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Review

Universal oxytocin prophylaxis is rock-sculpted? Atony is one cause, but not the main cause of postpartum hemorrhage

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Abstract

The WOMAN Trial found that tranexamic acid (TXA) reduces mortality due to bleeding in women with postpartum hemorrhage (PPH) after cesarean and vaginal births, with no adverse effects and no increase in thromboembolic events incidence.

On the other hand, the network meta-analysis of 196 randomized trials showed that all uterotonic agents are effective in preventing PPH ≥ 500 mL compared to placebo or no treatment at all. This meta-analysis also demonstrated that all agents, except for ergometrine and injectable prostaglandins, are effective in preventing PPH ≥ 1,000 mL compared to placebo or no treatment at all. But equally important is that no differences were observed in terms of maternal death, severe maternal morbidity, and Intensive Care Unit admissions.

This review tries to explain why, although prophylactic administration of uterotonics is able to reduce the amount of blood lost by women at childbirth, it is generally unable to save women's lives. The hope is that awareness of this evidence will lead to new lines of research and to a better understanding of the problem.

Keywords

Third stage of labor, prophylaxis, postpartum hemorrhage, tranexamic acid, synthetic oxytocin, obstetric labor complications.

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Introduction

Prophylactic administration of synthetic oxytocin (SynOX) during the third stage of labor results in a reduction in mean blood loss, but not in the number of severe postpartum bleeding and maternal deaths due to postpartum hemorrhage (PPH). The network meta-analysis of 196 randomized trials [1] showed that all uterotonic agents are effective in preventing PPH ≥ 500 mL compared to placebo or no treatment at all. At the same time, the same meta-analysis demonstrated that all agents, except for ergometrine and injectable prostaglandins, are effective in preventing PPH ≥ 1,000 mL compared to placebo or no treatment at all. In addition, no differences in the effects of uterotonic agents were observed compared to the reference uterotonic agent, oxytocin, for PPH ≥ 1,000 mL. Equally important is that no differences were observed in terms of maternal death, severe maternal morbidity, and Intensive Care Unit (ICU) admissions [1]. It is still to be established whether a reduction in average blood loss at childbirth is useful for women's health or if it's just functional to the reduction of postpartum anemia, without saving women's lives.

On the other hand, the WOMAN Trial found that tranexamic acid (TXA) reduces mortality due to bleeding in women with PPH after cesarean and vaginal births, with no adverse effects or increase in thromboembolic events incidence [2].

Similarities, differences and interactions between synthetic oxytocin and tranexamic acid

TXA, like SynOX, is able to reduce mean postpartum blood loss [3]. The two molecules are probably both equally effective in reducing postpartum blood loss, working however with a different mechanism of action.

SynOX binds to specific myometrial receptors, thus inducing myometrial contractions [4].

Conversely, TXA probably works in a different scenario. Pregnancy is characterized by a decrease in fibrinogenemia, due to postpartum intravascular fibrin deposition, which leads to an increase in fibrinogen consumption [5]. TXA prevents the conversion of plasminogen to plasmin, preventing fibrin breakdown, and ultimately stabilizing the fibrin matrix of clots. In fact, studies with biopsies of placental bed tissues examined under electronic microscope revealed that, immediately after a normal childbirth, an extravascular fibrin network is formed on the endometrial surface [6]. This may be one of the mechanisms by which TXA is able to reduce average blood loss when administered prophylactically, but this has yet to be demonstrated. Another mechanism is its ability to change the coagulation system, especially with underlying coagulation disorders not diagnosed during pregnancy [7].

Another important difference between SynOX and TXA is the longer half-life of TXA. As is well known, TXA is a synthetic analog of the amino acid lysine. It can be administered orally or by intravenous infusion. A 1-gram dose of TXA administered intravenously (10 mL of a 100 mg/mL solution) shows an onset of action within 5 minutes and a half-life of approximately 3 hours [8].

The longer half-life of TXA probably explains the positive long-term effects of this molecule. In a prospective randomized open-label blinded endpoint trial, Zhang et al. enrolled 2,258 women with one or more risk factors for PPH who underwent vaginal delivery [9]. This study demonstrated that participants randomly assigned in a 1:1 ratio to receive an intravascular infusion of 1 g TXA, in addition to SynOX, compared to placebo had a significantly lower incidence of severe PPH.

