limitations[2,4,5]	Partially applicable[6,7,8]	Study employed a decision-analytic model with average female life expectancy	**Early administration of Tranexamic acid** -$154 **Tranexamic acid given within 3 hours of diagnosis of PPH**	**Early administration of Tranexamic acid** 0.003 QALYs **Tranexamic acid given within 3 hours of diagnosis of PPH**	Tranexamic acid given within 3 hours of PPH diagnosis dominates	Early administration of tranexamic acid had a 99.8% probability of being cost-effective relative to no tranexamic acid

Study	Limitations	Applicability	Other comments	Incremental[1]			Uncertainty
				Costs	Effect	Cost effectivenss	
				-$232	0.004 QALYs		

[1] Relative to no tranexamic acid
[2] The model does not include all relevant comparators
[3] Cost of maternal death includes a US malpractice suit
[4] In the base case analysis the model assumes the same relative risk reduction as in the WOMAN trial although the benefit of tranexamic acid may be less in better resourced health care systems
[5] Outcomes in the WOMAN trial that did not show a statistically significant reduction were excluded from the model
[6] The cost-effectiveness model was designed to reflect the management of postpartum haemorrhage in the United States healthcare setting
[7] Costing from a societal perspective is different to the NICE reference case
[8] Analysis assessed cost-effectiveness using a cost-effectiveness threshold of £20,000 per QALY

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Unit costs

Resource	Unit costs	Source
Tranexamic acid	£3.00 [1]	BNF
Oxytocin	£0.80 [2]	BNF
Misoprostol	£0.84 [3]	BNF
Syntometrine (oxytocin and ergometrine)	£1.57 [4]	BNF

[1] Based on dose of 1g and Tranexamic acid 1g/10ml solution for injection ampoules at £15.00 for 5 ampoules
[2] Based on dose of 5 units and Oxytocin 5units/1ml solution for injection ampoules at £4.00 for 5 ampoules
[3] Based on dose of 1,000 micrograms and 200 microgram misoprostol at £10.03 for 60 tablets
[4] Based on dose of 1mL and Syntometrine 500 micrograms/1ml solution for injection ampoules at £7.87 for 5 ampoules

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Maternal death, blood loss volume and coagulation//coagulopathy/occlusive events/embolic events were prioritised as critical outcomes by the committee. Maternal death was prioritised as a critical outcome as postpartum haemorrhage can lead to maternal death if it is not controlled. Blood loss volume was also prioritised as this would be an indicator of the effectiveness of pharmacological treatments to reduce blood loss and consequently maternal deaths. Coagulation/coagulopathy and occlusive/embolic events were also prioritised as critical, as this could be a serious side effect of using pharmacological treatments for postpartum haemorrhage.

The committee agreed that as well as the critical outcomes, the need for additional pharmacological management of haemorrhage, and the need for additional surgical management of haemorrhage should be important outcomes. This would also give an indication of the effectiveness of the interventions as it would show whether they were effective enough to stop bleeding, or if further interventions had to be used. The committee also agreed that breastfeeding was an important outcome as women with high amounts of blood loss may find breastfeeding difficult. Women's and partner's experience and satisfaction of labour and birth and postnatal period was also chosen as an important outcome because postpartum haemorrhage can be a traumatic event for both the woman and her partner and the committee wanted to find out whether any of the interventions have an impact on satisfaction.

The quality of the evidence

The quality of the evidence for outcomes was assessed with GRADE and was rated as high to very low. The main reason why outcomes were downgraded was imprecision around the effect estimate. The risk of bias assessment indicated in some outcomes concerns over randomisation, blinding or participants and outcome assessors, subjective reporting of some outcomes, and lack of information on missing outcome data. There were also some concerns around inconsistency for some outcomes where subgroup analysis could not be performed. Some outcomes were downgraded due to unclear criteria for diagnosis of postpartum haemorrhage.

There was no evidence identified for the outcomes of breastfeeding or women's and partner's experience and satisfaction of labour and birth and postnatal period.

Benefits and harms

The committee discussed that PPH is a medical emergency which requires a coordinated team response and that pharmacological treatments form only a part of this response. Furthermore, a number of pharmacological treatments are often used in succession or in combination. The committee were aware that the 2014 version of the Intrapartum care guideline advised the use of oxytocin and ergometrine as first-line treatments, repeat doses of oxytocin, misoprostol or carboprost as second-line treatments, and tranexamic acid or clotting factors as adjuvant options. The committee discussed the fact that the choice of pharmacological treatments used to treat postpartum haemorrhage depended on the uterotonics that had been given previously for active management of the third stage of labour. For example, ergometrine cannot be repeated so if women had received ergometrine as part of active management of the third stage they could not receive it again for the management of postpartum haemorrhage. The committee agreed this had not been clear in the previous guideline and so reformulated the recommendations into a table which made this easier to describe.

The committee were aware that the NICE surveillance decision to review the evidence for the management of PPH was based primarily on the fact that new evidence was available for the benefits of tranexamic acid and so the committee reviewed all the evidence identified, but focused particularly on the role of tranexamic acid in the overall treatment pathway. However, the committee noted that the evidence presented did not provide any information regarding the ideal sequencing of pharmacological treatments for the management of PPH.

There was no evidence for the use of oxytocin compared to placebo or ergometrine compared to placebo, but the committee were aware from their own knowledge and experience that these agents were effective in practice and there was nothing in the evidence that suggested any harms and so they agreed not to change the recommendations to use these medicines for the treatment of PPH, depending on whether or not they had been used as part of active management. The committee were aware that the half-life of oxytocin was very short and that for the management of PPH it was preferable to set up an intravenous infusion of oxytocin to provide a more sustained effect.

The committee discussed the evidence for tranexamic acid, and agreed that there was a clear benefit compared to placebo in terms of maternal death due to bleeding. The committee discussed that, although the current recommendations advised tranexamic acid as adjuvant treatment after uterotonics have been tried first, due to the different mechanisms of actions, it would be logical if uterotonics and tranexamic acid could be given in combination. This use of combination therapy was reinforced by the evidence from the combination of tranexamic acid with oxytocin and ergometrine that showed benefits on blood loss volume and possible benefits on the need for additional surgical intervention, compared to oxytocin and ergometrine alone. The committee discussed the dose of tranexamic acid and noted that the recommended dose in the Summary of Product Characteristics is 1g given intravenously over 10 minutes. This can then be followed by an intravenous infusion. However, the committee discussed that in the case of ongoing postpartum haemorrhage it was more common practice to give a repeat injection after 30 minutes and that this was reflected in the international FIGO guidelines and the Welsh PPH guidelines.

The committee discussed the evidence for misoprostol and noted that although on its own it did not show any benefits compared to placebo, it showed equivalent efficacy to oxytocin alone and there was some evidence from a single study that when used in combination with oxytocin and ergometrine, it reduced the need for additional pharmacological and surgical treatment. The committee therefore agreed that misoprostol should remain one of the treatment options for PPH. The committee noted that misoprostol was given orally or rectally

and therefore may be of particular benefit in home births, midwife-led settings or before intravenous access could be established to give other uterotonics.

The committee discussed the evidence which showed a benefit of carbetocin over oxytocin in terms of the need for additional pharmacological and surgical management and carbetocin over tranexamic acid, with a reduced blood loss seen with carbetocin. The committee noted that carbetocin was now recommended for active management of the third stage of labour in women having a caesarean birth (see Evidence review M). They highlighted that carbetocin could not be repeated, but agreed that it could be used as an option when additional uterotonics were needed in women who had not previously received carbetocin.

The committee finally discussed the evidence for carboprost. This had shown benefit in combination with oxytocin at reducing blood loss at 2, 6 and 12 hours, compared to oxytocin alone, but the committee noted that by 24 hours the oxytocin alone arm was more effective at reducing blood loss. The committee also discussed the low quality of the evidence, however they were aware from their own experience that carboprost is not associated with any harm, that in the majority of cases the bleeding would have resolved by 12 hours and that as carboprost was still a useful second-line treatment in addition to oxytocin for up to 12 hours after birth, they agreed to retain it as part of the recommendations.

The committee discussed that some of the evidence was in women who had received oxytocin prophylaxis (that is, an injection of oxytocin as part of the active management of the third stage of labour) and some was for women who had not received this. In the UK, the majority of women still receive active management of the third stage, although physiological management (where no oxytocin is administered) may be more common in women who give birth at home or in a midwife-led unit. In the studies where sub-group analysis was possible, there was no difference between the outcomes for women whether or not they had had oxytocin prophylaxis, except for one outcome in the comparison of misoprostol versus oxytocin: women receiving oxytocin had less need for additional pharmacological management than women receiving misoprostol when analysed in all women and in women who had no oxytocin prophylaxis, but no benefit was seen in women who had received oxytocin prophylaxis. This reinforced the committee's view that the choice of agents to treat PPH should take into consideration the medication that has already been administered during the active third stage, and that giving women who had already received one dose of oxytocin another dose of oxytocin was unlikely to be the most effective strategy.

Cost effectiveness and resource use

The committee noted that the acquisition costs of all the medicines being recommended for the management of PPH were low and were likely to be far outweighed by the cost of a PPH, which if not treated promptly could lead to serious maternal consequences including ITU admission.

The evidence review identified 2 economic studies (Sudhof 2019, Howard 2022) in a United States setting which compared tranexamic acid to no tranexamic acid for women with postpartum haemorrhage. Whilst both studies found tranexamic acid to be cost-effective it was not possible for the committee to make recommendations for tranexamic acid as a first line treatment because its cost-effectiveness was not assessed against other uterotonics. Nevertheless, the committee believed it provided some cost-effectiveness justification to their recommendation to give tranexamic acid in combination with other uterotonic drugs to manage postpartum haemorrhage.

Other factors the committee took into account

The committee were disappointed that there was no evidence on breastfeeding or maternal experience or satisfaction and so made a research recommendation.

However, the committee did consider the use of the recommended drugs and the potential risk to babies who were breastfed after their mothers had received treatment for PPH. There are not considered any contraindications to breastfeeding for women who have received tranexamic acid, oxytocin, carbetocin or misoprostol, although additional monitoring of the baby may be considered.

Ergometrine may interfere with lactation although this is unlikely after short-term administration. Carboprost may be present in breast milk but is likely to be degraded in the baby's gastrointestinal tract, and so will not lead to systemic effects in the baby.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.34and 1.10.35 and a research recommendation. Other evidence supporting these recommendations can be found in the evidence review M on Uterotonics for the prevention of postpartum haemorrhage.

References – included studies

Effectiveness

Abbas 2019

Abbas, Dina F., Diop, Ayisha, Durocher, Jill et al. (2019) Using misoprostol to treat postpartum hemorrhage in home deliveries attended by traditional birth attendants. International Journal of Gynecology and Obstetrics 144(3): 290-296

Abbas 2020

Abbas, Dina F., Durocher, Jill, Byrne, Meagan E. et al. (2020) Testing a home-based model of care using misoprostol for prevention and treatment of postpartum hemorrhage: Results from a randomized placebo-controlled trial conducted in Badakhshan province, Afghanistan. Reproductive Health 17(1): 88

Blum 2010

Blum, Jennifer, Winikoff, Beverly, Raghavan, Sheila et al. (2010) Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. The Lancet 375(9710): 217-223

Dallaku 2019

Dallaku, Kastriot, Shakur-Still, Haleema, Beaumont, Danielle et al. (2019) No effect of tranexamic acid on platelet function and thrombin generation (ETAPlaT) in postpartum haemorrhage: a randomised placebo-controlled trial. Wellcome open research 4: 21

Diop 2020

Diop, Ayisha, Abbas, Dina, Martin, Roxanne et al. (2020) A double-blind, randomized controlled trial to explore oral tranexamic acid as adjunct for the treatment for postpartum hemorrhage. Reproductive Health 17(1): 34

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Lokugamage, A. U., Sullivan, K. R., Niculescu, I. et al. (2001) A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. Acta obstetricia et gynecologica Scandinavica 80(9): 835-9

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Maged, A. M.; Hassan, A. M.; Shehata, N. A. (2016) Carbetocin versus oxytocin in the management of atonic post partum haemorrhage (PPH) after vaginal birth: a randomised controlled trial. Archives of gynecology and obstetrics 293(5): 993-999

Mousa 2014

Mousa, Hatem A., Blum, Jennifer, Abou El Senoun, Ghada et al. (2014) Treatment for primary postpartum haemorrhage. The Cochrane database of systematic reviews: cd003249

Sahhaf 2014

Sahhaf, Farnaz, Abbasalizadeh, Shamsi, Ghojazadeh, Morteza et al. (2014) Comparison effect of intravenous tranexamic acid and misoprostol for postpartum haemorrhage. Nigerian medical journal : journal of the Nigeria Medical Association 55(4): 348-53

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Shakur, Haleema, Roberts, Ian, Fawole, Bukola et al. (2017) Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. The Lancet 389(10084): 2105-2116

Shakur 2018

Shakur, H., Beaumont, D., Pavord, S. et al. (2018) Antifibrinolytic drugs for treating primary postpartum haemorrhage. Cochrane Database of Systematic Reviews

Walraven 2004

Walraven, Gijs, Dampha, Yusupha, Bittaye, Bubacarr et al. (2004) Misoprostol in the treatment of postpartum haemorrhage in addition to routine management: a placebo randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 111(9): 1014-7

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Wang, Li; Jiang, Hong-Mei; Yang, Rui-Rui (2020) Carboprost tromethamine prevents caesarean section-associated postpartum hemorrhage. Tropical Journal of Pharmaceutical Research 19(4): 899-904

Widmer 2010

Widmer M, Blum J, Hofmeyr GJ et al. (2010) Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. Lancet (London, England) 375(9728): 1808-1813

Winikoff 2010

Winikoff, Beverly, Dabash, Rasha, Durocher, Jill et al. (2010) Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. Lancet (London, England) 375(9710): 210-6

Zeng 2022

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Zuberi 2008

Zuberi, Nadeem F., Durocher, Jill, Blum, Jennifer et al. (2008) Misoprostol in addition to routine treatment of postpartum hemorrhage: A hospital-based randomized-controlled trial in Karachi, Pakistan. BMC Pregnancy and Childbirth 8: 40

Economic

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Sudoh, Leanna S., Shainker, Scott A., Einerson, Brett D. (2019). Tranexamic acid in the routine treatment of postpartum hemorrhage in the United States: a cost-effectiveness analysis. Am J Obstet Gynecol 221(3) :275.e1-275.e12. doi: 10.1016/j.ajog.2019.06.030. Epub 2019 Jun 18.

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Howard DC, Jones AE, Skeith A, et al. Tranexamic acid for the treatment of postpartum hemorrhage: a cost-effectiveness analysis. Am J Obstet Gynecol MFM 2022;4:100588

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

Table 4: Review protocol

Field	Content
PROSPERO registration number	CRD42021262806
Review title	Effectiveness of pharmacological treatments for the management of postpartum haemorrhage
Review question	What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?
Objective	To update the recommendations in CG190 (2014) for the management of postpartum haemorrhage using pharmacological treatments. Surveillance has identified that there may be pharmacological treatments that are effective in managing postpartum haemorrhage that are not currently recommended.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • International Health Technology Assessment database Searches will be restricted by: • No date limitations • English language only • Human studies only Other searches: • Inclusion lists of systematic reviews

Field	Content
	• The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Pharmacological treatment for the management of postpartum haemorrhage.
Population	• Women who have given birth to a single baby at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women whose baby has not been identified before labour to be at high risk of adverse outcomes • Women with a diagnosis of primary postpartum haemorrhage within the first 24 hours after giving birth, defined as any of the following: o blood loss over 500mL o postpartum haemorrhage requiring blood transfusion o clinically defined postpartum haemorrhage
Intervention	Pharmacological treatments administered by any route and regimen: • Antifibrinolytic drugs (including, but not limited to: aprotinin, tranexamic acid [TXA]) • Uterotonic drugs (carbetocin, ergometrine, misoprostrol, oxytocin, • pitocin, prostaglandins (such as carboprost), syntometrine • A combination of the drugs listed above
Comparator	• Any of the above interventions compared to each other • Placebo
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (individual, cluster)

Field	Content
	Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion criteria	Population: • Women with medical conditions for which management of PPH with the interventions listed above are contraindicated (as specified in NG121 Intrapartum care for women with existing medical conditions or obstetric complications and their babies) • If any study or systematic review includes <1/3 of women with the above characteristics, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.
Context	This guideline will partly update the following: Intrapartum care for healthy women and babies (CG190)
Primary outcomes (critical outcomes)	• Maternal death • Blood loss volume • Coagulation/coagulopathy/occlusive events/embolic event
Secondary outcomes (important outcomes)	• Need for additional pharmacological management of haemorrhage • Need for additional surgical management of haemorrhage (for example hysterectomy, balloon tamponade, sutures, interventional radiology) • Breastfeeding • Women's and partner's experience and satisfaction of labour and birth and postnatal period
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and

Field	Content
	source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster randomised trials The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences: • Maternal death: statistical significance • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes ; +/- 0.5x control group SD for continuous outcomes
Analysis of subgroups	Evidence will be stratified by: • BMI: ○ Underweight range: <18.5 kg/m^2

Field	Content	
	○ Healthy weight range: 18.5 to 24.9 kg/m^2 ○ Overweight range: 25 to 29.99 kg/m^2 ○ Obesity range 1: 30 to 34.99 kg/m^2 ○ Obesity range 2: 35 to 39.99 kg/m^2 • Women who have had pharmacological prophylaxis for PPH vs women who have not • Women who have had oxytocin in labour vs women who have not • Parity (nulliparous vs mixed parity vs multiparous) • Country where the study was conducted: high income countries versus low and middle income countries (as defined by the OECD) Stratifications will be dealt with in a hierarchy (this is, first by BMI, then by women who have had pharmacological prophylaxis, then by women who have had oxytocin in labour, then by parity, and then by country where the study was conducted) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Age of woman (<35 vs >/= 35) • Ethnicity ○ White ○ Asian/Asian British ○ Black/African/Caribbean/Black British ○ Mixed/Multiple ethnic groups ○ Other ethnic group • Women with disability vs not • Deprived socioeconomic group vs not Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☒	Intervention

Field	Content	
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Birth
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	22/06/2021	
Anticipated completion date	22/03/2023	
Named contact	5a. Named contact Guideline Development Team National Guideline Alliance (NGA)5b. Named contact e-mail IPCupdate@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)	
Review team members	Guideline Development Team NGA: Senior Systematic Reviewer Systematic Reviewer	
Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team NGA, Centre for Guidelines, which is part of the National Institute for Health and Care Excellence (NICE)	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting,	

Field	Content	
	any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/cg190	
Other registration details	None	
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=262806	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	[Give words or phrases that best describe the review.]	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☐	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

BMI: Body Mass Index; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for

Health and Care Excellence; OECD: The Organisation for Economic Co-operation and Development; PPH: Postpartum haemorrhage; PRESS: Peer review of electronic search strategies; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: Risk of Bias Assessment Tool for Systematic Reviews; SD: standard deviation; TXA: tranexamic acid

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

Review question search strategies

Database: Medline – OVID interface

Date of last search: 07/12/2022

#	Searches
1	POSTPARTUM HEMORRHAGE/
2	((postpartum or post partum) adj3 h?emorrhag*).ti,ab.
3	PPH.ti,ab.
4	or/1-3
5	exp ANTIFIBRINOLYTIC AGENTS/
6	(antifibrinoly* or anti-fibrinoly* or antiplasmin? or anti-plasmin? or plasmin inhibitor? or aminocaproic acid or tranexamic acid or vitamin k* or alpha-2-antiplasmin or aminomethylbenzoic acid).mp.
7	APROTININ/
8	aprotinin.mp.
9	or/5-8
10	uterotonic?.mp.
11	exp OXYTOCICS/
12	(oxytocic? or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
13	exp PROSTAGLANDINS/
14	(prostaglandin? or carboprost).mp.
15	or/10-14
16	4 and 9
17	4 and 15
18	or/16-17
19	limit 18 to english language
20	LETTER/
21	EDITORIAL/
22	NEWS/
23	exp HISTORICAL ARTICLE/
24	ANECDOTES AS TOPIC/
25	COMMENT/
26	CASE REPORT/
27	(letter or comment*).ti.
28	or/20-27
29	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
30	28 not 29
31	ANIMALS/ not HUMANS/
32	exp ANIMALS, LABORATORY/
33	exp ANIMAL EXPERIMENTATION/
34	exp MODELS, ANIMAL/
35	exp RODENTIA/
36	(rat or rats or mouse or mice).ti.
37	or/30-36
38	19 not 37
39	META-ANALYSIS/
40	META-ANALYSIS AS TOPIC/
41	(meta analy* or metanaly* or metaanaly*).ti,ab.
42	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
43	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
44	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
45	(search* adj4 literature).ab.
46	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
47	cochrane.jw.
48	or/39-47
49	randomized controlled trial.pt.
50	controlled clinical trial.pt.
51	pragmatic clinical trial.pt.

