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UNIVERSITÀ DI ROMA

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Napoli, 6-7 Giugno 2019

È POSSIBILE PREVENIRE L'EMORRAGIA DEL POST-PARTUM?

Prof. Romolo Di Iorio

Dipartimento di Scienze Medico-Chirurgiche e Medicina Traslazionale
"Sapienza" Università di Roma

Mumtaz Mahal

Shah Jahan

POSTPARTUM HAEMORRHAGE (PPH)

Severe bleeding after giving birth, known as PPH, is the biggest single cause of mothers dying after childbirth

14m

mothers develop PPH each year globa

PPH can also lead to **hysterectomy** and **severe anaemia**

An estimated

100,000

women died from PPH in 2015

99% of these deaths were developing countries

woman

World Maternal Antifibrinolytic Trial

WHO analysis of causes of maternal death: a systematic review

Khalid S Khan, Daniel Wojdyla, Lale Say, A Metin Gülmezoglu, Paul F A Van Look

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Summary

Background The reduction of maternal deaths is a key international development goal. Evidence-based health policies and programmes aiming to reduce maternal deaths need reliable and valid information. We undertook a systematic review to determine the distribution of causes of maternal deaths.

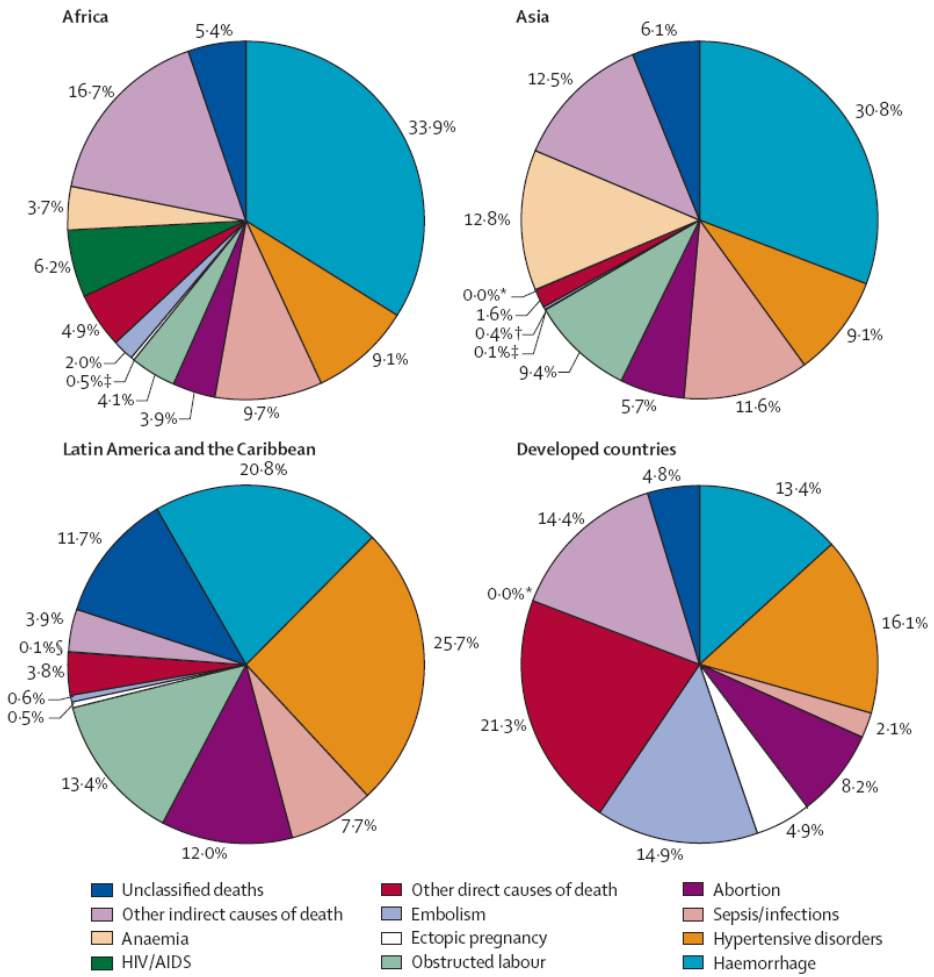
Methods We selected datasets using prespecified criteria, and recorded dataset characteristics, methodological features, and causes of maternal deaths. All analyses were restricted to datasets representative of populations. We analysed joint causes of maternal deaths from datasets reporting at least four major causes (haemorrhage, hypertensive disorders, sepsis, abortion, obstructed labour, ectopic pregnancy, embolism). We examined datasets reporting individual causes of death to investigate the heterogeneity due to methodological features and geographical region and the contribution of haemorrhage, hypertensive disorders, abortion, and sepsis as causes of maternal death at the country level.