All these physiological mechanisms suggest that TXA, as an antifibrinolytic agent, may be administered as an effective prophylaxis to control PPH.

On the other hand, the addition of prophylactic TXA greatly improves health outcomes in terms of blood loss reduction, above all in women with risk factors for PPH (**Tab. 1** [10]), like those with preoperative hemoglobin levels < 10.5 g/dL who undergo cesarean section [11].

However, SynOX and TXA do not work synergically, as demonstrated by inconclusive results of the studies where TXA was simply added to the SynOX as prophylaxis with no clinical improvement [11-23]. The two drugs maintain their action individually, without a cumulative synergy

Table 1. Categories of women at higher risk for postpartum hemorrhage (PPH) (modified from: Italian National Institute of Health, 2016 [10]).

Risk factors for PPH	Odds ratio (95% CI) in the literature
Multiple pregnancy	3.3 (1.0-10.6) 4.7 (2.4-9.1)
Previous PPH	3.6 (1.2-10.2)
Preeclampsia	5.0 (3.0-8.5) 2.2 (1.3-3.7)
Birth weight > 4,000 g	2.11 (1.62-2.76) 2.4 (1.9-2.9)
Failure to progress of the second stage	3.4 (2.4-4.7) 1.9 (1.2-2.9)
Prolongation of the third stage of labor	7.6 (4.2-13.5) 2.61 (1.83-3.72)
Retained placenta	7.83 (3.78-16.22) 3.5 (2.1-5.8) 6.0 (3.5-10.4)
Episiotomy	4.7 (2.6-8.4) 2.18 (1.68-2.76) 1.7 (1.2-2.5)
Perineal tear	1.4 (1.04-1.87) 2.4 (2.0-2.8) 1.7 (1.1-2.5)
Placenta accreta	3.3 (1.7-6.4)

PPH: postpartum hemorrhage; CI: confidence interval.

of action occurring. I therefore believe that these studies are not useful to understand how to reduce severe postpartum bleeding.

Therapeutic or prophylactic use of uterotonics in the third stage of labor?

Labor is physiologically associated with short-lasting pulses of oxytocin, which occur more frequently as labor progresses, reaching a maximal frequency of 3 pulses per 10 minutes at the end of the second stage of labor. During the third stage of labor, endogenous oxytocin secretion decreases, with only few pulses described [24]. The third stage of labor is therefore not characterized by an increase in endogenous oxytocin production.

PPH is related to progesterone signaling dysregulation [25]. Progesterone inhibits uterine contraction and induces uterine relaxation in late pregnancy [26]. However, we shouldn't forget that progesterone acts not only on uterine contractility, but also and above all on coagulation system [27].

Thus, I didn't observe any difference in terms of maternal death, severe maternal morbidity, and ICU admissions, when using uterotonics prophylactically because, as stated in the paper by Weeks [28]: "In settings with minimal health services, about one in 200 pregnancies will end in the mother's death from PPH. But most of these are caused by uterine rupture or placental pathology (abruption, previa or retained placenta), for which oxytocic drugs are relatively ineffective. Preventing maternal deaths from PPH globally will take more than oxytocin: providing safe blood transfusion and skilled surgery are likely to be far more important. The role of oxytocin in PPH is likely to be more about reducing the morbidity of postnatal anemia than reducing maternal deaths…".