#	Searches
52	randomi#ed.ab.
53	placebo.ab.
54	randomly.ab.
55	CLINICAL TRIALS AS TOPIC/
56	trial.ti.
57	or/49-56
58	38 and 48
59	38 and 57
60	or/58-59

Database: Embase – OVID interface

Date of last search: 07/12/2022

#	Searches
1	POSTPARTUM HEMORRHAGE/
2	((postpartum or post partum) adj3 h?emorrhag*).ti,ab.
3	PPH.ti,ab.
4	or/1-3
5	exp ANTIFIBRINOLYTIC AGENT/
6	(antifibrinoly* or anti-fibrinoly* or antiplasmin? or anti-plasmin? or plasmin inhibitor? or aminocaproic acid or tranexamic acid or vitamin k* or alpha-2-antiplasmin or aminomethylbenzoic acid).mp.
7	aprotinin.mp.
8	or/5-7
9	exp UTEROTONIC AGENT/
10	uterotonic?.mp.
11	(oxytocic? or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
12	exp *PROSTAGLANDIN/
13	(prostaglandin? or carboprost).mp.
14	or/9-13
15	4 and 8
16	4 and 14
17	or/15-16
18	limit 17 to english language
19	letter.pt. or LETTER/
20	note.pt.
21	editorial.pt.
22	CASE REPORT/ or CASE STUDY/
23	(letter or comment*).ti.
24	or/19-23
25	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
26	24 not 25
27	ANIMAL/ not HUMAN/
28	NONHUMAN/
29	exp ANIMAL EXPERIMENT/
30	exp EXPERIMENTAL ANIMAL/
31	ANIMAL MODEL/
32	exp RODENT/
33	(rat or rats or mouse or mice).ti.
34	or/26-33
35	18 not 34
36	SYSTEMATIC REVIEW/
37	META-ANALYSIS/
38	(meta analy* or metanaly* or metaanaly*).ti,ab.
39	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
40	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
41	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
42	(search* adj4 literature).ab.
43	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
44	((pool* or combined) adj2 (data or trials or studies or results)).ab.
45	cochrane.jw.
46	or/36-45
47	random*.ti,ab.
48	factorial*.ti,ab.
49	(crossover* or cross over*).ti,ab.
50	((doubl* or singl*) adj blind*).ti,ab.

#	Searches
51	(assign* or allocat* or volunteer* or placebo*).ti,ab.
52	CROSSOVER PROCEDURE/
53	SINGLE BLIND PROCEDURE/
54	RANDOMIZED CONTROLLED TRIAL/
55	DOUBLE BLIND PROCEDURE/
56	or/47-55
57	35 and 46
58	35 and 56
59	or/57-58

Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews – Wiley interface

Date of last search: 07/12/2022

#	Searches
#1	MeSH descriptor: [Postpartum Hemorrhage] this term only
#2	((postpartum or "post partum") near/3 (hemorrhag* or haemorrhag*)):ti,ab
#3	PPH:ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Antifibrinolytic Agents] explode all trees
#6	(antifibrinoly* or "anti-fibrinoly*" or antiplasmin* or "anti-plasmin*" or "plasmin inhibitor*" or "aminocaproic acid" or "tranexamic acid" or "vitamin k*" or "alpha-2-antiplasmin" or "aminomethylbenzoic acid"):ti,ab
#7	MeSH descriptor: [Aprotinin] this term only
#8	aprotinin:ti,ab
#9	#5 or #6 or #7 or #8
#10	uterotonic*:ti,ab
#11	MeSH descriptor: [Oxytocics] explode all trees
#12	(oxytocic* or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine):ti,ab
#13	MeSH descriptor: [Prostaglandins] explode all trees
#14	(prostaglandin* or carboprost):ti,ab
#15	#10 or #11 or #12 or #13 or #14
#16	#4 and #9
#17	#4 and #15
#18	#16 or #17

Database: International Health Technology Assessment

Date of last search: 07/12/2022

#	Searches
	"Postpartum Hemorrhage"[mh]
	OR All: postpartum hemorrrhage
	OR All: postpartum haemorrrhage
	OR All: post partum hemorrrhage
	OR All: post partum haemorrrhage

Health economics search strategies

Database: Medline – OVID interface

Date of last search: 07/12/2022

#	Searches
1	POSTPARTUM HEMORRHAGE/
2	((postpartum or post partum) adj3 h?emorrhag*).ti,ab.
3	PPH.ti,ab.
4	or/1-3
5	exp ANTIFIBRINOLYTIC AGENTS/
6	(antifibrinoly* or anti-fibrinoly* or antiplasmin? or anti-plasmin? or plasmin inhibitor? or aminocaproic acid or tranexamic acid or vitamin k* or alpha-2-antiplasmin or aminomethylbenzoic acid).mp.
7	APROTININ/
8	aprotinin.mp.

#	Searches
9	or/5-8
10	uterotonic?.mp.
11	exp OXYTOCICS/
12	(oxytocic? or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
13	exp PROSTAGLANDINS/
14	(prostaglandin? or carboprost).mp.
15	or/10-14
16	4 and 9
17	4 and 15
18	or/16-17
19	limit 18 to english language
20	LETTER/
21	EDITORIAL/
22	NEWS/
23	exp HISTORICAL ARTICLE/
24	ANECDOTES AS TOPIC/
25	COMMENT/
26	CASE REPORT/
27	(letter or comment*).ti.
28	or/20-27
29	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
30	28 not 29
31	ANIMALS/ not HUMANS/
32	exp ANIMALS, LABORATORY/
33	exp ANIMAL EXPERIMENTATION/
34	exp MODELS, ANIMAL/
35	exp RODENTIA/
36	(rat or rats or mouse or mice).ti.
37	or/30-36
38	19 not 37
39	ECONOMICS/
40	VALUE OF LIFE/
41	exp "COSTS AND COST ANALYSIS"/
42	exp ECONOMICS, HOSPITAL/
43	exp ECONOMICS, MEDICAL/
44	exp RESOURCE ALLOCATION/
45	ECONOMICS, NURSING/
46	ECONOMICS, PHARMACEUTICAL/
47	exp "FEES AND CHARGES"/
48	exp BUDGETS/
49	budget*.ti,ab.
50	cost*.ti,ab.
51	(economic* or pharmaco?economic*).ti,ab.
52	(price* or pricing*).ti,ab.
53	(financ* or fee or fees or expenditure* or saving*).ti,ab.
54	(value adj2 (money or monetary)).ti,ab.
55	resourc* allocat*.ti,ab.
56	(fund or funds or funding* or funded).ti,ab.
57	(ration or rations or rationing* or rationed).ti,ab.
58	ec.fs.
59	or/39-58
60	38 and 59

Database: Embase – OVID interface

Date of last search: 07/12/2022

#	Searches
1	POSTPARTUM HEMORRHAGE/
2	((postpartum or post partum) adj3 h?emorrhag*).ti,ab.
3	PPH.ti,ab.
4	or/1-3
5	exp ANTIFIBRINOLYTIC AGENT/
6	(antifibrinoly* or anti-fibrinoly* or antiplasmin? or anti-plasmin? or plasmin inhibitor? or aminocaproic acid or tranexamic acid or vitamin k* or alpha-2-antiplasmin or aminomethylbenzoic acid).mp.
7	aprotinin.mp.
8	or/5-7

#	Searches
9	exp UTEROTONIC AGENT/
10	uterotonic?.mp.
11	(oxytocic? or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine).mp.
12	exp *PROSTAGLANDIN/
13	(prostaglandin? or carboprost).mp.
14	or/9-13
15	4 and 8
16	4 and 14
17	or/15-16
18	limit 17 to english language
19	letter.pt. or LETTER/
20	note.pt.
21	editorial.pt.
22	CASE REPORT/ or CASE STUDY/
23	(letter or comment*).ti.
24	or/19-23
25	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
26	24 not 25
27	ANIMAL/ not HUMAN/
28	NONHUMAN/
29	exp ANIMAL EXPERIMENT/
30	exp EXPERIMENTAL ANIMAL/
31	ANIMAL MODEL/
32	exp RODENT/
33	(rat or rats or mouse or mice).ti.
34	or/26-33
35	18 not 34
36	HEALTH ECONOMICS/
37	exp ECONOMIC EVALUATION/
38	exp HEALTH CARE COST/
39	exp FEE/
40	BUDGET/
41	FUNDING/
42	RESOURCE ALLOCATION/
43	budget*.ti,ab.
44	cost*.ti,ab.
45	(economic* or pharmaco?economic*).ti,ab.
46	(price* or pricing*).ti,ab.
47	(financ* or fee or fees or expenditure* or saving*).ti,ab.
48	(value adj2 (money or monetary)).ti,ab.
49	resourc* allocat*.ti,ab.
50	(fund or funds or funding* or funded).ti,ab.
51	(ration or rations or rationing* or rationed).ti,ab.
52	or/36-51
53	35 and 52

Database: Cochrane Central Register of Controlled Trials – Wiley interface

Date of last search: 07/12/2022

#	Searches
#1	MeSH descriptor: [Postpartum Hemorrhage] this term only
#2	((postpartum or "post partum") near/3 (hemorrhag* or haemorrhag*)):ti,ab
#3	PPH:ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Antifibrinolytic Agents] explode all trees
#6	(antifibrinoly* or "anti-fibrinoly*" or antiplasmin* or "anti-plasmin*" or "plasmin inhibitor*" or "aminocaproic acid" or "tranexamic acid" or "vitamin k*" or "alpha-2-antiplasmin" or "aminomethylbenzoic acid"):ti,ab
#7	MeSH descriptor: [Aprotinin] this term only
#8	aprotinin:ti,ab
#9	#5 or #6 or #7 or #8
#10	uterotonic*:ti,ab
#11	MeSH descriptor: [Oxytocics] explode all trees
#12	(oxytocic* or carbetocin or ergometrine or misoprostrol or oxytocin or pitocin or syntometrine):ti,ab
#13	MeSH descriptor: [Prostaglandins] explode all trees
#14	(prostaglandin* or carboprost):ti,ab
#15	#10 or #11 or #12 or #13 or #14

#	Searches
#16	#4 and #9
#17	#4 and #15
#18	#16 or #17
#19	MeSH descriptor: [Economics] this term only
#20	MeSH descriptor: [Value of Life] this term only
#21	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#22	MeSH descriptor: [Economics, Hospital] explode all trees
#23	MeSH descriptor: [Economics, Medical] explode all trees
#24	MeSH descriptor: [Resource Allocation] explode all trees
#25	MeSH descriptor: [Economics, Nursing] this term only
#26	MeSH descriptor: [Economics, Pharmaceutical] this term only
#27	MeSH descriptor: [Fees and Charges] explode all trees
#28	MeSH descriptor: [Budgets] explode all trees
#29	budget*:ti,ab
#30	cost*:ti,ab
#31	(economic* or pharmaco?economic*):ti,ab
#32	(price* or pricing*):ti,ab
#33	(financ* or fee or fees or expenditure* or saving*):ti,ab
#34	(value near/2 (money or monetary)):ti,ab
#35	resourc* allocat*:ti,ab
#36	(fund or funds or funding* or funded):ti,ab
#37	(ration or rations or rationing* or rationed):ti,ab
#38	#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
#39	#18 and #38

Database: International Health Technology Assessment

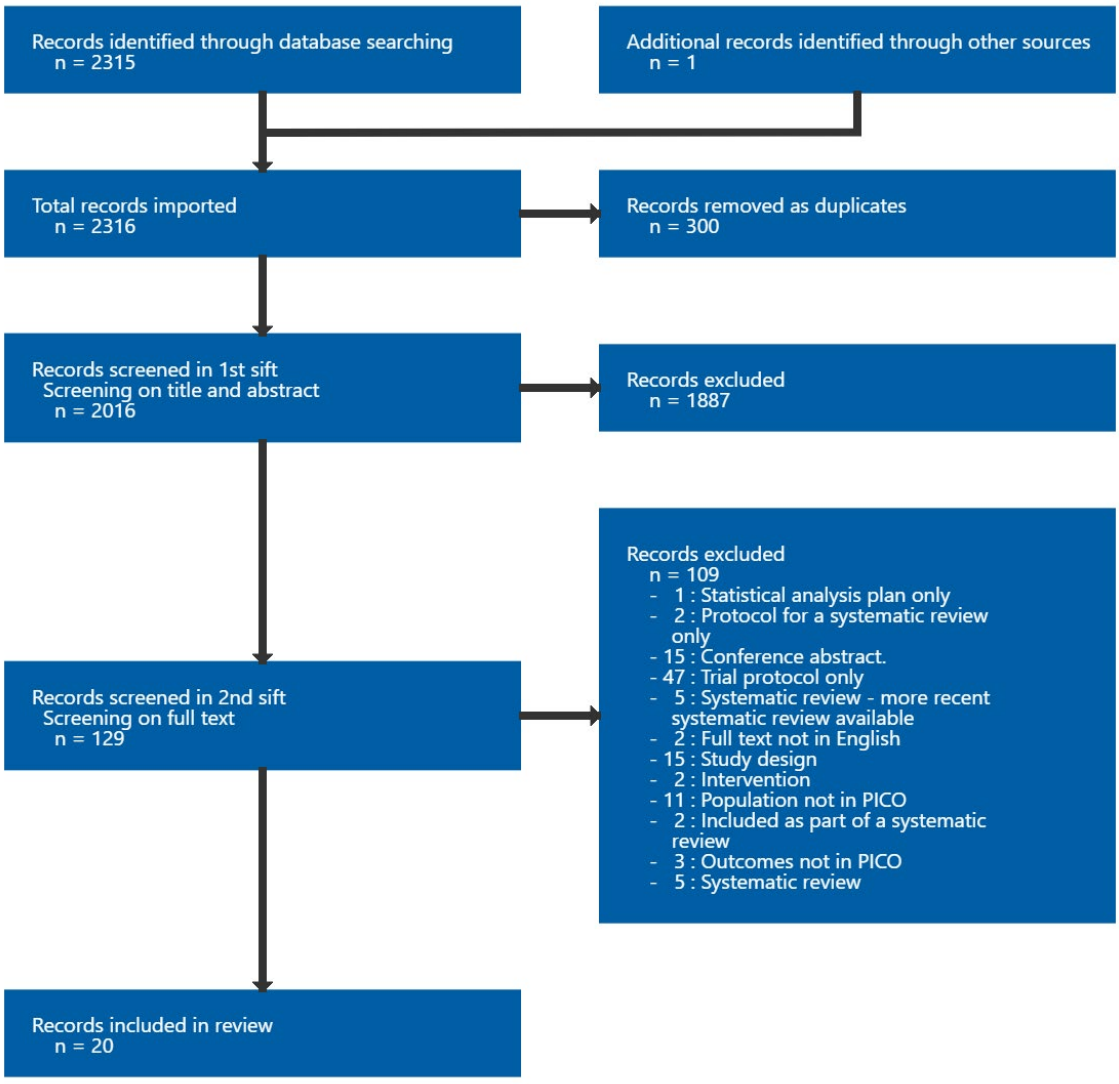
Date of last search: 07/12/2022

#	Searches
	"Postpartum Hemorrhage"[mh]
	OR All: postpartum hemorrrhage
	OR All: postpartum haemorrrhage
	OR All: post partum hemorrrhage
	OR All: post partum haemorrrhage

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

Figure 1: Study selection flow chart



Note: eleven publications were included in this review. However, as 2 of the publications are systematic reviews with 9 additional studies, these individual studies appear in the included records section of the PRISMA diagram.

Note: for this review, de-duplication was done outside of EPPI in EndNote for practical reasons, therefore the study selection flowchart does not accurately reflect the records removed as duplicates.

Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

Abbas, 2019

Bibliographic Reference	Abbas, Dina F.; Diop, Ayisha; Durocher, Jill; Byrne, Meagan E.; Winikoff, Beverly; Jehan, Nusrat; Zuberi, Nadeem; Ahmed, Zafar; Walraven, Gijs; Using misoprostol to treat postpartum hemorrhage in home deliveries attended by traditional birth attendants; International Journal of Gynecology and Obstetrics; 2019; vol. 144 (no. 3); 290-296

Study details

Country/ies where study was carried out	Pakistan
Study type	Randomised controlled trial (RCT)
Study dates	May 2012 to September 2014
Inclusion criteria	• Women had to agree to provide pre-and post-birth haemoglobin levels. • Women had to agree to participate in an exit interview, and give informed consent. • Women were given the treatment if postpartum haemorrhage was diagnosed. • Postpartum haemorrhage was diagnosed by visual estimation, by deteriorating clinical signs, or if blood loss reached 500ml on a bedpan under the woman's buttocks for approximately 1 hour after birth.
Exclusion criteria	No specific exclusion criteria
Patient characteristics	No baseline differences for age, parity, pre-birth haemoglobin, or number of women who received 600microgram oral misoprostol prophylaxis.

	Parity: Intervention: 3.2 ± 1.6 Control: 2.9 ± 1.65 Setting: Home Women received oral misoprostol prophylaxis immediately after birth of the neonate and before the birth of the placenta.
Intervention(s)/control	<u>Intervention</u> • 800microgram misoprostol administered sublingually, by a traditional birth attendant <u>Control</u> • Placebo administered sublingually, by a traditional birth attendant
Duration of follow-up	5 days after birth
Sources of funding	Not industry funded
Sample size	N=87 Intervention arm, n=49 Control arm, n=38 4 women received treatment without postpartum haemorrhage diagnosis, and were included in the analysis.