Findings 34 datasets (35 197 maternal deaths) were included in the primary analysis. We recorded wide regional variation in the causes of maternal deaths. Haemorrhage was the leading cause of death in Africa (point estimate 33·9%, range 13·3–43·6; eight datasets, 4508 deaths) and in Asia (30·8%, 5·9–48·5; 11, 16 089). In Latin America and the Caribbean, hypertensive disorders were responsible for the most deaths (25·7%, 7·9–52·4; ten, 11 777). Abortion deaths were the highest in Latin America and the Caribbean (12%), which can be as high as 30% of all deaths in some countries in this region. Deaths due to sepsis were higher in Africa (odds ratio 2·71), Asia (1·91), and Latin America and the Caribbean (2·06) than in developed countries.

Interpretation Haemorrhage and hypertensive disorders are major contributors to maternal deaths in developing countries. These data should inform evidence-based reproductive health-care policies and programmes at regional and national levels. Capacity-strengthening efforts to improve the quality of burden-of-disease studies will further validate future estimates.

WHO analysis of causes of maternal death: a systematic review

Khalid S Khan, Daniel Wojdyla, Lale Say, A Metin Gülmezoglu, Paul F A Van Look



Maternal mortality in Italy: a record-linkage study

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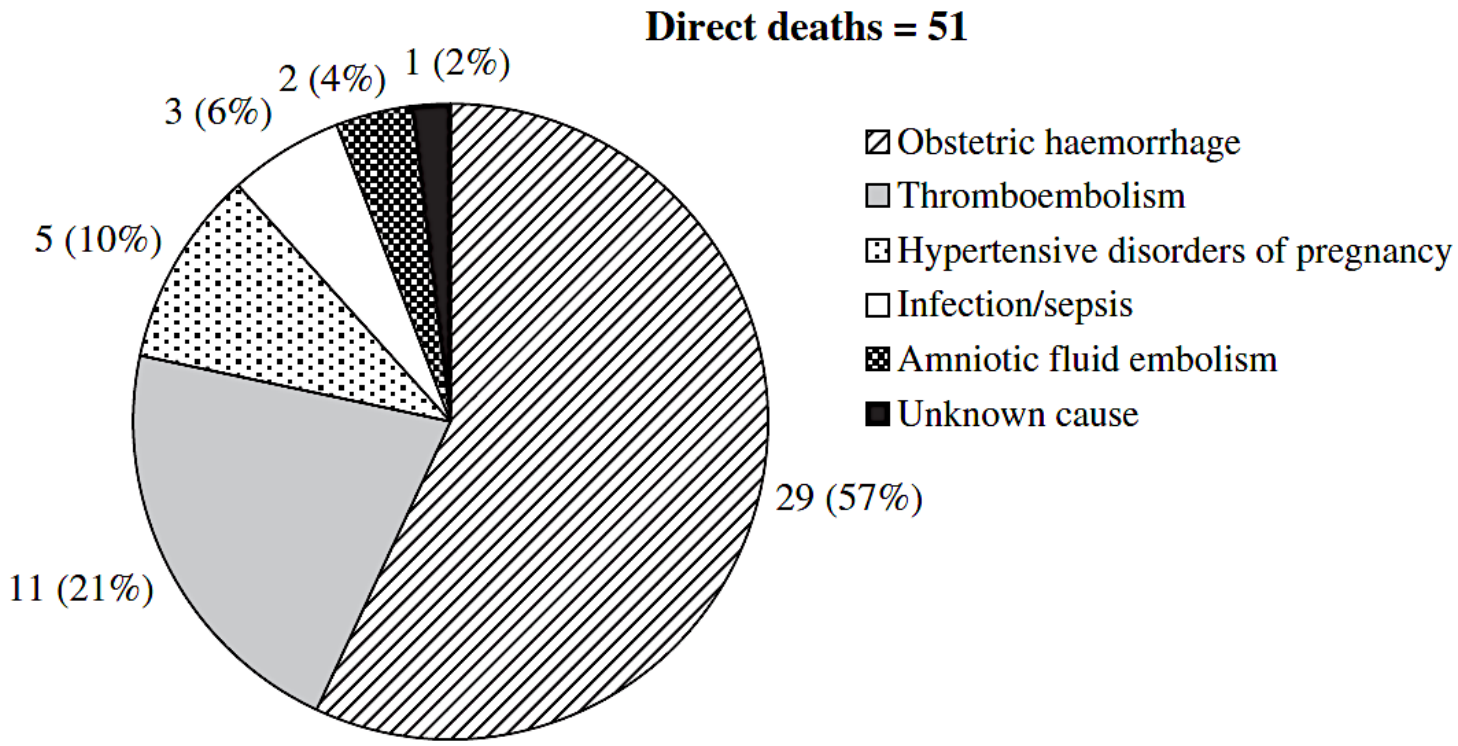