Currently, from a clinical point of view, the diagnosis of uterine atony is properly a diagnosis of exclusion, as Andrew Weeks and James Neilson argue: "Atonic uterus is the failure of the uterine muscle to contract adequately to stop blood flow to the placental bed after detachment of the placenta in the third stage of labor. The reported rate of atonic uterus in women with PPH in high-resource settings varies widely, from 30% to 79%. This is partially because the diagnosis of atony is often subjective and used in the absence of retained placental tissue or obvious trauma. Atony is also difficult to assess at the time of cesarean section, when the assessment is made on palpation of uterine tone rather than on vaginal blood loss, which is largely hidden under surgical drapes. In practice, the diagnosis is given in a wide range of clinical situations, from a woman with a small bleed after spontaneous vaginal birth to a woman bleeding heavily after emergency cesarean for obstructed labor…" [29]. In addition, according to data from Liverpool Women's Hospital: "14% of women who had an emergency cesarean section accounted for almost 40% of PPHs greater than 2,000 mL. Conversely, only 0.3% of the 28% of women who were low-risk and delivered in the Midwife-led Unit had massive PPHs, representing 8% of all massive PPHs occurring in the hospital. And this despite a growing number of women opting for a physiological third stage of labor without the use of oxytocin prophylaxis" [29]. The policy of universal prophylaxis of PPH with SynOX in the third stage of labor, when women reduce endogenous oxytocin secretion, can lead to an unnecessary medicalization of low-risk women.

Ian Roberts, Professor of Epidemiology and Public Health at the London School of Hygiene and Tropical Medicine in the UK, said: "The WHO strategy for reducing maternal mortality from PPH centers on the use of uterotonics, but there is no epidemiological evidence that uterine atony causes PPH or that uterotonics have any effect on maternal mortality… WHO is basing its policy on assumptions. The obstetrician treating a woman with PPH feels that her uterus is distended and decides

that the cause is uterine atony. That is not causation in any epidemiological sense; it is just an opinion" [30]. Ian Roberts continued: "WHO is stuck. They have classified uterotonics as life-saving, so they cannot realistically perform any randomized trials, but there is no evidence to back their position. They cannot say with certainty what effect uterotonics have, or whether the risks outweigh the benefits". He added that TXA is the only intervention proven to reduce maternal mortality from PPH in a randomized trial. Certainly, therapy with uterotonics is fundamental and vital to save women's lives, but we should still discuss universal prophylaxis since the two things are not equivalent. Therapeutic use of uterotonics is very different from their prophylactic use. In the end, I am in full agreement with the article by Talha Burki, who concludes as follows: "We clearly need multiple approaches to save lives. The approaches are not necessarily mutually exclusive" [30]. In an interesting study, Fahy et al. show that at their Tertiary Unit 344/3,075 low-risk women (11.2%) experienced PPH when managed with active management of PPH; on the contrary, at the Midwifery-led Unit, where women receiving holistic psycho-physiological care, PPH occurred in 10 of 361 women (2.8%). This study suggests that active management of PPH was associated with a 7-to-8-fold increase in PPH rates in women at low risk of PPH [31]. Other studies showed the same result [32, 33]. The physiopathological approach is often more effective than active treatment of the third stage of labor in low-risk women. Causes can be multiple: adoption of free-positions in labor, less use of episiotomy [34, 35], less use of cesarean sections [36], restrictive use of drugs, less augmentation of labor [37], privacy and confidentiality maintained during labor and childbirth; respect and courtesy shown to a women in labor and her childbirth companion; support and encouragement to women during labor and childbirth; involvement of childbirth companion, enhancing his/her role [38] and other behavioural approach could account to a PPH rate reduction [39]. However, it is very likely that the final mechanism by which many of these approaches are able to reduce PPH is their potential through proximity and empathy with the woman to increase endogenous oxytocin secretion [40, 41].

Conclusions

Choosing the best PPH prophylaxis is complicated, and treatment should be tailored. Probably, women at greater risk of PPH (**Tab. 1** [10]) could benefit from prophylactic treatment with uterotonics, but certainly not every woman needs this. Also, stimulating endogenous oxytocin production is probably more important than administering SynOX to every woman, especially if at low risk of having PPH. It is, therefore, very important to conduct and publish studies to investigate alternative to the simple universal use of SynOX in PPH prophylaxis. In contrast to universal prophylaxis with SynOX, early recognition and prompt treatment of PPH are essential to save women's lives. I am deeply convinced that instead of implementing universal prophylaxis with the same oxytocic drug to every woman, it would be important to identify categories of women at higher PPH risk (**Tab. 1** [10]) who deserve prophylaxis. In case not just prophylaxis but therapy is needed, drugs should be different depending on the level of risk. The even more important element is that the diagnosis should be timely and should lead to rapid treatment, which should be codified and established in protocols, discussed and simulated with all childbirth operators. A systematic bundle approach that involves readiness, recognition, response, and reporting should be implemented in every delivery and birthing facility [42, 43]. On the other hand, I believe that timely diagnosis and subsequent treatment with oxytocic drugs, TXA, and all other necessary therapeutic devices, will have beneficial consequences not only for low- and middle-income countries with limited resources and personnel, but also for high-income countries. Early detection of PPH and the use of a bundle of treatments is demonstrated to lead to a lower risk of severe PPH, the need for laparotomy for bleeding, and death from PPH, compared to usual care among patients having vaginal delivery [44]. It must be emphasized that early detection and prompt intervention are the keys to saving lives, also in high-income countries, regardless of etiology [45, 46].