Outcomes

Outcome	Intervention, , N = 49	Control, , N = 38
Maternal death No of events	n = 0	n = 0
Need for additional pharmacological management Received additional IV/IM oxytocin No of events	n = 11	n = 4

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation sequence was computer generated and random. Providers, trial staff and participants were masked to the sequence.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and care providers were blinded. Treatment and placebo drugs were visually similar. Modified intention to treat analysis was performed on all participants.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for nearly all women)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors were blindedto the intervention assignment until after the data had been collected)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Outcomes were reported as in the pre-specified protocol)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Section	Question	Answer
Overall bias and Directness	Risk of bias variation across outcomes	No variation between outcomes

Abbas, 2020

Bibliographic Reference	Abbas, Dina F.; Durocher, Jill; Byrne, Meagan E.; Winikoff, Beverly; Mirzazada, Shafiq; Pamiri, Shahfaqir; Testing a home-based model of care using misoprostol for prevention and treatment of postpartum hemorrhage: Results from a randomized placebo-controlled trial conducted in Badakhshan province, Afghanistan; Reproductive Health; 2020; vol. 17 (no. 1); 88

Study details

Country/ies where study was carried out	Afghanistan
Study type	Randomised controlled trial (RCT)
Study dates	August 2012 to February 2016
Inclusion criteria	• Agree to have pre- and post-birth haemoglobin measured. • Agree to have a community health worker in the room at time of birth to observe for signs of postpartum haemorrhage. • Agree to participate in an exit interview if diagnosed and treated for postpartum haemorrhage. • Be diagnosed with postpartum haemorrhage to receive the intervention or control treatment. • Postpartum haemorrhage was diagnosed by the community health worker, who received specific training to diagnose PPH. PPH was diagnosed as blood loss soaking through 2 cloths (1m by 1m cloths provided by trialists) OR visual estimation OR visible deterioration in the woman's condition (profuse bleeding, paleness, faintness, rapid breathing). • Using cloths is in line with guidance from Ministry of Publish Health Afghanistan
Exclusion criteria	None specified

Patient characteristics	No baseline difference in age, parity or pre-birth haemoglobin. Parity: Intervention: 3.1 ± 1.9 Control: 2.9 ± 1.8 Setting: Home Women self-administered 600 microgram (3 tablets) of misoprostol prophylaxis immediately after the birth of the baby
Intervention(s)/control	Intervention • After diagnosis with postpartum haemorrhage, the community health worker administered 800microgram misoprostol sublingually to the woman Control • After diagnosis with postpartum haemorrhage, the community health worker administered placebo sublingually to the woman
Duration of follow-up	5 days post birth
Sources of funding	Not industry funded
Sample size	N=79 Intervention arm, n=40 Control arm, n=39
Other information	91% of women had PPH diagnosed using cloths only. This is in line with PPH diagnosis in Afghanistan but there is no indication that this method equates to 500ml blood loss volume.

Outcomes

Outcome	Intervention, , N = 40	Control, , N = 39
Maternal death No of events	n = 0	n = 1
Need for additional pharmacological management Administered IV oxytocin at facility No of events	n = 17	n = 14
Need for additional pharmacological management Administered ergometrine No of events	n = 2	n = 6
Need for additional surgical management Surturing/tear repair No of events	n = 1	n = 1
Need for additional surgical management Hysterectomy/other surgery No of events	n = 0	n = 0

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was computer generated and concealed until after data collection.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and care providers were blinded to intervention assignment. Modified intention to treat analysis performed, all women receiving treatment were included in the analysis.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data are available for all women)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors were not aware of assigned intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Outcomes are reported as in the pre-specified protocol)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation between outcomes

Dallaku, 2019

Bibliographic Reference	Dallaku, Kastriot; Shakur-Still, Haleema; Beaumont, Danielle; Roberts, Ian; Huque, Sumaya; Delius, Maria; Holdenrieder, Stefan; Gliozheni, Orion; Mansmann, Ulrich; No effect of tranexamic acid on platelet function and thrombin generation (ETAPlaT) in postpartum haemorrhage: a randomised placebo-controlled trial; Wellcome open research; 2019; vol. 4; 21

Study details

Country/ies where study was carried out	Albania
Study type	Randomised controlled trial (RCT)
Study dates	November 2013 - January 2015

Inclusion criteria	• Women with primary postpartum haemorrhage (diagnosed on visual estimation of blood loss as >500ml after a vaginal birth or 1000ml or more after a caesarean birth; OR blood loos sufficient to cause haemodynamic instability).
Exclusion criteria	• If clinician was uncertain if TXA should be used in a particular woman.
Patient characteristics	No differences in baseline between groups for age, parity, gestational age or BMI. Nullipara Intervention: 57 (61.3 %) Control: 60 (63.8 %) Multipara Intervention: 36 (38.7 %) Control: 34 (36.2 %) Women were part of the larger WOMAN trial (Shakur 2017) where 96% of women received uterotonic prophylaxis. Whether oxytocin was given during labour is not reported.
Intervention(s)/control	Intervention: IV injection of 1g TXA at 1ml/minute. Control: Placebo. A second dose of study drugs was administered if bleeding did not stop after 30 minutes or restarted within 24 hours of the first dose. Women received the usual treatment for PPH in both groups.
Duration of follow-up	

Sources of funding	Not industry funded
Sample size	N=187 Intervention, n=93 Control, n=94
Other information	Sub-study of the WOMAN trial (Shakur 2017) included in Shakur 2018 Cochrane systematic review

Outcomes

Outcome	**Intervention, , N = 93**	**Control, , N = 94**
Fibrinogen (g/L) Mean (95% CI)	0.05 (-0.1 to 0.2)	0.13 (-0.01 to 0.27)

Critical appraisal

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants and care providers were masked to treatment allocation)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and caregivers were blinded to allocation and intention to treat analysis performed.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for most participants. Data for 6 participants in the intervention arm could not be collected due to the emergency of the situation. Missingness of this data is unlikely to affect the true value of the outcome.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring was appropriate and outcome assessors were blinded to the intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Outcomes are reported as in the pre-specified protocol.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation between outcomes

Diop, 2020

Bibliographic Reference	Diop, Ayisha; Abbas, Dina; Martin, Roxanne; Winikoff, Beverly; Ngoc, Nguyen Thi Nhu; Razafi, Ange; Tuyet, Hoang Thi Diem; A double-blind, randomized controlled trial to explore oral tranexamic acid as adjunct for the treatment for postpartum hemorrhage; Reproductive Health; 2020; vol. 17 (no. 1); 34

Study details

Country/ies where study was carried out	Senegal and Vietnam
Study type	Randomised controlled trial (RCT)
Study dates	October 2016 - January 2018
Inclusion criteria	• Vaginal birth • Written informed consent prior to birth

Exclusion criteria	• History of thrombosis • Clear contraindication for tranexamic acid
Patient characteristics	No significant differences at baseline between groups for age or parity. BMI not reported. Parity: Intervention: 0.85 Control: 0.61 Setting: Hospital All women received oxytocin prophylaxis. If women received oxytocin during labour not reported.
Intervention(s)/control	• Oral TXA 1950mg (3 x 650mg) and 800microgram misoprostol (4 x 200mmicrogram) sublingually • Placebo (orally) and 800microgram misoprostol (4 x 200microgram) sublingually
Duration of follow-up	• 2 hours
Sources of funding	Not industry funded
Sample size	• N= 260 women randomised • Excluded before treatment n= 2 • TXA group: n= 130 (130 included in analysis) • Placebo group: n= 128 (128 included in analysis)

Outcomes

Outcome	Placebo + Misoprostol, , N = 128	TXA + Misoprostol, , N = 130
Maternal death No of events	n = 0	n = 0
Blood loss volume 20 min post treatment (ml) Median (IQR)	750 (500 to 2200)	750 (550 to 1600)
Blood loss volume 40 min post treatment (ml) Median (IQR)	800 (500 to 2300)	800 (550 to 2000)
Blood loss volume 1 hour post treatment (ml) Median (IQR)	800 (500 to 2300)	800 (550 to 2000)
Blood loss volume 2 hours post treatment (ml) Median (IQR)	800 (500 to 2300)	800 (550 to 2000)
Need for additional pharmacological management Uterotonics, TXA IV No of events	n = 55	n = 62
Need for additional surgical management Uterine evacuation, uterine packing, uterine artery ligature, hysterectomy, tissue repair No of events	n = 19	n = 11
Need for additional surgical management Sutures No of events	n = 111	n = 108

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was computer generated. Participants and care providers were masked to the allocation until after data was collected.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and care providers were blinded to intervention assignment. Analysis was intention-to-treat.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data was available for nearly all women. Two women did not receive the intervention due to being unconscious and experiencing secondary postpartum haemorrhage. This is unlikely to have affected the outcome.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors were blinding to the intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Data were reported as per the pre-specified protocol)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation between outcomes

Javadi, 2015

Bibliographic Reference	Javadi E; Sadeghipour Z; Barikani A; Javadi M.; Tranexamic Acid in the Control of Uterine Atony During Labor; Biotech Health Sci; 2015; vol. 2 (no. 2); e26898

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	2012
Inclusion criteria	• Diagnosed with uterine atony during caesarean birth or vaginal birth. • Atony was presented by uterine prolapse with haemorrhage of more than 500ml after vaginal birth, or more than 1000ml after caesarean birth.
Exclusion criteria	• Women with a history of cardiovascular disease, liver disease, kidney disease, haemolytic disease blood-clotting disorders. • Women with a history of thromboembolism or thrombophlebitis. • Women who received general anaesthesia for caesarean birth.
Patient characteristics	No significant differences at baseline for age, parity or BMI. Parity ≥3: Intervention: 95.5% Control: 85.4% Setting: Hospital All women received oxytocin prophylaxis.
Intervention(s)/control	Intervention: 20 units of oxytocin infusion and 0.2mg of methergine (methylergometrine) and 1g tranexamic acid

	Control: 20 units of oxytocin and 0.2mg of methergine
Duration of follow-up	24 hours
Sources of funding	Not reported
Other information	N= 90 Intervention, n=45 Control, n=45

Outcomes

Outcome	**Routine treatment, , N = 45**	**TXA, , N = 45**
Blood loss 500 - 1000ml No of events	n = 2	n = 16
Blood loss 1000 - 2000ml No of events	n = 38	n = 28
Blood loss > 2000ml No of events	n = 5	n = 1
Thromboembolism No of events	n = 0	n = 0
Need for additional surgical management Uterine artery ligation, hysterectomy No of events	n = 16	n = 8

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Allocation sequence is described as random but no explanation of the method of randomisation. There is no information on asking of the sequence. No differences at baseline to suggest issues.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(No information regarding knowledge of the intervention. No information on the analysis method.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data available for all women)*
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Some of the volumes of blood were estimation by visual estimation only - this could have been influenced by knowledge of the intervention. However there is not enough information on how many women had the blood volume estimated in this way. It is also not clear if outcome assessors were blinded.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Data were reported as in the pre-specified protocol)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns over randomisation and blinding. However, no baseline imbalances to suggest an issue. Some concerns over the partially subjective reporting of blood volume loss in some women (number of these women not reported))*
Overall bias and Directness	Overall Directness	Directly applicable

Section	Question	Answer
Overall bias and Directness	Risk of bias variation across outcomes	No variation between outcomes

Kumari, 2022

Bibliographic Reference	Kumari, A.; Rohatgi, R.; A Double Blinded Randomised Clinical Trial to Compare the Effect of Intravenous Tranexamic Acid and Misoprostol for Postpartum Haemorrhage; European Journal of Molecular and Clinical Medicine; 2022; vol. 9 (no. 1); 539-545

Study details

Country/ies where study was carried out	India
Study type	Randomised controlled trial (RCT)
Study dates	February 2021 to November 2021
Inclusion criteria	• Women with postpartum haemorrhage 500-1500ml after usual therapy for controlling haemorrhage given (usual therapy: 20units syntocinon in 1L of Ringer serum, half an hour infusion. Implemented immediately after the removal of the placenta. If this fails then birth canal investigated for lacerations. Then retraction of uterus investigated and if no retraction monomanual uterine compression and then bimanual uterine compression performed). • Diagnosed with PPH after caesarean or vaginal birth.
Exclusion criteria	• Medical diseases or severe surgery including heart, liver or kidney disease • blood disorders • allergy to tranexamic acid • thromboembolic disorders • high-risk pregnancy complications such as severe preeclampsia.

Patient characteristics	**Age, years - mean (SD)** Intervention (TXA): 28.1 (5.3) Comparison (misoprostol): 27.7 (5.8) **Gestational age, weeks - mean (SD)** Intervention (TXA): 37.8 (3.5) Comparison (misoprostol): 37.5 (3.4) **BMI, kg/m2 - mean (SD)** Intervention (TXA): 27.6 (2.1) Comparison (misoprostol): 27 (2.5) **Parity - mean (SD)** Intervention (TXA): 1 (0.3) Comparison (misoprostol): 1 (0.3) No significant differences between groups for maternal age, gestational age, BMI, parity, or amount of haemorrhage. Amount of haemorrhage at entry into trail not reported.
Intervention(s)/control	Routine therapy to control PPH provided to both groups: • half an hour infusion of 20 unit syntocinon given immediately after removal of placenta • if this failed to control haemorrhage birth canal was investigated for cervical and vaginal lacerations • check for retraction of uterus and if no retraction perform manual uterine compressions (monomanual and bimanual)

	• if these failed then women were included into the study. **Intervention:** • IV tranexamic acid 1g • if there was relief in haemorrhage then next TXA dose given after 30 minutes **Comparison:** • 5 rectal 200 micrograms misoprostol pills were used. Bladder emptied before treatment in both groups. In case of treatment failure in both groups: • F2-alpha prostaglandin injection was used • in case of failure surgery methods used such as artery ligation, uterine compression sutures, balloon tamponade, selective arterial embolisation and finally hysterectomy.
Sources of funding	Not reported
Sample size	N=80 Intervention (TXA): n=40 Comparison (misoprostol): n=40

Outcomes

Outcome	**Intervention (TXA), , N = 40**	**Comparison (misoprostol), , N = 40**
Blood loss volume (Litres) Mean (SD)	1.21 (0.33)	1.19 (0.46)

Critical appraisal

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Study does not describe the randomisation methods only states that the study was double-blinded. Some concerns as baseline characteristics suggest that there was randomisation as there are no imbalances.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Study reports it was double blinded although no details provided, therefore unlikely to have been deviations if blinded. However, no information on whether there were deviations from the intended intervention. No mention of intention to treat analysis.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all 80 participants)*
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Study states it was double blinded but not enough detal, therefore assumed outcome assessors were blinded. Blood loss volume was measured using collecting bag method of sponges which can lead to*

Section	Question	Answer
		bias, however if outcome assessors were blinded this would not be a risk.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No previously published protocol to compare)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation

Maged, 2016

Bibliographic Reference	Maged, A. M.; Hassan, A. M.; Shehata, N. A.; Carbetocin versus oxytocin in the management of atonic post partum haemorrhage (PPH) after vaginal birth: a randomised controlled trial; Archives of gynecology and obstetrics; 2016; vol. 293 (no. 5); 993-999

Study details

Country/ies where study was carried out	Egypt
Study type	Randomised controlled trial (RCT)
Study dates	May 2013 to December 2014
Inclusion criteria	• Women who signed consent forms • Women with postpartum haemorrhage defined as vaginal bleeding >500ml after vaginal birth • Women who had uterine atony confirmed by abdominal palpitation

Exclusion criteria	• <37 weeks gestational age • Genital tract trauma • Coagulation defect • Women with hypertension or preeclampsia • Women with cardiac or renal or liver diseases • Women with epilepsy • Known hypersensitivity to carbetocin or oxytocin
Patient characteristics	No baseline differences between groups for age, parity, gestational age or BMI. Parity: Intervention: 0.66 ± 0.65 Control: 0.58 ± 0.78 Setting: Hospital labour wards It is suggested in the discussion that women received ergometrine as prophylaxis but this is not clear.
Intervention(s)/control	Intervention: Carbetocin 100 microgram diluted in 10ml saline and administered via IV. Control: 5 IU oxytocin (syntocinon) diluted in 10ml saline and administered via IV.
Sources of funding	Not industry funded
Sample size	N=100 Intervention, n=50 Control, n=50

Outcomes

Outcome	Intervention, , N = 50	Control, , N = 50
Maternal death No of events	n = 0	n = 0
Blood loss volume (ml) Mean (SD)	811 (389.17)	1010 (525.66)
Need for additional pharmacological management other uterotonics No of events	n = 10	n = 21
Need for additional surgical management Bakri balloon, B lynch stitch, artery ligation No of events	n = 2	n = 5

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Allocation was computer generated and concealed until the end of the study.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and care givers were not aware of the assigned intervention. Intention-to-treat not specified, but assumed as all those randomised were analysed.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all participants)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of measuring the outcome was appropriate and outcome assessors were blinded.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Data are presented as in the pre-specified protocol)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation between outcomes

Mousa, 2014

Bibliographic Reference	Mousa, Hatem A.; Blum, Jennifer; Abou El Senoun, Ghada; Shakur, Haleema; Alfirevic, Zarko; Treatment for primary postpartum haemorrhage; The Cochrane database of systematic reviews; 2014; (no. 2); cd003249

Study details

Country/ies where study was carried out	Blum 2010 Burkina Faso, Egypt, Turkey, Vietnam Hofmeyr 2004 South Africa Lokugamage 2001 South Africa Walraven 2004 Gambia

	Widmer 2010 Argentina, Egypt, South Africa, Thailand, and Vietnam Winikoff 2010 Ecuador, Egypt and Vietnam Zuberi 2008 Pakistan
Study type	Cochrane systematic review of Randomised Controlled Trials
Study dates	Blum 2010 2005-2008 Hofmeyr 2004 2002-2003 Lokugamage 2001 Not reported Walraven 2004 2002-2003 Widmer 2010 2005-2008 Winikoff 2010 2005-2008 Zuberi 2008 2005-2007
Inclusion criteria	Blum 2010

	• Women with postpartum haemorrhage assessed by clinical judgement or if reached 700ml during the first hour after birth Hofmeyr 2004 • Women bleeding more than expected at 10 minutes after birth, suspected to be caused by uterine atony • Requiring additional uterotonic treatment Lokugamage 2001 • Women were included if the uterus was poorly contracted within 24 hours of birth • Blood loss greater than 500 ml, and visible signs of continued heavy vaginal bleeding Walraven 2004 • Women with PP blood loss of 500ml or more within 1 hour of birth from inadequate uterine contraction Widmer 2010 • Clinically diagnosed PPH suspected to be due to uterine atony • Need for additional uterotonics Winikoff 2010 • PPH exceeding 700ml • Women for whom oxytocic drugs during second and third stages of labour was not routine practice Zuberi 2008 • Women with PPH defined as blood loss of 500ml
Exclusion criteria	Blum 2010 • Women whose PPH was suspected to have a cause other than uterine atony

	• If women did not receive oxytocin during third stage of labour • If they had a caesarean birth Hofmeyr 2004 None specified Lokugamage 2001 • Women with hypertension, cardiac abnormalities, ongoing severe asthma, connective tissue disorders, haemorrhage due to genital tract trauma, contraindications to prostaglandins Walraven 2004 • Women who had a caesarean birth • Blood loss <500ml in the first hour of birth • Birth before 28 weeks gestation Widmer 2010 • Women who had a caesarean birth • If misoprostol could not be given sublingually • Any severe allergic or bleeding disorders • Temperature higher than 38.5 • Birth defined as miscarriage • Placenta was not delivered Winikoff 2010 • Known allergy to prostaglandin • Had received uterotonic drugs in labour • Had a caesarean section • Delivered outside the study site

	• Postpartum bleeding not suspected to be due to atony Zuberi 2008 • Women who had a caesarean birth • Women who delivered at gestational age less than 28 weeks • Not consenting
Patient characteristics	Blum 2010 • *No significant differences between age, parity, gestational age. • All women had prophylactic oxytocin during third stage of labour. • Parity: Approx 60% nulliparious Hofmeyr 2004 • *No significant differences between age or parity (where recorded). Parity not recorded for all hospitals. gestational age not reported. • Approx 70% received oxytocin of 20 IU or more before enrolment and approx 30% received ergometrine before enrolment. • Parity: Intervention 1.61, Placebo 1.75 Lokugamage 2001 • *No significant differences between age, parity, gestational age or weight. • Prophylaxis oxytocin or during labour not reported. • Parity: Misoprostol 1.77, Synto-: 2 Walraven 2004 • *No significant differences between age, parity, gestational age. • Women received prophylaxis oxytocin or syntometrine. Number receiving each not reported. • Parity 6 or above: approx 15% both arms.