preventive healthcare

primordial prevention

to avoid the development of risk factors during intrauterine and/or newborn life

primary prevention

to reduce or avoid occurrence of disease

i.e.: stop smoking, healthy diet, exercise, folic acid, HPV vaccine

secondary prevention

to detect and address an existing disease prior to the appearance of symptoms

i.e.: screening methods (PAP, mammography)

tertiary prevention

to reduce the progression of symptomatic disease such as disability or death

i.e.: surgical procedures that halt the spread or progression of disease, insulin

quaternary prevention

to mitigate or avoid results of unnecessary or excessive interventions in the health system

fetal programming

general population

disease

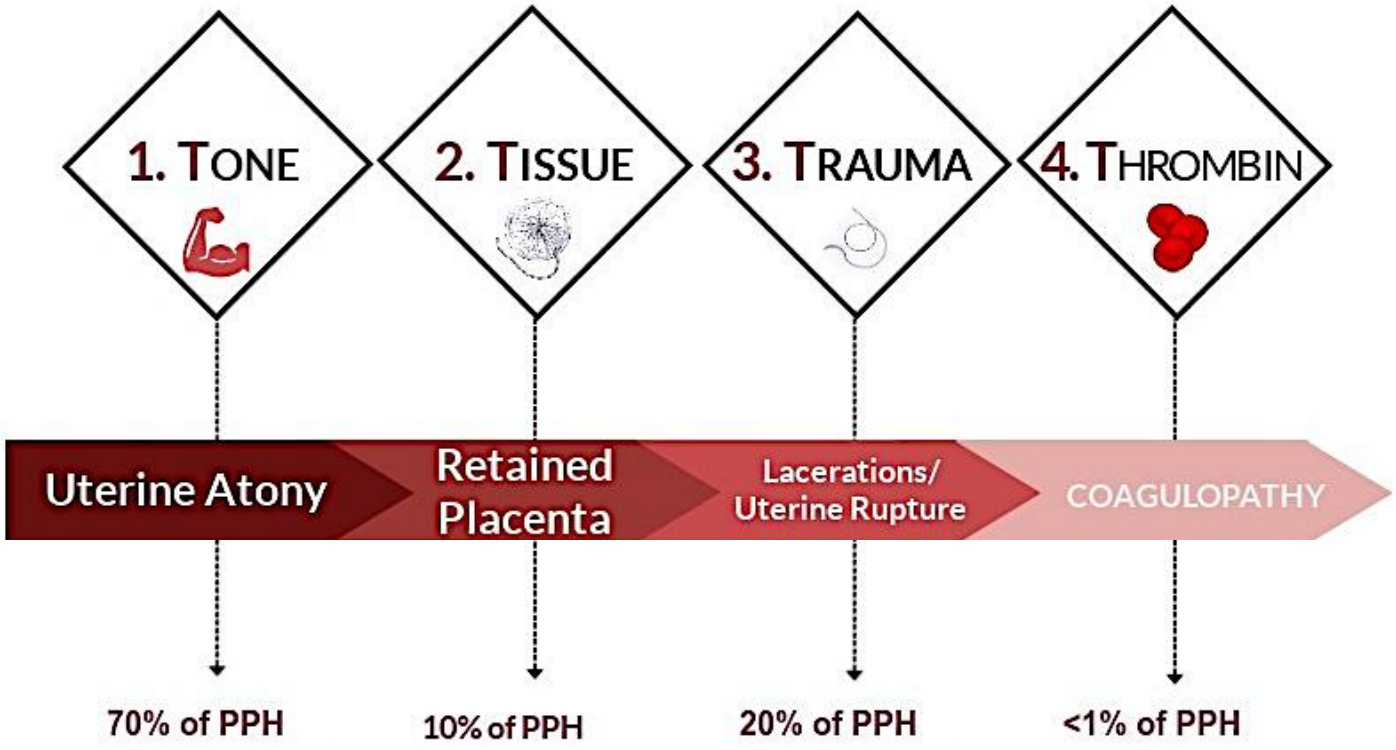
progression of disease

overtreatment

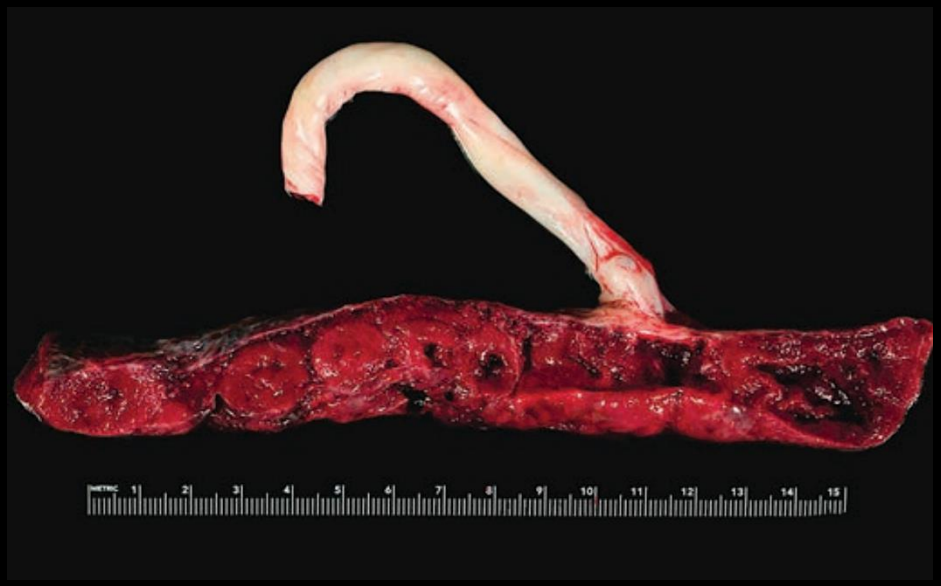