Ultimately, SynOX administration is useful to reduce blood loss during childbirth and anaemia that follows. Given the serious consequences of anemia on the maternal/neonatal dyad, this effect is very important, especially, but not only, for low- and middle-income countries. However women and caregivers need to know that this is SynOX prophylaxis role.

Therefore, it is vital to understand that atony is one of the causes for PPH, but not the main one, so that we can focus on the real causes and on the appropriate etiological therapies, not according on the "one fits all" logic.

Note

To enhance readability, acronyms have also been used in the citations throughout the text.

Declaration of interest

The Author declares that there are no competing interests.

References

1. Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, Williams MJ, Diaz V, Pasquale J, Chamillard M, Widmer M, Tunçalp Ö, Hofmeyr GJ, Althabe F, Gülmezoglu AM, Vogel JP, Oladapo OT, Coomarasamy A. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018;12(12):CD011689.
2. WOMAN Trial Collaborators. 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. Lancet. 2017;389(10084):2105-16. Erratum in: Lancet. 2017;389(10084):2104.
3. Ragusa A, Ficarola F, Ferrari A, Spirito N, Ardovino M, Giraldi D, Stuzziero E, Rinaldo D, Procaccianti R, Larciprete G, De Luca C, D'Avino S, Principi G, Angioli R, Svelato A. Tranexamic acid versus oxytocin prophylaxis in reducing post-partum blood loss, in low-risk pregnant women: TRANOXY STUDY, a phase III randomized clinical trial. EClinicalMedicine. 2024;73:102665.
4. Uvnäs-Moberg K. The physiology and pharmacology of oxytocin in labor and in the peripartum period. Am J Obstet Gynecol. 2024;230(3S):S740-58.
5. Butwick AJ. Postpartum hemorrhage and low fibrinogen levels: the past, present and future. Int J Obstet Anesth. 2013;22(2):87-91.
6. Ludwig H. Surface structure of the human term placenta and of the uterine wall post partum in the screen scan electron microscope. Am J Obstet Gynecol. 1971;111(3):328-44.
7. Hews-Girard JC, Galica J, Goldie C, James P, Tranmer JE. Identifying the effect of inherited bleeding disorders on the development of postpartum hemorrhage: a population-based, retrospective cohort study. Res Pract Thromb Haemost. 2023;7(2):100104.
8. Ker K, Sentilhes L, Shakur-Still H, Madar H, Deneux-Tharaux C, Saade G, Pacheco LD, Ageron FX, Mansukhani R, Balogun E, Brenner A, Prowse D, Arribas M, Ahmadzia H, Chaudhri R, Olayemi O, Roberts I; Anti-fibrinolytics Trialists Collaborators Obstetric Group. Tranexamic acid for postpartum bleeding: a systematic review and individual patient data meta-analysis of randomised controlled trials. Lancet. 2024;404(10463):1657-67.
9. Zhang P, Jia YJ, Lv Y, Fan YF, Geng H, Zhao Y, Song H, Cui HY, Chen X. Effects of tranexamic acid preconditioning on the incidence of postpartum haemorrhage in vaginal deliveries with identified risk factors in China: a prospective, randomized, open-label, blinded endpoint trial. Ann Med. 2024;56(1):2389302.
10. Italian National Institute of Health. Emorragia post partum: come prevenirla, come curarla. Linea Guida 26. Available at: https://www.epicentro.iss.it/itoss/pdf/SNLG_EPP-2016web_corrige.pdf, date of publication: January 2012, last update: January 2016, last access: February 2025.
11. Lee SH, Kwek ME, Tagore S, Wright A, Ku CW, Teong ACA, Tan AWM, Lim SWC, Yen DYT, Ang CYX, Sultana R, Lim CHF, Mathur D, Mathur M. Tranexamic acid, as an adjunct to oxytocin prophylaxis, in the prevention of postpartum haemorrhage in women undergoing elective caesarean section: A single-centre double-blind randomised controlled trial. BJOG. 2023;130(9):1007-15.
12. Sentilhes L, Winer N, Azria E, Sénat MV, Le Ray C, Vardon D, Perrotin F, Desbrière R, Fuchs F, Kayem G, Ducarme G, Doret-Dion M, Huissoud C, Bohec C, Deruelle P, Darsonval A, Chrétien JM, Seco A, Daniel V, Deneux-Tharaux C; Groupe de Recherche en Obstétrique et Gynécologie. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. N Engl J Med. 2018;379(8):731-42.
13. Shahid A, Khan A. Tranexamic acid in decreasing blood loss during and after caesarean section. J Coll Physicians Surg Pak. 2013;23(7):459-62.
14. Simonazzi G, Bisulli M, Saccone G, Moro E, Marshall A, Berghella V. Tranexamic acid for preventing postpartum blood loss after cesarean delivery: a systematic review and meta-analysis of randomized controlled trials. Acta Obstet Gynecol Scand. 2016;95(1):28-37.
15. Anti-fibrinolytics Trialists Collaborators – Obstetric Trialists Group; Ker K, Shakur-Still H, Sentilhes L, Pacheco LD, Saade G, Deneux-Tharaux C, Brenner A, Mansukhani R, Ageron FX, Prowse D, Chaudhri R, Olayemi O, Roberts I. Tranexamic acid for the prevention of postpartum bleeding: Protocol for a systematic review and individual patient data meta-analysis. Gates Open Res. 2023;7:3.
16. Neumann BG, Metgud MC, Hoffman MK, Patil K, Savanur M, Hanji V, Ganachari MS, Somannavar M, Goudar SS. Tranexamic acid to reduce blood loss in women at high risk of postpartum hemorrhage undergoing cesarean delivery-a randomized controlled trial. AJOG Glob Rep. 2024;4(1):100316.
17. Gungorduk K, Yıldırım G, Asıcıoğlu O, Gungorduk OC, Sudolmus S, Ark C. Efficacy of intravenous tranexamic acid in reducing blood loss after elective cesarean section: a prospective, randomized, double-blind, placebo-controlled study. Am J Perinatol. 2011;28(3):233-40.
18. Abdel-Aleem H, Alhusaini TK, Abdel-Aleem MA, Menoufy M, Gülmezoglu AM. Effectiveness of tranexamic acid on