	Widmer 2010 • *No significant differences between age and parity. Gestational age not reported. • 98% received oxytocin during third stage labour. • Approx 90% received any uterotonics before study treatment. • Parity: Approx 40% nulliparous Winikoff 2010 • *No significant differences between age, parity, gestational age. • No oxytocin prophylaxis. • Parity: Approx 46% nulliparous. Zuberi 2008 • *No significant differences between age and parity. Gestational age not reported. • Parity - nulliparous: 62.1% misoprostol 40.6% placebo • All women received oxytocics before study treatment. All settings in hospital
Intervention(s)/control	Blum 2010 Intervention: 800 microgram (4x200 microgram) misoprostol sublingually + 1 ampoule IV saline Control: 40 IU intravenous oxytocin + 4 placebo pills Hofmeyr 2004 Intervention: 5 x 200microgram misoprostol (1 orally, 2 sublingually and 2 rectally) Control: 5 x inactive placebo (administered the same as the intervention)

	All women were first managed by the routine treatment for PPH = oxytocin by IV infusion and/or oxytocin/ergometrine at clinicians discretion. Lokugamage 2001 Intervention: IM placebo 2ml saline + IV fusion placebo crystalloid + 800 microgram (4 tablets) misoprostol rectally administered Control: IM syntometrine (5IU oxytocin and 500microgram ergometrine) + IV infusion oxytocin (10IU in 500ml saline) + 4 placebo tablets rectally administered Walraven 2004 Intervention: Misoprostol 3 x 200microgram (1 tablet orally and 2 sublingually) Control: Placebo tablets (1 tablet orally and 2 sublingually) Widmer 2010 Intervention: Misoprostol 3 x 200microgram sublingually Control: Placebo 3 x sublingually Winikoff 2010 Intervention: IV saline + Misoprostol 800 microgram (4 x 200microgram) Control: 40 IU IV oxytocin + 4 x placebo tablets Zuberi 2008 Intervention: Misoprostol 3 x 200microgram Control: Matching placebo
Sources of funding	Not industry funded
Sample size	Blum 2010

	N=809 Intervention, n=407 Control, n=402 Hofmeyr 2004 N=244 (6 excluded as data sheets did not have pack numbers 238 included in analysis) Intervention, n=117 Control, n=121 Lokugamage 2001 N=64 Intervention, n=32 Control, n=32 Walraven 2004 N=160 Intervention, n=79 Control, n=81 Widmer 2010 N=1422 Intervention, n=705 Control, n=717 Winkoff 2010 N=978 Intervention, n=488 Control, n=490

	Zuberi 2008 N=61 Intervention, n=29 Control, n=32

Outcomes

Blum 2010

Outcome	**Intervention, , N = 407**	**Control, , N = 402**
Maternal death No of events	n = 1	n = 1
Blood loss volume (ml) Mean (SD)	279 (251)	252 (205)
Need for additional pharmacological management Additional uterotonic drugs No of events	n = 40	n = 46
Need for additional surgical management Hysterectomy, other surgery No of events	n = 10	n = 9

Hofmeyr 2004

Outcome	**Intervention, , N = 117**	**Control, , N = 121**
Maternal death No of events	n = 3	n = 0

Outcome	Intervention, , N = 117	Control, , N = 121
Blood loss volume (ml) Mean (SD)	168 (163)	176 (173)
Need for additional pharmacological management Need for additional uterotonics No of events	n = 63	n = 63
Need for additional surgical management Hysterectomy No of events	n = 3	n = 0

Lokugamage 2001

Outcome	Intervention, , N = 32	Control, , N = 32
Need for additional pharmacological management Additional uterotonics No of events	n = 2	n = 11
Need for additional surgical management Hysterectomy No of events	n = 0	n = 1

Walraven 2004

Outcome	Intervention, , N = 79	Control, , N = 81
Maternal death No of events	n = 0	n = 0

Outcome	Intervention, , N = 79	Control, , N = 81
Blood loss volume (ml) Mean (SD)	325 (264)	410 (397)
Need for additional pharmacological management Use of additional uterotonics No of events	n = 3	n = 5
Need for additional surgical management Hysterectomy No of events	n = 0	n = 2

Widmer 2010

Outcome	Intervention, , N = 705	Control, , N = 717
Maternal death No of events	n = 2	n = 0
Blood loss volume (ml) Mean (SD)	250 (223)	248 (229)
Need for additional pharmacological management Use of uterotonics No of events	n = 188	n = 203

Winikoff 2010

Outcome	Intervention, , N = 488	Control, , N = 490
Maternal death	n = 0	n = 0

Outcome	Intervention, , N = 488	Control, , N = 490
No of events		
Blood loss volume (ml) Mean (SD)	244 (186)	190 (174)
Need for additional pharmacological management Additional uterotonics No of events	n = 61	n = 31
Need for additional surgical management Hysterectomy or other surgery No of events	n = 0	n = 0

Zuberi 2008

Outcome	Intervention, , N = 29	Control, , N = 32
Maternal death No of events	n = 0	n = 0
Blood loss volume (ml) Mean (SD)	175 (168)	187 (207)
Need for additional surgical management Balloon tamponade or uterine packing No of events	n = 2	n = 7

Critical appraisal

ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool

Study	Answer
Blum 2010	Random sequence generation: Low risk Allocation concealment: Low risk Blinding: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Unclear risk
Hofmeyr 2004	Random sequence generation: Low risk Allocation concealment: Low risk Blinding: Low risk

Study	Answer
	Incomplete outcome data: Low risk Selective reporting: Unclear risk Other bias: Unclear risk
Lokugamage 2001	Random sequence generation: Low risk Allocation concealment: Low risk Blinding: High risk Incomplete outcome data: Low risk Selective reporting: High risk Other bias: High risk
Walraven 2004	Random sequence generation: Low risk Allocation concealment: Low risk Blinding: Unclear risk Incomplete outcome data: Low risk Selective reporting: Unclear risk Other bias: Unclear risk
Widmer 2010	Random sequence generation: Low risk Allocation concealment: Low risk Blinding: Low risk Incomplete outcome data: Low risk Selective reporting: Unclear risk Other bias: Unclear risk
Winikoff 2010	Random sequence generation: Low risk Allocation concealment: Low risk Blinding: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Unclear risk
Zuberi 2008	Random sequence generation: Low risk Allocation concealment: Low risk Blinding: Low risk Incomplete outcome data: Unclear risk

Study	Answer
	Selective reporting: Low risk Other bias: High risk

Shakur, 2018

Bibliographic Reference	Shakur, H.; Beaumont, D.; Pavord, S.; Gayet-Ageron, A.; Ker, K.; Mousa, H. A.; Antifibrinolytic drugs for treating primary postpartum haemorrhage; Cochrane Database of Systematic Reviews; 2018; (no. 2)

Study details

Country/ies where study was carried out	Ducloy-Bouthors 2011 France Sahhaf 2014 Iran Shakur 2017 Albania, Bangladesh, Burkina Faso, Cameroon, Colombia, Cote d'Ivoire, Democratic Republic of Congo, Egypt, Ethiopia, Ghana, Jamaica, Kenya, Nepal, Nigeria, Pakistan, Papua New Guinea, Sudan, Tanzania, United Kingdom, Uganda, Zambia
Study type	Cochrane systematic review of Randomised Controlled Trials
Study dates	Ducloy-Bouthors 2011 2005-2008 Sahhaf 2014 2011- 2013 Shakur 2017 2010-2016

Inclusion criteria	Ducloy-Bouthors 2011 • Women with PPH >800ml within hours after a vaginal birth. Sahhaf 2014 • Women with PPH 500-1500ml after a caesarean or vaginal birth. • Women had already received routine treatment for controlling PPH. Shakur 2017 • Women aged 16 or older with clinically defined PPH. • PPH defined as: >500ml after a vaginal birth, OR >1000ml after a caesarean birth, OR estimated blood loss enough to compromise haemodynamic status.
Exclusion criteria	Ducloy-Bouthors 2011 • Women less than 18 years old • No informed consent • Caesarean births • Women with a known haemostatic abnormality • Women with a history of thrombosis or epilepsy Sahhaf 2014 • No informed consent Shakur 2017 • Any contraindication to tranexamic acid such as a thromboembolic event during pregnancy
Patient characteristics	Ducloy-Bouthors 2011 • *No significant differences between groups for age, parity, gestational age or weight

	• Setting - obstetric units • *Women with PPH >500ml were given oxytocin (30 U/30 minutes), and if these procedures were inefficacious, sulprostone was administered (500 µg in 1 hour). Women with PPH >800ml were included in the study. Sahhaf 2014 • *No significant differences between groups for age, parity, gestational age or weight • Setting - hospital • *All women received 20 IU syntocinon in one litre of Ringer serum, over half an hour after birth of placenta. Shakur 2017 • *No significant differences between groups for age, parity, gestational age or weight • Setting - hospitals or maternal health facilities • 96% women received prophylaxis oxytocin
Intervention(s)/control	Ducloy-Bouthors 2011 Intervention • IV administration of loading dose of 4g TXA mixed with 50ml saline, over 1 hour • Maintenance dose of 1g/hour for 6 hours Control • No TXA Sahhaf 2014 Intervention • IV administration of 1g TXA, another dose 30 minutes later

	• Prostaglandin F2a injection given in case of treatment failure Control • 5 200 micrograms rectal misoprostol • Prostaglandin F2a injection given in case of treatment failure Shakur 2017 Intervention • IV administration of 2x500mg ampoules TXA = 1g at rate of 1ml/minute • Second dose of 2x500mmg ampoules TXA = 1g at rate of 1ml/minute if after 30 minutes bleeding continues, OR if it stops and restarts within 24 hours of first dose • *28% of intervention group received second dose Control • Placebo (sodium chloride 0.9%)
Duration of follow-up	
Sources of funding	Not industry funded
Sample size	Ducloy-Bouthors 2011 N=152 Intervention arm, n=78 Control arm, n=74 Sahhaf 2014

	N=200 Intervention arm, n=100 Control arm, n=100 <u>Shakur 2017</u> N=20060 Intervention arm, n=10051 Control arm, n=10009

Outcomes

Ducloy-Bouthors 2011

Outcome	**Intervention, , N = 77**	**Control, , N = 74**
Maternal death No of events	n = 0	n = 0
Blood loss volume (ml) Mean (SD)	280 (320)	387 (409)
Occlusive/embolic events DVT No of events	n = 2	n = 1
Need for additional pharmacological management Prostagladins No of events	n = 36	n = 34

Outcome	Intervention, , N = 77	Control, , N = 74
Need for additional surgical management Arterial ligation, or embolisation or PP curettage after day 7 No of events	n = 6	n = 9

Sahhaf 2014

Outcome	Intervention, , N = 100	Control, , N = 100
Blood loss volume (Litres) Mean (SD)	1.2 (0.3)	1.2 (0.5)

Shakur 2017

Outcome	Intervention, , N = 10051	Control, , N = 10009
Maternal death No of events	n = 227	n = 256
Occlusive/embolic events DVT or pulmonary embolism or myocardial infarction or stroke No of events	n = 30	n = 34
Need for additional pharmacological management Prostaglandins, oxytocin, ergometrine or misoprostol No of events	n = 9996	n = 9930
Need for additional surgical management Hysterectomy, arterial ligation, embolisation, tamponade, removal of placenta, laparotomy No of events	n = 2298	n = 2435

Outcome	Intervention, , N = 10051	Control, , N = 10009
Need for additional surgical management Brace sutures No of events	n = 300	n = 250

Critical appraisal

ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(Authors did not perform sensitivity analysis as intended as attrition was low in the individual studies)*
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable

Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool.

Study	Answer
Ducloy-Bouthors 2011	Random sequence generation: Low risk Allocation concealment: Unclear risk Blinding of participants and personnel: High risk Blinding of outcome assessment: Unclear risk Incomplete outcome data: Low risk Selective reporting: Unclear risk Other bias: Low risk
Sahhaf 2014	Random sequence generation: Unclear risk Allocation concealment: Unclear risk Blinding of participants and personnel: High risk Blinding of outcome assessment: High risk Incomplete outcome data: Unclear risk Selective reporting: Unclear risk Other bias: Unclear risk
Shakur 2017	Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk

Wang, 2020

Bibliographic Reference	Wang, Li; Jiang, Hong-Mei; Yang, Rui-Rui; Carboprost tromethamine prevents caesarean section-associated postpartum hemorrhage; Tropical Journal of Pharmaceutical Research; 2020; vol. 19 (no. 4); 899-904

Study details

Country/ies where study was carried out	China
Study type	Randomised controlled trial (RCT)
Study dates	October 2016 to August 2018
Inclusion criteria	Women who had postpartum haemorrhage after a caesarean birth. Postpartum definition given as >500 ml within 24 hours.
Exclusion criteria	Women with: • impaired coagulation • blood disease • liver disease • scarred uterus • myoma of uterus • abruption, adhesion, implantation and previa of placenta.
Patient characteristics	No significant differences between groups for age, gestational age, parity and causes of haemorrhage. Parity: Approximately 50% primiparous, 50% multiparous. Setting in a hospital. All women received prophylaxis oxytocin.
Intervention(s)/control	<u>Intervention</u> • Women were given 250microgram of carboprost tromethamine injection. • If the drug did not take effect, injection was repeated. Time interval between repeated injections was no less that 15 minutes, and total dosage <2mg.

	Control • If the contraction condition was not good, continuous treatment with 20-50U of oxytocin was given.
Duration of follow-up	5 days post birth
Sources of funding	Not reported
Sample size	N=100 Intervention arm, n=50 Control arm, n=50
Other information	The study defines postpartum haemorrhage as blood volume loss >500ml. However, they do not specify the method of diagnosis of postpartum haemorrhage in the sample in the study. Study blood loss volumes are fewer than 500ml, however, the study describes subtracting amniotic volume from these readings, so this could be the explanation for a less than 500ml reading.

Outcomes

Outcome	**Intervention, N = 50**	**Control, N = 50**
Blood loss volume 2 hours after birth (ml) Mean (SD)	265.36 (16.48)	289.45 (18.24)
Blood loss volume 6 hours after birth (ml) Mean (SD)	321.96 (29.85)	373.81 (20.16)
Blood loss volume 12 hours after birth (ml) Mean (SD)	376.85 (37.36)	427.44 (29.5)
Blood loss volume 24 hours after birth (ml) Mean (SD)	468.94 (39.75)	409.49 (24.61)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Allocation was generated using a random number table but there is no information in regards to concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(There is no information regarding blinding of participants, or whether there were deviations from intended interventions. There is no information on whether there was an intention-to-treat analysis.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(There is limited information on missing outcome data. When reporting of adverse events, it can be seen that 9 women are missing from each arm (18%). This could be due to severity of bleeding, and therefore inability to follow women to collect data on adverse events, but this is not clear from the study. The proportions of missing outcome data are the same between groups so this is unlikely to affect effect estimates.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Although there is no information on whether outcome assessors knew of the assigned intervention, blood volume loss was measured objectively using a suction device.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(There is no pre-specified protocol to compared reported and planned outcomes.)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation between outcomes

Zeng, 2022

Bibliographic Reference	Zeng, X.; Huang, D.; Luo, X.; Gong, H.; Wang, X.X.; Comparison of Clinical Effects of Intravenous Tranexamic Acid and Carbetocin in the Treatment of Postpartum Hemorrhage; Indian Journal of Pharmaceutical Sciences; 2022; vol. 84; 158-162

Study details

Country/ies where study was carried out	China
Study type	Randomised controlled trial (RCT)
Study dates	January 2019 to June 2020
Inclusion criteria	• Diagnosis of postpartum haemorrhage >=500ml • full-term singleton pregnancy • if after birth there were unclear uterine contours, soft uterine texture, and increased red bleeding.
Exclusion criteria	• Medical diseases such as history of heart disease and hypertension • major surgical history • allergy to tranexamic acid • thromboembolic diseases • high-risk pregnancy such as severe preeclampsia.
Patient characteristics	**Maternal age, years - mean (SD):** Intervention (carbetocin): 25.18 (5.04) Comparison (TXA): 24.22 (6.12) **Gestational age, weeks - mean (SD):** Intervention (carbetocin): 39.54 (1.23) Comparison (TXA): 39.69 (1.21)

	<u>Postpartum haemorrhage blood volume, ml - mean (SD)</u> Intervention (carbetocin): 798.72 (25.67) Comparison (TXA) 813.79 (24.52) No significant differences between groups.
Intervention(s)/control	Both groups received IV oxytocin 10 unit after birth of baby. Intervention: • 100mg of carbetocin IV (reported in paper as this; believed to be error and dose actually 100 micrograms). Comparison: • IV TXA 0.5g with carbamic acid • Another dose 1 hour later. Both groups then received pressure to the lower abdomen if there was weak of no contraction. If the vagina did not continue to bleed then participants would be included in the study, if there was bleeding they would be excluded. (Unclear sentence in the full text of the study).
Sources of funding	Not reported
Sample size	N=80 Intervention, n=40

	Comparison, n=40
Other information	Various typo errors in the body of the full text of the study making it difficult to understand the detail of the intervention and comparison. The results tables are only labelled as experimental/observation group and comparison group. However based on the abstract and the discussion section it becomes clear that the intervention group is carbetocin, and the comparison group is tranexamic acid.

Outcomes

Outcome	**Intervention (carbetocin), , N = 40**	**Comparison (TXA), , N = 40**
Blood loss volume 2hours postpartum (ml) Mean (SD)	214.45 (20.25)	305.07 (23.01)
Blood loss volume 24hours postpartum (ml) Mean (SD)	285.37 (12.55)	401.11 (21.96)
Coagulation - fibrinogen 24 hours after treatment (seconds) (assumed response time as reported in seconds) Mean (SD)	457.34 (45.2)	450.48 (46.36)

Critical appraisal

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Study states it was randomised but not enough detail on allocation concealment. There are no imbalances on baseline characteristics so likely to have been randomised,)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Study describes double blinding but not in enough detail. Unlikely to have been deviations if study was double blinded however no information on deviations and no information on intention to treat analysis)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Study reports double blinding but it is not clear that the outcomes assessors were the ones blinded as this detail is not specified. Blood loss volume measure by bag collection of sponges therefore there could be bias if the outcome assessors were not blinded. Coagulation was measured by response time of fibrinogen so also subject to bias if outcome assessors were not blinded. Therefore some concerns as assumed blinded but not clear.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No pre-specified protocol available.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation

BMI: body mass index; CI: confidence interval; IM: intramuscular; IV: intravenous; IQR: interquartile range; PPH: postpartum haemorrhage; RCT: randomised controlled trial; TXA: tranexamic acid

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Comparison 1: misoprostol versus placebo

Figure 2: Maternal death (combined)

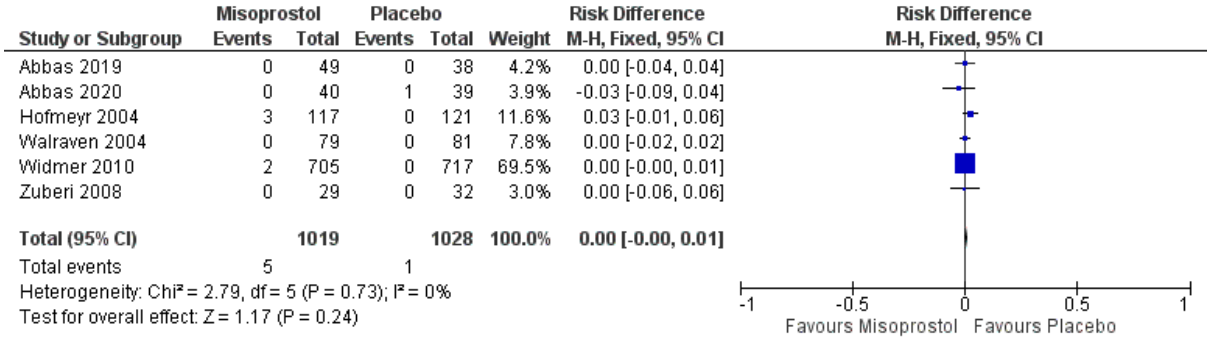


Figure 3: Maternal death (women who had oxytocin prophylaxis)

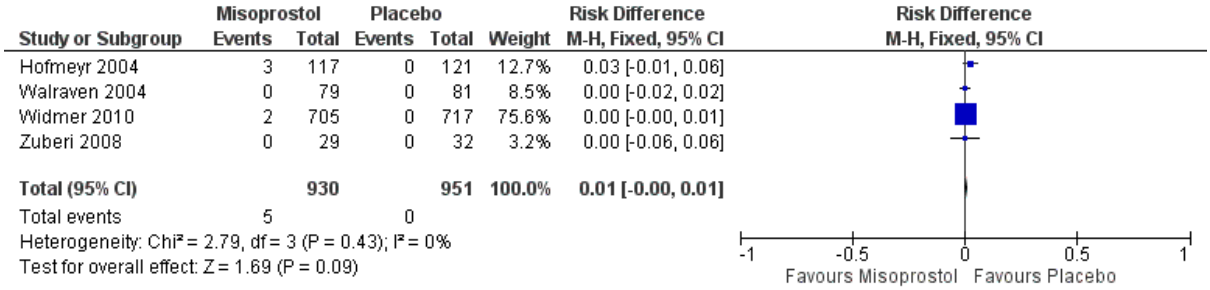


Figure 4: Maternal death (no oxytocin prophylaxis)

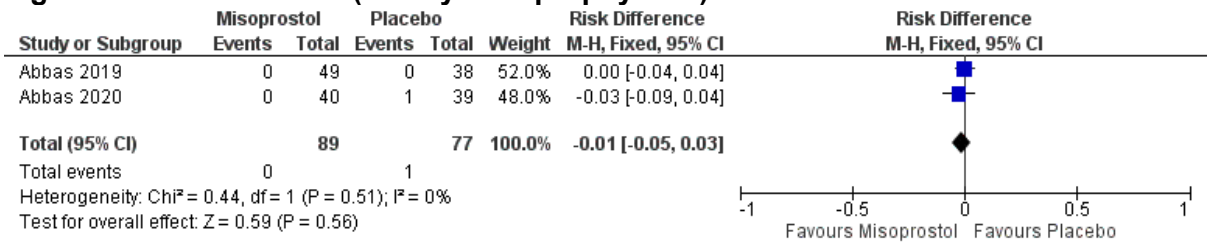


Figure 5: Blood loss volume

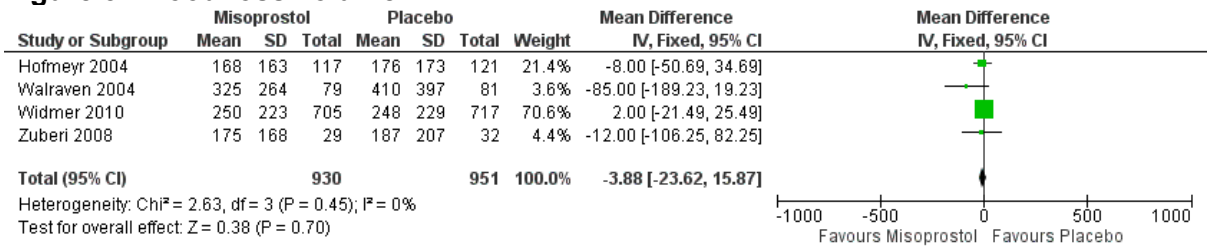


Figure 6: Need for additional pharmacological management (combined)

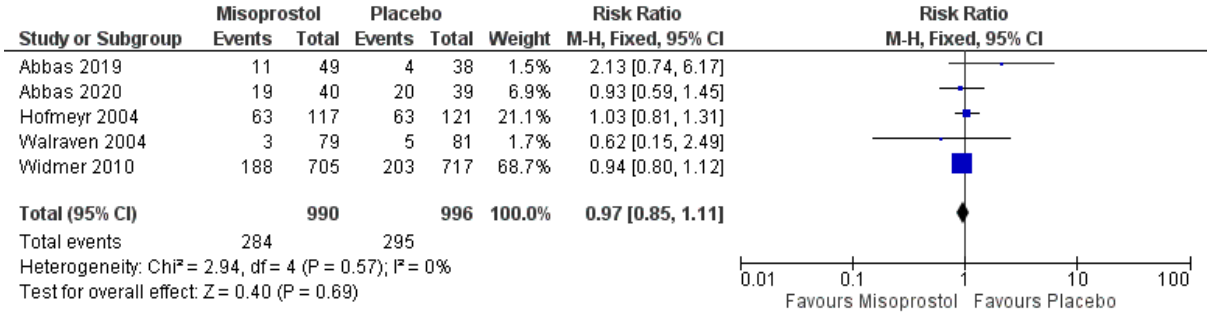


Figure 7: Need for additional pharmacological management (women who had oxytocin prophylaxis)

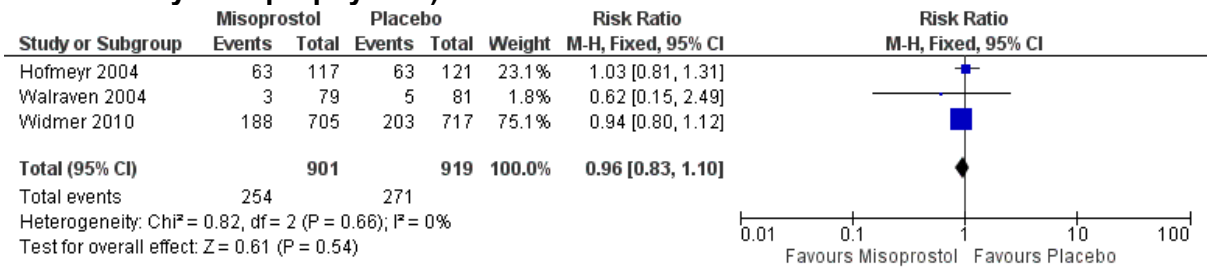


Figure 8: Need for additional pharmacological management (no oxytocin prophylaxis)

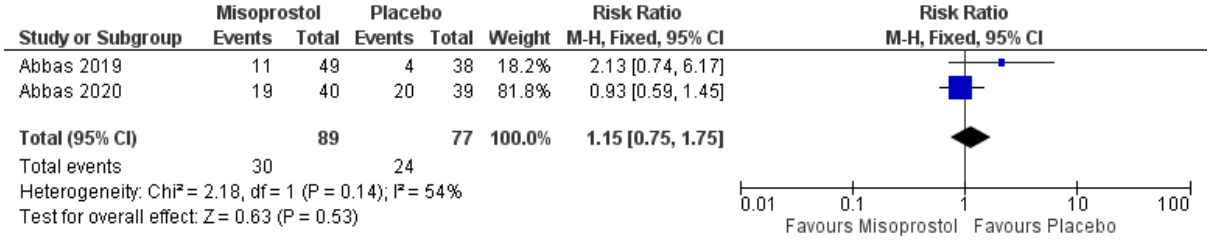


Figure 9: Need for additional surgical management (combined)

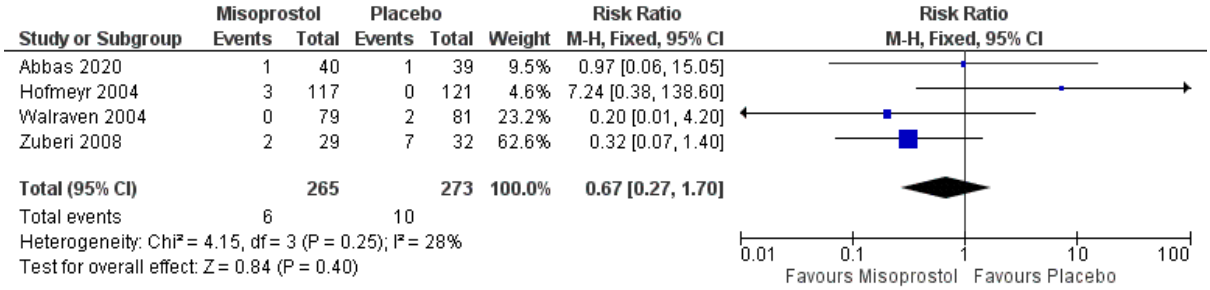
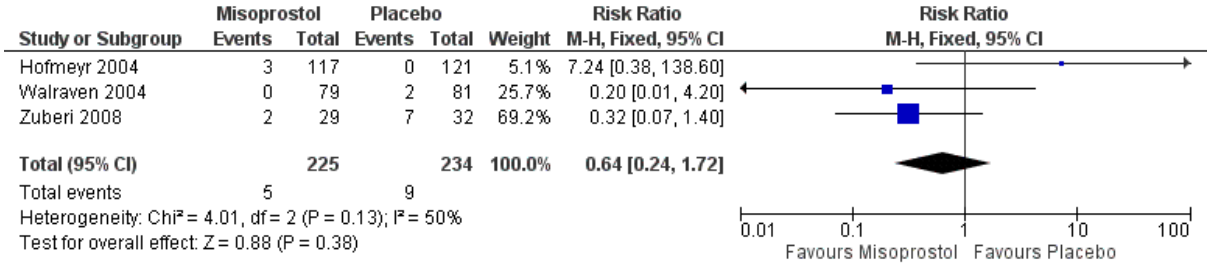


Figure 10: Need for additional surgical management (women who had oxytocin prophylaxis)



Comparison 2: misoprostol versus oxytocin

Figure 11: Maternal death (combined)

Figure 12: Need for additional pharmacological management (combined)

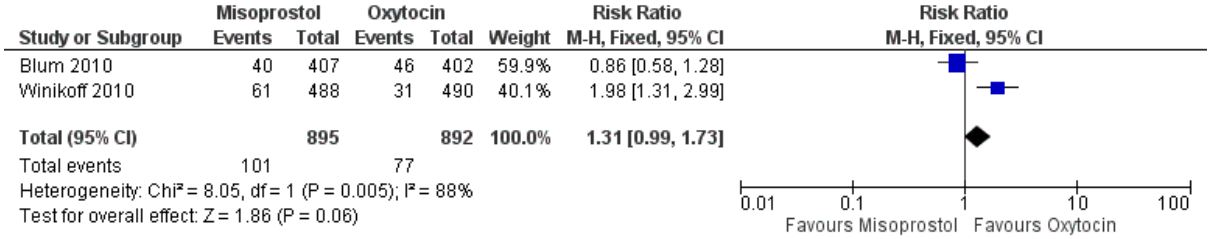
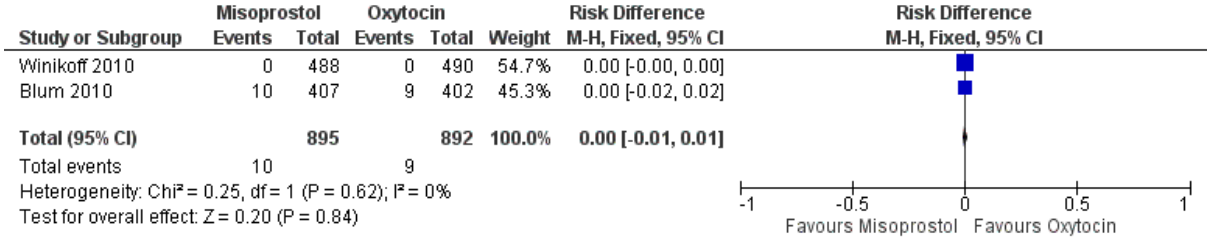


Figure 13: Need for additional surgical management (combined)



Comparison 3: TXA versus placebo

Figure 14: Maternal death

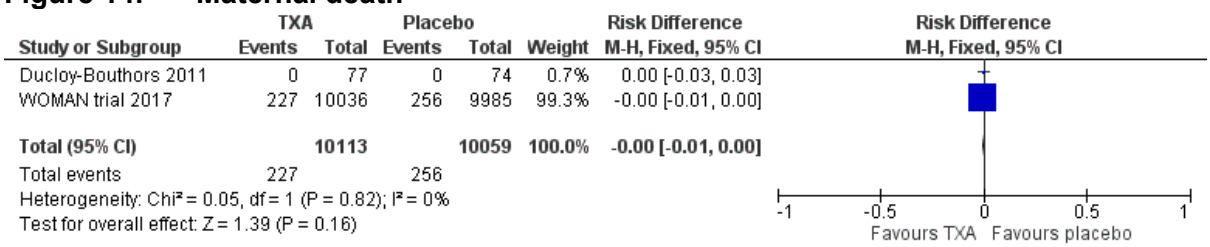


Figure 15: Occlusive/embolic event

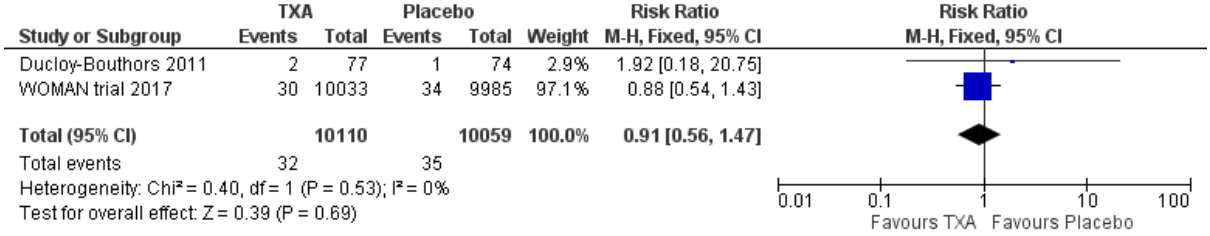


Figure 16: Need for additional pharmacological management

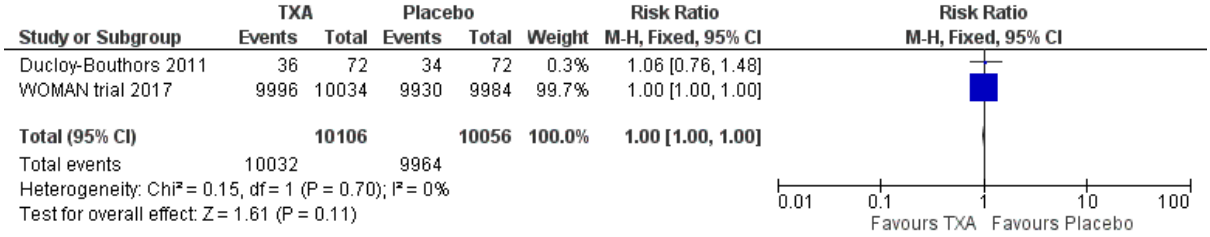
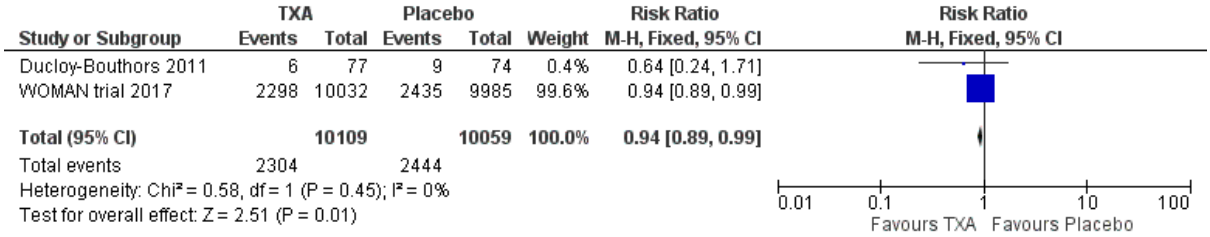
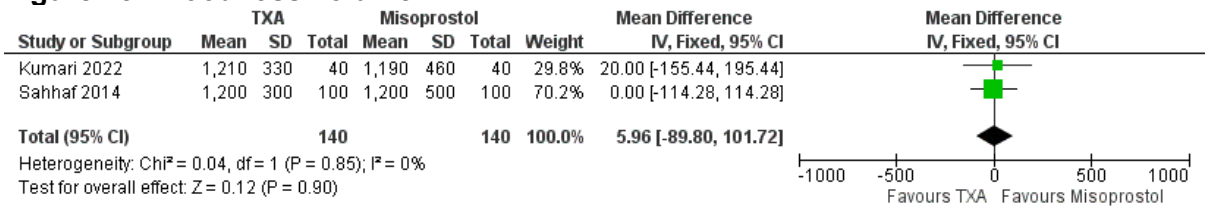


Figure 17: Need for additional surgical management



Comparison 8: TXA versus misoprostol

Figure 18: Blood loss volume



Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

Table 5: Evidence profile for comparison 1: misoprostol versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Placebo	Relative (95% CI)	Absolute		
Maternal death (combined)												
6 (Abbas 2019; Abbas 2020; Hofmeyr 2004; Walraven 2004; Widmer 2010; Zuberi 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/1019 (0.49%)	1/1028 (0.1%)	RD 0 (0 to 0.01)	0 more per 1000 (from 0 more to 10 more)	HIGH	CRITICAL
Maternal death (oxytocin prophylaxis)												
4 (Hofmeyr 2004; Walraven 2004; Widmer 2010; Zuberi 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/930 (0.54%)	0/951 (0%)	RD 0.01 (0 to 0.01)	10 more per 1000 (from 0 more to 10 more)	HIGH	CRITICAL
Maternal death (no oxytocin prophylaxis)												
2 (Abbas 2019; Abbas 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/89 (0%)	1/77 (1.3%)	RD -0.01 (-0.05 to 0.03)	10 fewer per 1000 (from 50 fewer to 30 more)	VERY LOW	CRITICAL
Blood loss volume (oxytocin prophylaxis) (measured with: ml; Better indicated by lower values)												
4 (Hofmeyr 2004; Walraven 2004; Widmer 2010; Zuberi 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	930	951	-	MD 3.88 lower (23.62 lower to 15.87 higher)	HIGH	CRITICAL
Need for additional pharmacological management (combined)												
5 (Abbas 2019; Abbas 2020; Hofmeyr 2004; Walraven 2004; Widmer 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	284/990 (28.7%)	295/996 (29.6%)	RR 0.97 (0.85 to 1.11)	9 fewer per 1000 (from 44 fewer to 33 more)	HIGH	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Placebo	Relative (95% CI)	Absolute		
Need for additional pharmacological management (oxytocin prophylaxis)												
3 (Hofmeyr 2004; Walraven 2004; Widmer 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	254/901 (28.2%)	271/919 (29.5%)	RR 0.96 (0.83 to 1.10)	12 fewer per 1000 (from 50 fewer to 29 more)	HIGH	CRITICAL
Need for additional pharmacological management (no oxytocin prophylaxis)												
2 (Abbas 2019; Abbas 2020)	randomised trials	no serious risk of bias	serious[3]	serious[1]	very serious[4]	none	30/89 (33.7%)	24/77 (31.2%)	RR 1.15 (0.75 to 1.75)	47 more per 1000 (from 78 fewer to 234 more)	VERY LOW	IMPORTANT
Need for additional surgical management (combined)												
4 (Abbas 2020; Hofmeyr 2004; Walraven 2004; Zuberi 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	6/265 (2.3%)	10/273 (3.7%)	RR 0.67 (0.27 to 1.7)	12 fewer per 1000 (from 27 fewer to 26 more)	LOW	IMPORTANT
Need for additional surgical management (oxytocin prophylaxis)												
3 (Hofmeyr 2004; Walraven 2004; Zuberi 2008)	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	5/225 (2.2%)	9/234 (3.8%)	RR 0.64 (0.24 to 1.72)	14 fewer per 1000 (from 29 fewer to 28 more)	VERY LOW	IMPORTANT
Need for additional surgical management (no oxytocin prophylaxis)												
1 (Abbas 2020)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[4]	none	1/40 (2.5%)	1/39 (2.6%)	RR 0.97 (0.06 to 15.05)	1 fewer per 1000 (from 24 fewer to 360 more)	VERY LOW	IMPORTANT

CI: confidence interval; RD: risk difference; RR: risk ratio
1 Population is indirect due to unclear diagnosis of postpartum haemorrhage
2 Sample size <200
3 Serious heterogeneity
4 95% CI crosses 2 MIDs