blood loss in patients undergoing elective cesarean section: randomized clinical trial. J Matern Fetal Neonatal Med. 2013;26(17):1705-9.
19. Yang F, Wang H, Shen M. Effect of preoperative prophylactic intravenous tranexamic acid on perioperative blood loss control in patients undergoing cesarean delivery: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2023;23(1):420.
20. Yang H, Zheng S, Shi C. [Clinical study on the efficacy of tranexamic acid in reducing postpartum blood lose: a randomized, comparative, multicenter trial]. [Article in Chinese]. Zhonghua Fu Chan Ke Za Zhi. 2001;36(10): 590-2.
21. Gungorduk K, Asıcıoğlu O, Yıldırım G, Ark C, Tekirdağ Aİ, Besımoglu B. Can intravenous injection of tranexamic acid be used in routine practice with active management of the third stage of labor in vaginal delivery? A randomized controlled study. Am J Perinatol. 2013;30(5):407-13.
22. Bachotiya R, Mathuriya G, Chauhan D, Bachotiya R. A Prospective Study to Evaluate the Efficacy of Trenexamic Acid in Addition to Oxytocin for Prevention of Post Partum Hemorrhage. Central India J Med Res. 2024;3(1):16-9.
23. Gupta V, Sehgal A, Tandon R, Pandher DK, Tahlan A. Effect of prophylactic tranexamic acid in normal vaginal delivery. Int J Reprod Contracept Obstet Gynecol. 2022;11(11):3097-103.
24. Fuchs AR, Romero R, Keefe D, Parra M, Oyarzun E, Behnke E. Oxytocin secretion and human parturition: pulse frequency and duration increase during spontaneous labor in women. Am J Obstet Gynecol. 1991;165(5 Pt 1):1515-23.
25. Westergaard D, Steinthorsdottir V, Stefansdottir L, Rohde PD, Wu X, Geller F, Tyrmi J, Havulinna AS, Solé-Navais P, Flatley C, Ostrowski SR, Pedersen OB, Erikstrup C, Sørensen E, Mikkelsen C, Bruun MT, Aagaard Jensen B, Brodersen T, Ullum H; FinnGen; Danish Blood Donor Study Genomic Consortium; Estonian Biobank Research Team; Nordic Collaboration for Womens and Reproductive Health; Magnus P, Andreassen OA, Njolstad PR, Kolte AM, Krebs L, Nyegaard M, Hansen TF, Feenstra B, Daly M, Lindgren CM, Thorleifsson G, Stefansson OA, Sveinbjornsson G, Gudbjartsson DF, Thorsteinsdottir U, Banasik K, Jacobsson B, Laisk T, Laivuori H, Stefansson K, Brunak S, Nielsen HS. Genome-wide association meta-analysis identifies five loci associated with postpartum hemorrhage. Nat Genet. 2024;56(8):1597-603.
26. Yin Z, Li Y, He W, Li D, Li H, Yang Y, Shen B, Wang X, Cao Y, Khalil RA. Progesterone inhibits contraction and increases TREK-1 potassium channel expression in late pregnant rat uterus. Oncotarget. 2017;9(1):651-61.
27. Kuhl H. Effects of progestogens on haemostasis. Maturitas. 1996;24(1-2):1-19.
28. Weeks AD. Oxytocin is needed, but it is no magic bullet. BJOG. 2016;123(13):2086.
29. Weeks AD, Neilson JP. Rethinking our approach to postpartum haemorrhage and uterotonics. BMJ. 2015;351:h3251.
30. Burki T. Understanding postpartum haemorrhage. Lancet. 2023;402(10402):601.
31. Fahy K, Hastie C, Bisits A, Marsh C, Smith L, Saxton A. Holistic physiological care compared with active management of the third stage of labour for women at low risk of postpartum haemorrhage: a cohort study. Women Birth. 2010;23(4):146-52.
32. Almutairi WM. Literature Review: Physiological Management for Preventing Postpartum Hemorrhage. Healthcare (Basel). 2021;9(6):658.
33. Erickson EN, Lee CS, Grose E, Emeis C. Physiologic childbirth and active management of the third stage of labor: A latent class model of risk for postpartum hemorrhage. Birth. 2019;46(1):69-79.
34. Borovac-Pinheiro A, Ribeiro FM, Pacagnella RC. Risk Factors for Postpartum Hemorrhage and its Severe Forms with Blood Loss Evaluated Objectively - A Prospective Cohort Study. Rev Bras Ginecol Obstet. 2021;43(2):113-8.
35. Widmer M, Piaggio G, Hofmeyr GJ, Carroli G, Coomarasamy A, Gallos I, Goudar S, Gülmezoglu AM, Lin SL, Lumbiganon P, Mugerwa K, Owa O, Qureshi Z, Althabe F. Maternal characteristics and causes associated with refractory postpartum haemorrhage after vaginal birth: a secondary analysis of the WHO CHAMPION trial data. BJOG. 2020;127(5): 628-34.
36. Bestman PL, Nget M, Kolleh EM, Moeng E, Brhane T, Fang JQ, Luo J. A comparative analysis of Postpartum Hemorrhage incidence and influencing factors between nulliparous and multiparous women in Hunan Province, China: A multicenter retrospective cohort study. Prev Med Rep. 2024;38:102580.
37. Jafarabady K, Eshraghi N, Zare F, Shokouhi N, Abbasi M, Mahdiyar P, Bakhtiyari M. Association of oxytocin augmentation with postpartum hemorrhage: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2024;37(1):2369210.
38. World Health Organization. Support during labour and childbirth. In: Counselling for Maternal and Newborn Health Care: A Handbook for Building Skills. Available at: https://www.ncbi.nlm.nih.gov/books/NBK304186/, date of publication: 2013, last access: February 2025.
39. Riches J, Jafali J, Twabi HH, Chimwaza Y, Onrust M, Bilesi R, Gadama L, Kachale F, Kuyere A, Makhaza L, Makuluni R, Munthali L, Musopole O, Ndamala C, Phiri DA, Coomarasamy A, Merriel A, Waitt C, Odland ML, Lissauer D. Avoidable factors associated with maternal death from postpartum haemorrhage: a national Malawian surveillance study. BMJ Glob Health. 2025;10(1):e015781.
40. Saxton A, Fahy K, Rolfe M, Skinner V, Hastie C. Does skin-to-skin contact and breast feeding at birth affect the rate of primary postpartum haemorrhage: Results of a cohort study. Midwifery. 2015;31(11):1110-7.
41. Ragusa A, Svelato A, Fogolari M, Ficarola F, Plotti F, De Luca C, D'Avino S, Davini F, De Cesaris M, Messina G, Bertolini A, Marci R, Angeletti S, Angioli R, Terranova C. The