Table 6: Evidence profile for comparison 2: misoprostol versus oxytocin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Oxytocin	Relative (95% CI)	Absolute		
Maternal death (combined)												
2 (Blum 2010; Winikoff 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/895 (0.11%)	1/892 (0.11%)	RD 0 (0 to 0)	0 more per 1000 (from 0 fewer to 0 more)	HIGH	CRITICAL
Maternal death (oxytocin prophylaxis)												
1 (Blum 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/407 (0.25%)	1/402 (0.25%)	POR 0.99 (0.06 to 15.82)	0 fewer per 1000 (from 10 fewer to 10 more)	LOW	CRITICAL
Maternal death (no uterotonic prophylaxis)												
1 (Winikoff 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/488 (0%)	0/490 (0%)	RD 0 (0 to 0)	0 more per 1000 (from 0 fewer to 0 more)	HIGH	CRITICAL
Blood loss volume (combined) (measured with: ml; Better indicated by lower values)												
2 (Blum 2010; Winikoff 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	895	892	-	MD 44.86 higher (26.5 to 63.22 higher)	HIGH	CRITICAL
Blood loss volume (oxytocin prophylaxis) (measured with: ml; Better indicated by lower values)												
1 (Blum 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	407	402	-	MD 27 higher (4.56 lower to 58.56 higher)	MODERATE	CRITICAL
Blood loss volume (no uterotonic prophylaxis) (measured with: ml; Better indicated by lower values)												
1 (Winikoff 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	488	490	-	MD 54 higher (31.42 to 76.58 higher)	MODERATE	CRITICAL
Need for additional pharmacological management (combined)												
2 (Blum 2010; Winikoff 2010)	randomised trials	no serious risk of bias	very serious[3]	no serious indirectness	serious[4]	none	101/895 (11.3%)	77/892 (8.6%)	RR 1.31 (0.99 to 1.73)	27 more per 1000 (from 1 fewer to 63 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Oxytocin	Relative (95% CI)	Absolute		
Need for additional pharmacological management (oxytocin prophylaxis)												
1 (Blum 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	40/407 (9.8%)	46/402 (11.4%)	RR 0.86 (0.58 to 1.28)	16 fewer per 1000 (from 48 fewer to 32 more)	LOW	IMPORTANT
Need for additional pharmacological management (no uterotonic prophylaxis)												
1 (Winikoff 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/488 (12.5%)	31/490 (6.3%)	RR 1.98 (1.31 to 2.99)	62 more per 1000 (from 20 more to 126 more)	HIGH	IMPORTANT
Need for additional surgical management (combined)												
2 (Blum 2010; Winikoff 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/895 (1.1%)	9/892 (1%)	RD 0 (-0.01 to 0.01)	0 fewer per 1000 (from 10 fewer to 10 more)	HIGH	IMPORTANT
Need for additional surgical management (oxytocin prophylaxis)												
1 (Blum 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/407 (2.5%)	9/402 (2.2%)	RR 1.10 (0.45 to 2.67)	2 more per 1000 (from 12 fewer to 37 more)	LOW	IMPORTANT
Need for additional surgical management (no uterotonic prophylaxis)												
1 (Winikoff 2010)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/488 (0%)	0/490 (0%)	RD 0 (0 to 0)	0 more per 1000 (form 0 fewer to 0 more)	HIGH	IMPORTANT

CI: confidence interval; POR: Peto odds ratio; RD: risk difference; RR: risk ratio
1 95% CI crosses 2 MIDs
2 95% CI crosses 1 MID (0.5x control group SD, for 'blood loss volume (oxytocin prophylaxis) = 54.5, for 'blood loss volume (no uterotonic prophylaxis) = 75)
3 Very serious heterogeneity
4 95% CI crosses 1 MID

Table 7: Evidence profile for comparison 3: TXA versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute		
Maternal death (combined)												
2 (Ducloy-Bouthors 2011; Shakur 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	227/10113 (2.2%)	256/10059 (2.5%)	RD 0 (-0.01 to 0.00)	0 fewer per 1000 (from 10 fewer to 0 more)	HIGH	CRITICAL
Maternal death (high income)												
1 (Ducloy-Bouthers 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/77 (0%)	0/74 (0%)	RD 0 (-0.03 to 0.03)	0 fewer per 1000 (from 30 fewer to 30 more)	LOW	CRITICAL
Maternal death (mixed income, L/M/H)												
1 (Shakur 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	227/10036 (2.3%)	256/9985 (2.6%)	RR 0.88 (0.74 to 1.05)	3 fewer per 1000 (from 7 fewer to 1 more)	MODERATE	CRITICAL
Maternal death due to bleeding												
1 (Shakur 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	155/10036 (1.5%)	191/9985 (1.9%)	RR 0.81 (0.65 to 1.00)	4 fewer per 1000 (from 7 fewer to 0 more)	HIGH	CRITICAL
Blood loss volume (measured with: ml; Better indicated by lower values)												
1 (Ducloy-Bouthors 2011)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	77	74	-	MD 107 lower (224.44 lower to 10.44 higher)	LOW	CRITICAL
Occlusive/embolic event (combined)												
2 (Ducloy-Bouthors 2011; Shakur 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	32/10110 (0.32%)	35/10059 (0.35%)	RR 0.91 (0.56 to 1.47)	0 fewer per 1000 (from 2 fewer to 2 more)	LOW	CRITICAL
Occlusive/embolic event (high income)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute		
1 (Ducloy-Bouthers 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	2/77 (2.6%)	1/74 (1.4%)	RR 1.92 (0.18 to 20.75)	12 more per 1000 (from 11 fewer to 267 more)	LOW	CRITICAL
Occlusive/embolic event (mixed income L/M/H)												
1 (Shakur 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	30/10033 (0.3%)	34/9985 (0.34%)	RR 0.88 (0.54 to 1.43)	0 fewer per 1000 (from 2 fewer to 1 more)	LOW	CRITICAL
Coagulation – fibrinogen levels (measured with: difference from baseline (g/L); Better indicated by lower values												
1 (Dallaku 2019)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	93	-	MD 0.08 lower (0.28 lower to 0.12 higher)	HIGH	CRITICAL
Need for additional pharmacological management (combined)												
2 (Ducloy-Bouthors 2011; Shakur 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10032/10106 (99.3%)	9964/10056 (99.1%)	RR 1 (1 to 1)	0 fewer per 1000 (from 0 fewer to 0 more)	HIGH	IMPORTANT
Need for additional pharmacological management (high income)												
1 (Ducloy-Bouthers 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	36/72 (50%)	34/72 (47.2%)	RR 1.06 (0.76 to 1.48)	28 more per 1000 (from 113 fewer to 227 more)	LOW	IMPORTANT
Need for additional pharmacological management (mixed income L/M/H)												
1 (Shakur 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9996/10034 (99.6%)	9930/9984 (99.5%)	RR 1 (1 to 1)	0 more per 1000 (from 0 fewer to 0 more)	HIGH	IMPORTANT
Need for additional surgical management (combined)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute		
2 (Ducloy-Bouthors 2011; Shakur 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2304/10109 (22.8%)	2444/10059 (24.3%)	RR 0.94 (0.89 to 0.99)	15 fewer per 1000 (from 2 fewer to 27 fewer)	HIGH	IMPORTANT
Need for additional surgical management (high income)												
1 (Ducloy-Bouthors 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	6/77 (7.8%)	9/74 (12.2%)	RR 0.64 (0.24 to 1.71)	44 fewer per 1000 (from 92 fewer to 86 more)	LOW	IMPORTANT
Need for additional surgical management (mixed income L/M/H)												
1 (Shakur 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2298/10032 (22.9%)	2435/9985 (24.4%)	RR 0.94 (0.89 to 0.99)	15 fewer per 1000 (from 2 fewer to 27 fewer)	HIGH	IMPORTANT

CI: confidence interval; MD: mean difference; RD: risk difference; RR: risk ratio
1 Sample size <200
2 95% CI crosses 1 MID
3 Serious risk of bias in the evidence contributing to the outcomes as per RoB assessment in Shakur 2018 (systematic review)
4 95% CI crosses 1 MID (0.5x control group SD, for blood loss volume = -204.5)
5 95% CI crosses 2 MIDs

Table 8: Evidence profile for comparison 4: TXA plus misoprostol versus placebo plus misoprostol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA + misoprostol	Placebo + misoprostol	Relative (95% CI)	Absolute		
Maternal death												
1 (Diop 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0/130 (0%)	0/128 (0%)	RD 0 (-0.02 to 0.02)	0 more per 1000 (from 20 fewer to 20 more)	MODERATE	CRITICAL
Blood loss volume 20 minutes post treatment (measured with: ml; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA + misoprostol	Placebo + misoprostol	Relative (95% CI)	Absolute		
1 (Diop 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	130	128		Median in tranexamic acid: 750 (range: 550 to 1600), Median in placebo: 750 (range: 500 to 2200)	MODERATE	CRITICAL
Blood loss volume 40 minutes post treatment (measured with: ml; Better indicated by lower values)												
1 (Diop 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	130	128		Median in tranexamic acid: 800 (range 550 to 2000), Median in placebo: 800 (range 500 to 2300)	MODERATE	CRITICAL
Blood loss volume 1 hour post treatment (measured with: ml; Better indicated by lower values)												
1 (Diop 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	130	128		Median in tranexamic acid: 800 (range 550 to 2000), Median in placebo: 800 (range 500 to 2300)	MODERATE	CRITICAL
Blood loss volume 2 hours post treatment (measured with: ml; Better indicated by lower values)												
1 (Diop 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	130	128		Median in tranexamic acid: 800 (range 550 to 2000), Median in placebo: 800 (range 500 to 2300)	MODERATE	CRITICAL
Need for additional pharmacological management												
1 (Diop 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	62/130 (47.7%)	55/128 (43%)	RR 1.11 (0.85 to 1.45)	47 more per 1000 (from 64 fewer to 193 more)	MODERATE	IMPORTANT
Need for additional surgical management												
1 (Diop 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	11/130 (8.5%)	19/128 (14.8%)	RR 0.57 (0.28 to 1.15)	64 fewer per 1000 (from 107 fewer to 22 more)	MODERATE	IMPORTANT
Need for additional surgical management - sutures												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA + misoprostol	Placebo + misoprostol	Relative (95% CI)	Absolute		
1 (Diop 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	108/130 (83.1%)	111/128 (86.7%)	RR 0.96 (0.88 to 1.04)	35 fewer per 1000 (from 104 fewer to 35 more)	HIGH	IMPORTANT

CI: confidence interval; RD: risk difference; RR: risk ratio
1 Sample size between 200 and 400
2 95% CI crosses 1 MID

Table 9: Evidence profile for comparison 5: TXA plus oxytocin plus ergometrine versus oxytocin plus ergometrine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA + oxytocin + ergometrine	Oxytocin + ergometrine	Relative (95% CI)	Absolute		
Blood loss volume 500-1000ml												
1 (Javadi 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/45 (35.6%)	2/45 (4.4%)	RR 8 (1.95 to 32.79)	311 more per 1000 (from 42 more to 1000 more)	MODERATE	CRITICAL
Blood loss volume 1000-2000ml												
1 (Javadi 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/45 (62.2%)	38/45 (84.4%)	RR 0.74 (0.57 to 0.96)	220 fewer per 1000 (from 34 fewer to 363 fewer)	LOW	CRITICAL
Blood loss volume >2000ml												
1 (Javadi 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/45 (2.2%)	5/45 (11.1%)	RR 0.2 (0.02 to 1.64)	89 fewer per 1000 (from 109 fewer to 71 more)	VERY LOW	CRITICAL
Embblic event - thromboembolism												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA + oxytocin + ergometrine	Oxytocin + ergometrine	Relative (95% CI)	Absolute		
1 (Javadi 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/45 (0%)	0/45 (0%)	RD 0 (-0.04 to 0.04)	0 fewer per 1000 (from 40 fewer to 40 more)	VERY LOW	CRITICAL
Need for additional surgical management												
1 (Javadi 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/45 (17.8%)	16/45 (35.6%)	RR 0.5 (0.24 to 1.05)	178 fewer per 1000 (from 270 fewer to 18 more)	LOW	IMPORTANT

CI: confidence interval; RD: risk difference; RR: risk ratio
1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 1 MID
3 95% CI crosses 2 MIDs
4 Sample size <200

Table 10: Evidence profile for comparison 6: misoprostol versus syntometrine plus oxytocin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Syntometrine + oxytocin	Relative (95% CI)	Absolute		
Need for additional pharmacological management												
1 (Lokugamage 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/32 (6.3%)	11/32 (34.4%)	RR 0.18 (0.04 to 0.76)	282 fewer per 1000 (from 83 fewer to 330 fewer)	LOW	IMPORTANT
Need for additional surgical management												
1 (Lokugamage 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/32 (0%)	1/32 (3.1%)	POR 0.14 (0 to 6.82)	30 fewer per 1000 (from 110 fewer to 50 more)	VERY LOW	IMPORTANT

CI: confidence interval; POR: Peto odds ratio; RR: risk ratio
1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB assessment in Mousa 2014 (systematic review)
2 95% CI crosses 2 MIDs

Table 11: Evidence profile for comparison 7: carbetocin versus oxytocin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbetocin	Oxytocin	Relative (95% CI)	Absolute		
Maternal death												
1 (Maged 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/50 (0%)	0/50 (0%)	RD 0 (-0.04 to 0.04)	0 fewer per 1000 (from 40 fewer to 40 more)	LOW	CRITICAL
Blood loss volume (measured with: ml; Better indicated by lower values)												
1 (Maged 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50	50	-	MD 199 lower (380.29 to 17.71 lower)	MODERATE	CRITICAL
Need for additional pharmacological management												
1 (Maged 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	10/50 (20%)	21/50 (42%)	RR 0.48 (0.25 to 0.91)	218 fewer per 1000 (from 38 fewer to 315 fewer)	MODERATE	IMPORTANT
Need for additional surgical management												
1 (Maged 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	2/50 (4%)	5/50 (10%)	RR 0.4 (0.08 to 1.97)	60 fewer per 1000 (from 92 fewer to 97 more)	LOW	IMPORTANT

CI: confidence interval; MD: mean difference; RD: risk difference; RR: risk ratio
1 Sample size <200
2 95% CI crosses 1 MID (0.5x control group SD, for 'blood loss volume' = 262.83)
3 95% CI crosses 1 MID
4 95% CI crosses 2 MIDs

Table 12: Evidence profile for comparison 8: TXA versus misoprostol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Misoprostol	Relative (95% CI)	Absolute		
Blood loss volume (measured with: ml; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Misoprostol	Relative (95% CI)	Absolute		
2 (Kumari 2022; Sahhaf 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	140	140	-	MD 5.96 higher (89.90 lower to 101.72 higher)	LOW	CRITICAL

CI: confidence interval; MD: mean difference
1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB assessment in Shakur 2018 (systematic review)

Table 13: Evidence profile for comparison 9: carboprost plus oxytocin versus oxytocin alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carboprost + oxytocin	Oxytocin	Relative (95% CI)	Absolute		
Blood loss volume 2hrs after birth (measured with: ml; Better indicated by lower values)												
1 (Wang 2020)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	50	-	MD 24.09 lower (30.9 to 17.28 lower)	LOW	CRITICAL
Blood loss volume 6hrs after birth (measured with: ml; Better indicated by lower values)												
1 (Wang 2020)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	50	-	MD 51.85 lower (61.83 to 41.87 lower)	LOW	CRITICAL
Blood loss volume 12hrs after birth (measured with: ml; Better indicated by lower values)												
1 (Wang 2020)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	50	-	MD 50.59 lower (63.78 to 37.4 lower)	LOW	CRITICAL
Blood loss volume 24hrs after birth (measured with: ml; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carboprost + oxytocin	Oxytocin	Relative (95% CI)	Absolute		
1 (Wang 2020)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	50	-	MD 59.45 higher (46.49 to 72.41 higher)	LOW	CRITICAL

CI: confidence interval; MD: mean difference
1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 Population is indirect due to unclear diagnosis of postpartum haemorrhage

Table 14: Evidence profile for comparison 10: carbetocin versus tranexamic acid

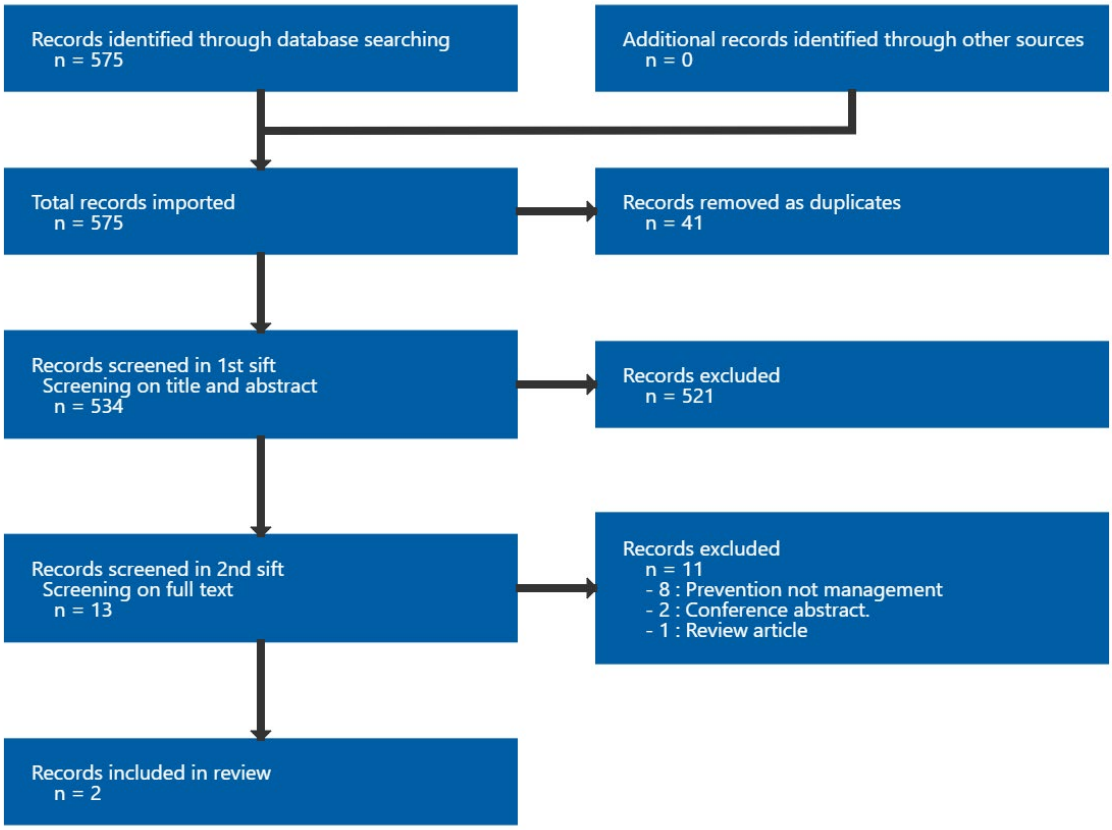
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbetocin	Tranexamic acid	Relative (95% CI)	Absolute		
Blood loss volume (measured with: ml, 2 hours postpartum; Better indicated by lower values)												
1 (Zeng 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 90.62 lower (100.12 to 81.12 lower)	LOW	CRITICAL
Blood loss volume (measured with: ml, 24 hours postpartum; Better indicated by lower values)												
1 (Zeng 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 115.74 lower (123.58 to 107.90 lower)	LOW	CRITICAL
Coagulation - fibrinogen response time (measured with: seconds; Better indicated by lower values)												
1 (Zeng 2022)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	40	-	MD 6.86 higher (13.21 lower to 26.93 higher)	VERY LOW	CRITICAL

CI: confidence interval; MD: mean difference
1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 95% CI crosses 1 MID (0.5x control group SD, for 'coagulation' = 21.81)

Appendix G Economic evidence study selection

Economic study selection for: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

Figure 19: Study selection flowchart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

Table 15: Economic evidence tables

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author & year: Sudhof 2019 **Country:** United States **Type of economic analysis:** CEA and CUA **Source of funding:** None declared	**Intervention:** Tranexamic acid given at any time Tranexamic acid given within 3 hours of birth **Comparator:** No tranexamic acid	**Population characteristics:** Women with postpartum haemorrhage in the US **Modelling approach:** Decision tree using Treeage 2018 (Williamstown, MA) **Source of baseline data:** Marshall 2017 **Source of effectiveness data:** Shakur 2017 (WOMAN trial) **Source of cost data:** Published literature and drugs.com	**Primary CEA:** **Costs:** Health care perspective **Mean saving:** No TXA: $0 TXA any time: $2.83 TXA≤ 3 hours: $7.53 **Laparotomies averted per 100,000 births** No TXA: 0 TXA any time: 8 TXA≤ 3 hours: **Deaths averted per 100,000 births** No TXA: 0 TXA any time: 0.23 TXA≤ 3 hours: 0.35	**Primary CEA:** **ICERs**: TXA within 3 hours of birth was dominant **Probability of being cost effective:** >99.9 % probability that the TXA strategies were cost saving **Sensitivity analysis:** A one-way threshold analysis suggested TXA was cost saving for a relative risk reduction in PPH of >4.7% **Secondary CUA:** TXA within 3 hours of birth was dominant	**Currency:** USD($) **Cost year:** 2018 **Time horizon:** *CEA:* Childbirth to 6 weeks postpartum *CUA:* Female life expectancy in the United States **Discounting:** Costs and utilities discounted at 3% in CUA **Applicability:** The study was deemed to be only *partially applicable* to the UK because it was based

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			<u>Secondary CUA:</u> **Mean cost:** No TXA: $783 TXA any time: $626 TXA≤ 3 hours: $532 **Mean QALY:** No TXA: 50.02 TXA any time: 50.05 TXA≤ 3 hours: 50.06	:	on a US setting and costs **Limitations:** • Maternal costs include the cost of a US malpractice suit but any reduction in deaths arising from TXA is not due to malpractice • The model does not include alternative pharmacological treatments • The model assumes the same relative reduction as Shakur 2017, although the benefits of TXA may be less in better resourced health care systems, although this was addressed through sensitivity analysis **Other comments:** Very limited reporting of Monte Carlo simulation and does not include other comparator treatments

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author & year: Howard 2022 **Country:** United States **Type of economic analysis:** CUA **Source of funding:** None declared	**Intervention:** Early administration of TXA in those diagnosed with PPH Tranexamic acid given within 3 hours of diagnosis with PPH **Comparator:** Current standard of care (No TXA)	**Population characteristics:** Women with postpartum haemorrhage in the US **Modelling approach:** Decision tree using Treeage 2016 (Williamstown, MA) **Source of baseline data:** Marshall 2017 and . Centers for Disease Control and Prevention. Pregnancy mortality surveillance system. **Source of effectiveness data:** WOMAN trial collaborators 2017 **Source of cost data:** Published literature and Lexicom.Inc (2020)	**Costs:** Societal perspective **Mean saving:** No TXA: $1,151 TXA: $997 TXA≤ 3 hours: $919 **Maternal death** No TXA: 0.00052 TXA: 0.00041 TXA≤ 3 hours: 0.00036 **Laparotomies after vaginal birth** No TXA: 0.00018 TXA: 0.00012 TXA≤ 3 hours: 0.00009 **Reoperations after caesarean** No TXA: 0.00310 TXA: 0.00198 TXA≤ 3 hours: .00155 **QALYs** No TXA: 27.091 TXA: 27.094 TXA≤ 3 hours: 27.095	**ICERs**: Early TXA and TXA within 3 hours of diagnosis with PPH was dominant **Probability of being cost effective:** Early administration of TXA had a 99.8% probability of being cost-effective relative to no TXA **Sensitivity analysis:** A one-way threshold analysis suggested early administration of TXA was dominant for maternal haemorrhage of greater than 0.002% A one-way threshold analysis suggested early administration of TXA was cost saving providing the cost of a single dose of TXA was less than $183 and cost-effective (at a cost-effectiveness threshold of $100,000 per QALY) up to a cost per TXA dose of $496	**Currency:** USD($) **Cost year:** 2019 **Time horizon:** *CUA:* Female life expectancy in the United States **Discounting:** Utilities discounted at 3% in CUA **Applicability:** The study was deemed to be only *partially applicable* to the UK because it was based on a US setting and costs **Limitations:** • The cost perspective differs from the NICE reference case • The model does not include alternative pharmacological treatments

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				For TXA given within 3 hours of diagnosis of PPH, TXA was cost saving providing the cost per dose of TXA was less than $267 and cost-effective (at a cost-effectiveness threshold of $100,000 per QALY) providing the cost per TXA dose was less than $712 :	• The model assumes the same relative reduction as the WOMAN (2017) trial, although the benefits of TXA may be less in better resourced health care systems, although this was addressed through sensitivity analysis

CEA = cost-effectiveness analysis; CUA = cost-utility analysis; QALYs = Quality adjusted life years; TXA = tranexamic acid; UK = United Kingdom; US = United States; USD = United States dollars

Appendix I Economic model

Economic model for review question: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

Excluded effectiveness studies

Table 16: Excluded studies and reasons for their exclusion

Study	Reason
(2017) Tranexamic acid for post-partum haemorrhage in the WOMAN trial. Lancet 390(10102): 1582-1583	- Study design Correspondence only to the WOMAN trial
Anonymous (2001) Misprostol as postpartum oxytocic?. South African Medical Journal 91(5): 351	- Study design Editorial comment
Ayedi, M., Jarraya, A., Smaoui, M. et al. (2011) Effect of tranexamic acid on post partum hemorrhage by uterine atony: A preliminary result of a randomized, placebocontrolled trial. European Journal of Anaesthesiology 28(suppl48): 165	- Conference abstract
Aziz, Samia, Rossiter, Shania, Homer, Caroline S. E. et al. (2021) The cost-effectiveness of tranexamic acid for treatment of postpartum hemorrhage: A systematic review. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics	- Study design Systematic review of cost effectiveness studies, considered for economics
Bagheri, Fatemeh Zahra, Azadehrah, Mahboobeh, Shabankhani, Bizhan et al. (2022) Rectal vs. sublingual misoprostol in cesarean section: Three-arm, randomized clinical trial. Caspian journal of internal medicine 13(1): 84-89	- Population not in PICO Women did not have PPH
Beigi, A., Tabarestani, H., Moini, A. et al. (2009) Sublingual misoprostol versus intravenous oxytocin in the management of postpartum hemorrhage. Tehran university medical journal 67(8): 556-561	- Population not in PICO Not women with post-partum haemorrhage
Blum, J. (2012) Misoprostol: A proven technology for prevention and treatment of PPH-overview of the clinical evidence. International Journal of Gynecology and Obstetrics 119(suppl3): 172	- Conference abstract
Blum, J., Winikoff, B., Raghavan, S. et al. (2009) Treatment of postpartum hemorrhage with sublingual misoprostol versus oxytocin: Results from a randomized noninferiority trial among women receiving prophylactic oxytocin. International Journal of Gynecology and Obstetrics 107(suppl2): S22-S23	- Conference abstract Full published results included
Bouthors, A. S., Hennart, B., Jeanpierre, E. et al. (2018) Therapeutic and pharmaco-biological, dose-ranging multicentre trial to determine the optimal dose of TRAnexamic acid to reduce blood loss in haemorrhagic CESarean delivery (TRACES): study protocol for a randomised, double-blind, placebo-controlled trial. Trials 19(1nopagination)	- Trial protocol only Full results assessed under Ducloy-Bouthors 2022
Cao, Yanxia, Sun, Baoli, Gu, Yongzhong et al. (2020) Efficacy of misoprostol combined with mifepristone on postpartum hemorrhage and its effects on coagulation function. International Journal of Clinical and Experimental Medicine 13(4): 2234-2240	- Population not in PICO Women do not have post-partum haemorrhage

Study	Reason
Casais, P., Ocampo, C., Salgado, P. et al. (2020) Prevalence and management of post partum hemorrhage in latin america: An overview of systematic reviews. Research and Practice in Thrombosis and Haemostasis 4(suppl1): 1297-1298	- Conference abstract
ChiCtr (2018) Therapeutic efficacy and safety of carbetocin on postpartum hemorrhage. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1800015613	- Trial protocol only Published results not located
Cornelissen, Laura, Woodd, Susannah, Shakur-Still, Haleema et al. (2019) Secondary analysis of the WOMAN trial to explore the risk of sepsis after invasive treatments for postpartum hemorrhage. International Journal of Gynecology and Obstetrics 146(2): 231-237	- Outcomes not in PICO Secondary analysis of the WOMAN trial
Ctri (2012) "Role of Tranexamic Acid (TXA) to reduce the bleeding in post delivery cases". http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2012/05/002622	- Trial protocol only Unable to locate full results
Dao, B., Blum, J., Dabash, R. et al. (2009) Side effect profiles for misoprostol and oxytocin in the treatment of postpartum hemorrhage. International Journal of Gynecology and Obstetrics 107(suppl2): 150	- Conference abstract
Davis, Steven, Nawab, Aria, van Nispen, Christiaan et al. (2020) The Role of Tranexamic Acid in the Management of an Acutely Hemorrhaging Patient. Hospital Pharmacy	- Study design Literature review
Della Corte, Luigi, Saccone, Gabriele, Locci, Mariavittoria et al. (2020) Tranexamic acid for treatment of primary postpartum hemorrhage after vaginal delivery: a systematic review and meta-analysis of randomized controlled trials. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 33(5): 869-874	- Systematic review Not included for primary studies, as a Cochrane review has been included which reports the same RCTs
Dresang, Lee; Kredit, Sheila; Vellardita, Lia (2019) Does tranexamic acid reduce mortality in women with postpartum hemorrhage?. The Journal of family practice 68(9): E12-E13	- Study design Not a systematic review or a randomised controlled trial
Ducloy-Bouthors, A. S., Baptiste, A., Hennart, B. et al. (2017) TRAnexamic acid to reduce blood loss in hemorrhagic CESarean delivery: Therapeutic and pharmaco-biological dose-ranging multicenter randomized double blind placebo controlled study: TRACES trial methodology. Thrombosis Research 151(supplement1): S112-S113	- Trial protocol only Full results not yet published
Ducloy-Bouthors, A. S., Depret, S., Provost, N. et al. (2010) Tranexamic acid reduces blood loss in postpartum haemorrhage. Results from the French randomized controlled study EXADE. Pathophysiology of Haemostasis and Thrombosis 37(suppl1): a170	- Conference abstract
Ducloy-Bouthors, A. S., Depret-Mosser, S., Duhamell, A. et al. (2011) Tranexamic acid reduces blood loss in post-partum haemorrhage. Thrombosis Research 127(suppl3): 128	- Conference abstract. Full results included in Ducloy-Bouthors 2011
Ducloy-Bouthors, A. S., Duhamel, A., Broisin, F. et al. (2012) Tranexamic acid reduces blood loss in post-partum haemorrhage by reducing hyperfibrinolysis. British journal of anaesthesia 108: ii191	- Conference abstract. Full results included

Study	Reason
Ducloy-Bouthors, A. S., Duhamel, A., Jude, B. et al. (2012) High dose tranexamic acid reduces blood loss in post-partum haemorrhage. International Journal of Gynecology and Obstetrics 119(suppl3): 331	- Conference abstract Full results have been included
Ducloy-Bouthors, A. S., Jeanpierre, E., Hennart, B. et al. (2017) TRAnexamic acid to reduce blood loss in haemorrhagic CESarean delivery: Therapeutic and pharmaco-biological dose-ranging multicentre randomised double-blind placebo-controlled study: TRACES trial methodology. Transfusion Medicine 27(supplement1): 61-62	- Trial protocol only Full results assessed under Ducloy-Bouthors 2022
Ducloy-Bouthors, A., Depret, S., Jude, B. et al. (2010) Tranexamic acid reduces blood loss in postpartum haemorrhage. Critical Care 14(suppl1): S124-S125	- Conference abstract Full results included under Ducloy-Bouthors 2011
Ducloy-Bouthors, Anne-Sophie, Gilliot, Sixtine, Kyheng, Maeva et al. (2022) Tranexamic acid dose-response relationship for antifibrinolysis in postpartum haemorrhage during Caesarean delivery: TRACES, a double-blind, placebo-controlled, multicentre, dose-ranging biomarker study. British journal of anaesthesia 129(6): 937-945	- Outcomes not in PICO No outcomes of interest matching the protocol
Euctr, F. R. (2015) Study on the efficacy and safety of a therapeutic strategy of post partum haemorrhage comparing early administration of human fibrinogen versus placebo in patients treated with intravenous prostaglandins following vaginal delivery. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-002484-26-FR	- Trial protocol only Full results located but not included as intervention does not meet PICO
Euctr, F. R. (2015) Study to determine tranxamic acid's effect on the bleedings that occurs within the haemorrhagic caesarean. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2015-002499-26-FR	- Trial protocol only Full results not yet published
Euctr, G. B. (2008) Randomized controlled trial comparing the effect of carbetocin vs syntocinon and ergometrine on postpartum haemorrhage in patients undergoing elective caesarean section - C.A.S.E. Trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2007-002341-20-GB	- Trial protocol only Full results not located
Euctr, G. B. (2019) The Carboprost or Oxytocin Postpartum haemorrhage Effectiveness Study. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-001829-11-GB	- Trial protocol only Trial still ongoing
Eyeberu, Addis, Getachew, Tamirat, Amare, Getachew et al. (2022) Use of tranexamic acid in decreasing blood loss during and after delivery among women in Africa: a systematic review and meta-analysis. Archives of gynecology and obstetrics	- Systematic review Relevant studies have already been included in this review
Fahrenholtz, Charles G.; Bonanno, Laura S.; Martin, Jennifer B. (2019) Tranexamic acid as adjuvant treatment for postpartum hemorrhage: a systematic review protocol. JBI database of systematic reviews and implementation reports 17(8): 1565-1572	- Protocol for a systematic review only
Ferrari, Filippo Alberto, Garzon, Simone, Raffaelli, Ricciarda et al. (2022) Tranexamic acid for the prevention and the treatment of primary postpartum	- Intervention Systematic review where most of the

Study	Reason
haemorrhage: a systematic review. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology: 1-13	included studies are looking at the prevention of PPH. Two of the included studies looking at treatment of PPH are already included under a Cochrane systematic review
Ferrer, Pili, Roberts, Ian, Sydenham, Emma et al. (2009) Anti-fibrinolytic agents in post partum haemorrhage: a systematic review. BMC pregnancy and childbirth 9: 29	- Population not in PICO Systematic review, references checked but not women with postpartum haemorrhage
Gulmezoglu, M., Alfirevic, Z., Elbourne, D. et al. (2009) Tranexamic acid for the treatment of postpartum haemorrhage: An international, randomised, double blind, placebo controlled trial (woman trial - Protocol Number ISRCTN76912190). International Journal of Gynecology and Obstetrics 107(suppl2): 500	- Trial protocol only Full published results included WOMAN trial
Henry, Jaime and McFarland, Allison (2015) The effectiveness of tranexamic acid at reducing postoperative blood loss following cesarean section: A systematic review of quantitative evidence protocol. JBI Library of Systematic Reviews 13(6): 72-81	- Protocol for a systematic review only
Hofmeyr, G. Justas, Maholwana, Babalwa, Walraven, Gijs et al. (2005) Misoprostol to treat postpartum haemorrhage: A systematic review. BJOG: An International Journal of Obstetrics and Gynaecology 112(5): 547-553	- Systematic review - more recent systematic review available A more recent Cochrane Systematic review with the same included studies has been included (Mousa 2014)
Hofmeyr, G. Justus, Gulmezoglu, A. Metin, Novikova, Natalia et al. (2009) Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bulletin of the World Health Organization 87(9): 666-77	- Intervention Majority of included studies do not meet the PICO as focused on the prevention of PPH. 3 studies which do meet the PICO have already been included
Hough, A., Koukounari, A., Shakur-Still, H. et al. (2019) Stillbirths and neonatal deaths among women with postpartum haemorrhage: An analysis of rates and risks in the WOMAN trial. BJOG: An International Journal of Obstetrics and Gynaecology 126(supplement2): 69	- Outcomes not in PICO Secondary data analysis from the WOMAN trial. The outcomes reported here are not listed

Study	Reason
	in the PICO. Maternal death is reported here and listed in the PICO but has been reported in the main results of the WOMAN trial which has been included
Huang, Xiaojuan, Xue, Wanxing, Zhou, Jin et al. (2022) Effect of Carbetocin on Postpartum Hemorrhage after Vaginal Delivery: A Meta-Analysis. Computational and mathematical methods in medicine 2022: 6420738	- Intervention Systematic review with included studies focused on the prevention of PPH and not the treatment of PPH
Hunt, B. J. (2013) Tranexamic acid for the treatment of postpartum haemorrhage-preliminary results of the woman trial. Transfusion Medicine 23(suppl1): 7	- Conference abstract Full results published in the WOMAN trial which has been included
Igboke, Francis Nwabueze, Obi, Vitus Okwuchukwu, Dimejesi, Benedict Ikechukwu et al. (2022) Tranexamic acid for reducing blood loss following vaginal delivery: a double-blind randomized controlled trial. BMC pregnancy and childbirth 22(1): 178	- Population not in PICO Women do not have PPH. Study looking at the prevention of PPH and not the treatment of PPH
Irct138812223548N (2010) The effect of misoprostrol in reduction of postpartum hemorrhage. http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT138812223548N1	- Trial protocol only Full results located but not included as population not women with postpartum haemorrhage
Irct20091023002624N (2017) Effect of tranexamic acid on postpartum hemorrhage. http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20091023002624N22	- Trial protocol only Full results located but not included as population does not meet PICO as not women with postpartum haemorrhage
Irct20120215009014N (2019) Comparison of the effect of extracts of the date, dill and grape seed versus placebo on postpartum hemorrhage in fourth stage of labor. http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20120215009014N300	- Trial protocol only Published results not sought as intervention does not match PICO
Irct2012122411862N (2013) Evaluation of effect of intra venuos Tranexamic acid and Misoprostol on Post Partum Hemorrhage and side effects of	- Trial protocol only

Study	Reason
hemorrhage. http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2012122411862N1	Published results included under Sahhaf 2014
Irct2013052613473N (2013) Tranexamic acid for treatment of postpartum hemorrhage. http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2013052613473N1	- Trial protocol only Published results included under Javadi 2015
Irct2013080514275N (2014) Effect of misoprostol and oxytocin in controlling of hemorrhage after cesarean. http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2013080514275N1	- Trial protocol only Published results located but not included as not women with post-partum haemorrhage
Irct2017052029485N (2017) Effect of tranexamic acid on postpartum hemorrhage of natural delivery in Shariati hospital (2014-15). http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2017052029485N3	- Trial protocol only Full results located but not included as population does not meet PICO as not women with postpartum haemorrhage
Irct20180819040830N (2020) Tranexamic Acid for Decreasing the Blood Loss. http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20180819040830N2	- Trial protocol only Published results not sought at population is not women with postpartum haemorrhage
Isrctn (2013) Evaluation of intrauterine balloon tamponade efficacy with condom catheter in the severe postpartum hemorrhage management in Benin and Mali. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN01202389	- Trial protocol only Published results located but not included as intervention does not meet PICO
Isrctn (2018) The carboprost or oxytocin postpartum haemorrhage effectiveness study. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN16416766	- Trial protocol only Trial still ongoing
Jin, J. Z. (2015) The application effect of integrated medicine combined with nursing intervention on patients with postpartum hemorrhage. Chinese medicine modern distance education of china [zhong guo zhong yi yao xian dai yuan cheng jiao yu] 13(18): 77-78	- Trial protocol only Published results not searched for as intervention does not meet PICO
Kushtagi, P. and Verghese, L. M. (2006) Evaluation of two uterotonic medications for the management of the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 94(1): 47-8	- Population not in PICO Not women with post-partum haemorrhage
Leas, B. and Umscheid, C. A. (2011) Active management and treatment of postpartum hemorrhage.	- Study design Review of systematic reviews. Studies checked but have