endogenous oxytocin after manipulative osteopathic treatment in full-term pregnant women. Eur Rev Med Pharmacol Sci. 2024;28(3):1155-62.

42. Atallah F, Goffman D. Improving Healthcare Responses to Obstetric Hemorrhage: Strategies to Mitigate Risk. Risk Manag Healthc Policy. 2020;13:35-42.
43. Vogel JP, Nguyen PY, Ramson J, De Silva MS, Pham MD, Sultana S, McDonald S, Adu-Bonsaffoh K, McDougall ARA. Effectiveness of care bundles for prevention and treatment of postpartum hemorrhage: a systematic review. Am J Obstet Gynecol. 2024;231(1):67-91.
44. Gallos I, Devall A, Martin J, Middleton L, Beeson L, Galadanci H, Alwy Al-Beity F, Qureshi Z, Hofmeyr GJ, Moran N, Fawcus S, Sheikh L, Gwako G, Osoti A, Aswat A, Mammoliti KM, Sindhu KN, Podesek M, Horne I, Timms R, Yunas I, Okore J, Singata-Madliki M, Arends E, Wakili AA, Mwampashi A, Nausheen S, Muhammad S, Latthe P, Evans C, Akter S, Forbes G, Lissauer D, Meher S, Weeks A, Shennan A, Ammerdorffer A, Williams E, Roberts T, Widmer M, Oladapo OT, Lorencatto F, Bohren MA, Miller S, Althabe F, Gülmezoglu M, Smith JM, Hemming K, Coomarasamy A. Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage. N Engl J Med. 2023;389(1):11-21.
45. Clarke-Deelder E, Opondo K, Achieng E, Garg L, Han D, Henry J, Guha M, Lightbourne A, Makin J, Miller N, Otieno B, Borovac-Pinheiro A, Suarez-Rebling D, Menzies NA, Burke T, Oguttu M, McConnell M, Cohen J. Quality of care for postpartum hemorrhage: A direct observation study in referral hospitals in Kenya. PLOS Glob Public Health. 2023;3(3):e0001670.
46. Main E, Martin C, Linda L, Thomas A. Definition, Early Recognition and Rapid Response to Obstetric Hemorrhage Using Triggers. In: California Maternal Quality Care Collaborative (CMQCC). Improving Health Care Response to Obstetric Hemorrhage, V3.0. A CMQCC Quality Improvement Toolkit. Available at: https://www.cmqcc.org/sites/default/files/HEMToolkit_03252022%20Errata%207.2022%20%282%29.pdf, date of publication: July 2022, last access: February 2025.