Study	Reason
	already included more recent systematic reviews
Leduc, Dean; Senikas, Vyta; Lalonde, Andre B. (2018) No. 235-Active Management of the Third Stage of Labour: Prevention and Treatment of Postpartum Hemorrhage. Journal of Obstetrics and Gynaecology Canada 40(12): e841-e855	- Study design Not a systematic review or randomised controlled trial
Leduc, Dean, Senikas, Vyta, Lalonde, Andre B. et al. (2009) Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 31(10): 980-993	- Study design Not a systematic review or a randomised controlled trial
Li, B., Miners, A., Shakur, H. et al. (2018) Tranexamic acid for treatment of women with post-partum haemorrhage in Nigeria and Pakistan: a cost-effectiveness analysis of data from the WOMAN trial. The lancet. Global health 6(2): e222-e228	- Study design Cost effectiveness analysis of the WOMAN trial which has been included in this review. Study considered for economics
Li, X., Wang, H., Wang, J. et al. (2002) Prophylactic and therapeutic effect of misoprofil plus oxytocin on postpartum hemorrhage in patients with pregnancy-induced hypertension syndrome. Journal of postgraduates of medicine 25(7): 34-35	- Full text not in English Article in Chinese
Likis, F. E., Sathe, N. A., Morgans, A. K. et al. (2015) Management of postpartum hemorrhage.	- Systematic review - more recent systematic review available Only 1 of the included studies in this systematic review meets our PICO. This has been included in a more recent systematic review
Mirzazada, S. (2012) Misoprostol for the treatment of PPH following its use for prevention (Afghanistan & Pakistan). International Journal of Gynecology and Obstetrics 119(suppl3): 223	- Conference abstract. Conference abstract only, full text has been assessed under Abbas 2019 and 2020
Moosivand, A., Foroughi Moghadam, M., Khedmati, J. et al. (2016) Cost-utility analysis of carbetocin versus oxytocin for managing postpartum hemorrhage. Value in Health 19(3): a177	- Conference abstract
Mousa, H. A., Blum, J., Abou El Senoun, G. et al. (2013) Treatment for primary postpartum haemorrhage - A cochrane systematic review. Archives of Disease in Childhood: Fetal and Neonatal Edition 98(suppl1)	- Conference abstract
Murphy, Deirdre J., MacGregor, Honor, Munishankar, Bhagya et al. (2009) A randomised controlled trial of oxytocin 5IU and placebo infusion versus oxytocin 5IU and 30IU infusion for the control of blood loss at elective	- Population not in PICO

Study	Reason
caesarean section-Pilot study. ISRCTN 40302163. European Journal of Obstetrics and Gynecology and Reproductive Biology 142(1): 30-33	Not women with post-partum haemorrhage
Nandal, I., Kochar, S.P.S., Dahiya, A. et al. (2022) Role of Intravenous Tranexamic Acid in Reducing Blood Loss during Caesarean Delivery. International Medical Journal 29(1): 23-25	- Intervention Tranexamic acid given as part of prevention not for treatment of postpartum haemorrhage
Nct (2018) Misoprostol Before and After Cesarean Section. https://clinicaltrials.gov/show/NCT03463070	- Trial protocol only Results have not been posted
Nct (2019) Oral Tranexamic Acid Plus Sublingual Misoprostol in Atonic Postpartum Hemorrhage. https://clinicaltrials.gov/show/NCT03870256	- Trial protocol only Full results not published
Nct (2014) Ergometrine Versus Oxytocin in the Management of Atonic Post-partum Haemorrhage (PPH) in Women Delivered Vaginally. https://clinicaltrials.gov/show/NCT02306733	- Trial protocol only Full results not published
Nct (2014) Carbetocin Versus Oxytocin in the Management of Atonic Post Partum Haemorrhage (PPH) in Women Delivered Vaginally: a Randomised Controlled Trial. https://clinicaltrials.gov/show/NCT02304055	- Trial protocol only Results published under Maged 2016
Nct (2009) Tranexamic Acid for the Treatment of Postpartum Haemorrhage: an International Randomised, Double Blind, Placebo Controlled Trial. Http://clinicaltrials.gov/show/nct00872469	- Trial protocol only Full results located and included (WOMAN trial)
Nct (2011) Misoprostol for Treatment of Postpartum Haemorrhage (PPH) in Home Births. https://clinicaltrials.gov/show/NCT01508429	- Trial protocol only For decision on full published results see Abbas 2020
Nct (2011) Treatment of Postpartum Haemorrhage (PPH) Using Misoprostol in Home Births. https://clinicaltrials.gov/show/NCT01485562	- Trial protocol only For decision on published results see Abbas 2019
Nct (2019) Carbetocin Versus Oxytocin Plus Sublingual Misoprostol in the Management of Atonic Postpartum Hemorrhage. https://clinicaltrials.gov/show/NCT03870503	- Trial protocol only Published results not located
Nct (2014) Fibrinogen in Haemorrhage of Delivery. https://clinicaltrials.gov/show/NCT02155725	- Trial protocol only Published results located but not included as intervention does not meet PICO
Nct (2005) Misoprostol in the Treatment of Postpartum Hemorrhage. https://clinicaltrials.gov/show/NCT00116480	- Trial protocol only Published results included under Zuberi 2008
Nct (2015) Carbetocin Versus Ergometrine in the Management of Atonic Post Partum Haemorrhage (PPH) in Women Delivered Vaginally. https://clinicaltrials.gov/show/NCT02410759	- Trial protocol only Published results not located
Nct (2005) Misoprostol for the Treatment of Postpartum Hemorrhage. https://clinicaltrials.gov/show/NCT00116350	- Trial protocol only

Study	Reason
	Published results included, Blum 2010 and Winikoff 2010
Nct (2016) Effectiveness of Tranexamic Acid When Used as an Adjunct to Misoprostol for the Treatment of Postpartum Hemorrhage. https://clinicaltrials.gov/show/NCT02805426	- Trial protocol only Published results included under Diop 2020
Nct (2009) World Maternal Antifibrinolytic Trial. https://clinicaltrials.gov/show/NCT00872469	- Trial protocol only Published results included WOMAN trial
Nct (2010) Intrarectal Misoprostol in Postpartum Haemorrhage. https://clinicaltrials.gov/show/NCT01116050	- Trial protocol only Published results not located
Nct (2016) Tranexamic Acid to Reduce Blood Loss in Hemorrhagic Caesarean Delivery. https://clinicaltrials.gov/show/NCT02797119	- Trial protocol only Trial still ongoing
Nct (2016) IV Versus IM Administration of Oxytocin for Postpartum Bleeding. https://clinicaltrials.gov/show/NCT02954068	- Trial protocol only Published results not searched for as population not women with postpartum haemorrhage
Nct (2012) Misoprostol for Treatment of Postpartum Hemorrhage at Community-level Births in Egypt. https://clinicaltrials.gov/show/NCT01619072	- Trial protocol only Published results not located
Nct (2018) Sublingual Misoprostol With or Without Intravenous Tranexamic Acid During Hemorrhagic Cesarean Section. https://clinicaltrials.gov/show/NCT03774706	- Trial protocol only Trial still ongoing
Nct (2012) Oxytocin, Carbetocin and Misopristol for Treatment of Postpartum Hemorrhage: a Multicentric Randomized Trial. https://clinicaltrials.gov/show/NCT01600612	- Trial protocol only Published results not located
Nct (2018) Second-Line Uterotonics in Postpartum Hemorrhage: a Randomized Clinical Trial. https://clinicaltrials.gov/show/NCT03584854	- Trial protocol only Trial is still ongoing
Nct (2015) Carbetocin Versus Oxytocin in Caesarean Section for the Control of Postpartum Haemorrhage. https://clinicaltrials.gov/show/NCT02396303	- Trial protocol only Published results not located
Okonofua, Friday Ebhodaghe, Ogu, Rosemary Nkemdilim, Akuse, James Terkura et al. (2014) Assessment of sublingual misoprostol as first-line treatment for primary post-partum hemorrhage: results of a multicenter trial. The journal of obstetrics and gynaecology research 40(3): 718-22	- Study design Not a randomised controlled trial
Oladapo, Olufemi T., Blum, Jennifer, Abalos, Edgardo et al. (2020) Advance misoprostol distribution to pregnant women for preventing and treating postpartum haemorrhage. Cochrane Database of Systematic Reviews 2020(6): cd009336	- Intervention Systematic review where included studies do not meet the PICO as intervention is for prophylaxis of post-partum haemorrhage

Study	Reason
Olefile, Kabelo M.; Khondowe, Oswell; M'Rithaa, Doreen (2013) Misoprostol for prevention and treatment of postpartum haemorrhage: A systematic review. Curationis 36(1): E1-10	- Population not in PICO
Olufowobi, O., Afnan, M., Sorinola, O. et al. (2002) A randomized study comparing rectally administered misoprostol versus syntometrine combined with an oxytocin infusion for the cessation of primary postpartum hemorrhage. Acta obstetricia et gynecologica Scandinavica 81(10)	- Study design Letter regarding a randomised controlled trial already included (Lokugamage 2001)
Pactr (2020) Tranexamic acid for reducing blood loss following vaginal delivery. http://www.who.int/trialsearch/Trial2.aspx?TrialID=PACTR202010828881019	- Trial protocol only Full results not found, but population is not women with postpartum haemorrhage
Pactr (2020) EFFECT OF TRANEXAMIC ACID ON PRIMARY POSTPARTUM HAEMORRHAGE IN AT â€“ RISK WOMEN AT ABUTH, ZARIA: a RANDOMIZED CONTROLLED STUDY. http://www.who.int/trialsearch/Trial2.aspx?TrialID=PACTR202004568331645	- Trial protocol only Published results not located
Parry Smith, William R., Papadopoulou, Argyro, Thomas, Eleanor et al. (2020) Uterotonic agents for first-line treatment of postpartum haemorrhage: a network meta-analysis. Cochrane Database of Systematic Reviews 2020(11): cd012754	- Study design Network Meta-analysis - references checked and studies relevant to PICO have been included
Peitsidis, Panagiotis and Kadir, Rezan A. (2011) Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. Expert opinion on pharmacotherapy 12(4): 503-16	- Systematic review - more recent systematic review available References checked and 1 study is of relevance, but has been included as part of a more recently published systematic review (Ducloy-Bouthors 2011)
Prata, N., Mbaruku, G., Campbell, M. et al. (2005) Controlling postpartum hemorrhage after home births in Tanzania. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 90(1): 51-5	- Study design Not a randomised controlled trial
Rangel, Rita de Cassia Teixeira, Souza, Maria de Lourdes de, Bentes, Cheila Maria Lins et al. (2019) Care technologies to prevent and control hemorrhage in the third stage of labor: a systematic review. Tecnologias de cuidado para prevencao e controle da hemorragia no terceiro estagio do parto: revisao sistematica. 27: e3165	- Systematic review - more recent systematic review available A more recent Cochrane review with the relevant included studies

Study	Reason
	from this systemtatic review has been included
Sentilhes, L., Lasocki, S., Ducloy-Bouthors, A. S. et al. (2015) Tranexamic acid for the prevention and treatment of postpartum haemorrhage. British journal of anaesthesia 114(4): 576-87	- Systematic review - more recent systematic review available One included study matching the PICO which has been included as part of a more recent systematic review
Shaheen, Nighat and Khalil, Safia (2019) Safety and efficacy of 600ug sublingual misoprostol versus 10 U intramuscular Oxytocin for management of third stage of labor. Rawal Medical Journal 44(1): 137-140	- Population not in PICO
Shakur, H., Elbourne, D., Gülmezoglu, M. et al. (2010) The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. Trials 11: 40	- Trial protocol only Full results have been included
Shakur, Haleema, Roberts, Ian, Edwards, Philip et al. (2016) The effect of tranexamic acid on the risk of death and hysterectomy in women with post-partum haemorrhage: statistical analysis plan for the WOMAN trial. Trials 17(1): 249	- Statistical analysis plan only
Sheldon, Wendy R., Blum, Jennifer, Durocher, Jill et al. (2012) Misoprostol for the prevention and treatment of postpartum hemorrhage. Expert opinion on investigational drugs 21(2): 235-50	- Study design Not a systematic review (literature review)
Slctr (2011) Anticipatory management vs standard management of postpartum haemorrhage. http://www.who.int/trialsearch/Trial2.aspx?TrialID=SLCTR/2011/010	- Trial protocol only Published results not located
Suhrabi, Zainab, Akbari, Malihe, Taghinejad, Hamid et al. (2019) Comparing the effect of dextrose and oxytocin to reduce postpartum haemorrhage: Randomised controlled trial. Journal of Clinical and Diagnostic Research 13(7): QC09-QC11	- Population not in PICO Not women with post-partum haemorrhage
Takagi, S., Yoshida, T., Togo, Y. et al. (1976) The effects of intramyometrial injection of prostaglandin F2alpha on severe post-partum hemorrhage. Prostaglandins 12(4): 565-579	- Population not in PICO Post-partum haemorrhage not as defined in the PICO
Widmer, Mariana, Blum, Jennifer, Hofmeyr, G. Justus et al. (2010) Misoprostol as an adjunct to standard uterotonics for treatment of postpartum hemorrhage: A multicentre, double-blind randomized trial. Obstetrical and Gynecological Survey 65(10): 609-610	- Study design Editorial comment only. Actual trial included separately under Widmer 2010
Widmer, Mariana, Blum, Jennifer, Hofmeyr, G. Justus et al. (2010) Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. Lancet (London, England) 375(9728): 1808-13	- Included as part of a systematic review

Study	Reason
	Included in Cochrane review Mousa 2014
Winikoff, B., Dabash, R., Durocher, J. et al. (2009) Treatment of postpartum hemorrhage with sublingual misoprostol versus oxytocin: Results from a randomized, non-inferiority trial among women not exposed to oxytocin during labor. International Journal of Gynecology and Obstetrics 107(suppl2): 59	- Conference abstract Full results included under Winikoff 2010
Zhou, M., Yang, C. Y., Zhao, Y. et al. (2006) Clinical value of adjuvant therapy with estrogen for postpartum hemorrhage. Nan fang yi ke da xue xue bao [Journal of Southern Medical University] 26(6): 865-866	- Full text not in English Article in Chinese

Excluded economic studies

Table 17: Excluded studies and reasons for their exclusion

Study	Reason
Aziz, Samia, Rossiter, Shania, Homer, Caroline S. E. et al. (2021) The cost-effectiveness of tranexamic acid for treatment of postpartum hemorrhage: A systematic review. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics	- Review article
Bandara, S.; Angala, P.; Haloob, R. (2017) Carbitocin: A cost-effective tool to save lives!. BJOG: An International Journal of Obstetrics and Gynaecology 124(supplement1): 27	- Prevention not management
Gallos, Ioannis, Williams, Helen, Merriel, Abi et al. (2019) Uterotonic drugs to prevent postpartum haemorrhage: A network meta-analysis. Health Technology Assessment 23(9): 1-356	- Prevention not management
Howard, Dagnie, Skeith, Ashley E., Lai, Jasmine et al. (2018) Routine use of tranexamic acid in postpartum hemorrhage: A cost-effectiveness analysis. Obstetrics and Gynecology 131(supplement1): 171S-172S	- Conference abstract
Lawrie, Theresa A., Rogozinska, Ewelina, Sobiesuo, Pauline et al. (2019) A systematic review of the cost-effectiveness of uterotonic agents for the prevention of postpartum hemorrhage. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 146(1): 56-64	- Prevention not management
Luni, Yasmin, Borakati, Aditya, Matah, Arti et al. (2017) A prospective cohort study evaluating the cost-effectiveness of carbetocin for prevention of postpartum haemorrhage in caesarean sections. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 37(5): 601-604	- Prevention not management
Moosivand, A., Foroughi Moghadam, M., Khedmati, J. et al. (2016) Cost-utility analysis of carbetocin	- Conference abstract

Study	Reason
versus oxytocin for managing postpartum hemorrhage. Value in Health 19(3): a177	
Morris, C., Siassakos, D., Draycott, T. J. et al. (2013) Cost comparison of routine carbetocin use at caesarean section. BJOG: An International Journal of Obstetrics and Gynaecology 120(suppl1): 119-120	- Prevention not management
Patel, B. and Haloob, R. (2014) Carbitocin: A cost-effective tool to save lives. BJOG: An International Journal of Obstetrics and Gynaecology 121(suppl2): 88-89	- Prevention not management
Pickering, Karen, Gallos, Ioannis D., Williams, Helen et al. (2019) Uterotonic Drugs for the Prevention of Postpartum Haemorrhage: A Cost-Effectiveness Analysis. PharmacoEconomics - open 3(2): 163-176	- Prevention not management
van der Nelson, Helen A., Draycott, Tim, Siassakos, Dimitrios et al. (2017) Carbetocin versus oxytocin for prevention of post-partum haemorrhage at caesarean section in the United Kingdom: An economic impact analysis. European journal of obstetrics, gynecology, and reproductive biology 210: 286-291	- Prevention not management

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of pharmacological treatments for the management of postpartum haemorrhage?

K.1.1 Research recommendation

What is the impact of pharmacological interventions for the management of postpartum haemorrhage on breastfeeding and women's and their birth companions' experience and satisfaction in the postnatal period?

K.1.2 Why this is important

Postpartum haemorrhage (PPH) is one of the leading causes of maternal death globally. PPH is usually managed using pharmacological interventions as first-line, but no studies were identified for inclusion in the review that looked at the effects of these interventions on breastfeeding or women's or their birth companions' experiences and satisfaction in the postnatal period.

K.1.3 Rationale for research recommendation

Table 18: Research recommendation rationale

Importance to 'patients' or the population	Postpartum haemorrhage is an emergency situation and so pharmacological treatments are usually selected based on their effectiveness. However, the available treatments have differing side-effect profiles and may impact on the woman in the postnatal period, particularly in relation to breastfeeding. It is therefore important to consider these effects when considering the risk/benefit profile of different treatment options.
Relevance to NICE guidance	There were no data available on the impact of these pharmacological treatments on breastfeeding or on women's or their birth companions' experience, to assist the committee when making their recommendations.
Relevance to the NHS	The use of treatments which do not impair the postnatal experience for women, and are likely to allow early initiation of successful breastfeeding are likely to lead to less utilisation of NHS resources.
National priorities	High – maternal safety and experience is a high profile national priority.
Current evidence base	No data were available on these outcomes in the included studies for this review.
Equality considerations	None known

K.1.4 Modified PICO table

Table 19: Research recommendation modified PICO table

Population	• Women with a diagnosis of primary postpartum haemorrhage within the first 24

	hours after giving birth, defined as any of the following: ○ blood loss over 500mL ○ postpartum haemorrhage requiring blood transfusion ○ clinically defined postpartum haemorrhage
Intervention	Pharmacological treatments administered by any route and regimen: • Antifibrinolytic drugs (including, but not limited to: aprotinin, tranexamic acid) • Uterotonic drugs (carbetocin, ergometrine, misoprostrol, oxytocin, pitocin, prostaglandins (such as carboprost), syntometrine A combination of the drugs listed above
Comparator	• Any of the above interventions compared to each other • Placebo
Outcome	• Breastfeeding rates • Women's experiences, satisfaction and quality of life
Study design	Mixed methods – quantitative and qualitative
Timeframe	Short term (24 hours after birth); medium term (6 weeks after birth); long-term (6 months after birth)
Additional information	None