Fattori di rischio	Eziologia	Odds ratio (95% CI)
Gravidanza multipla	Tono	3,3 (1,0-10,6) 4,7 (2,4-9,1)
Precedente EPP	Tono	3,6 (1,2-10,2)
Preeclampsia	Trombina, Tono	5,0 (3,0-8,5) 2,2 (1,3-3,7)
Peso alla nascita >4.000 gr	Tono	2,11 (1,62-2,76) 2,4 (1,9-2,9)
Mancata progressione del secondo stadio	Tono	3,4 (2,4- 4,7) 1,9 (1,2-2,9)

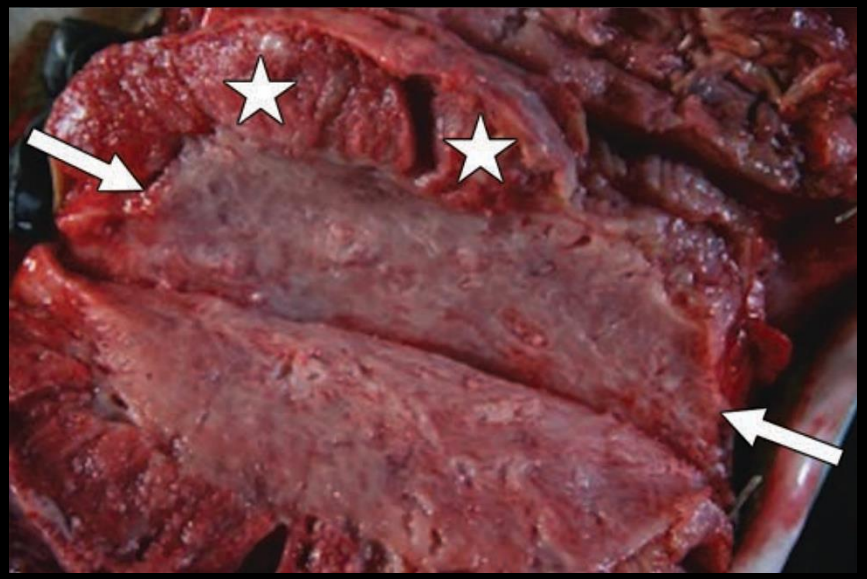
Fattori di rischio	Eziologia	Odds ratio (95% CI)
Prolungamento del terzo stadio del travaglio	Tono	7,6 (4,2-13,5) 2,61 (1,83-3,72)
Placenta ritenuta	Tessuto	7,83 (3,78-16,22) 3,5 (2,1-5,8) 6,0 (3,5-10,4)
Placenta accreta	Tessuto	3,3 (1,7-6,4)
Episiotomia	Trauma	4,7 (2,6-8,4) 2,18 (1,68-2,76) 1,7 (1,2-2,5)
Lacerazione perineale	Trauma	1,4 (1,04-1,87) 2,4 (2,0-2,8) 1,7 (1,1-2,5)

FOUR T's of PostPartum Hemorrhage



tissue





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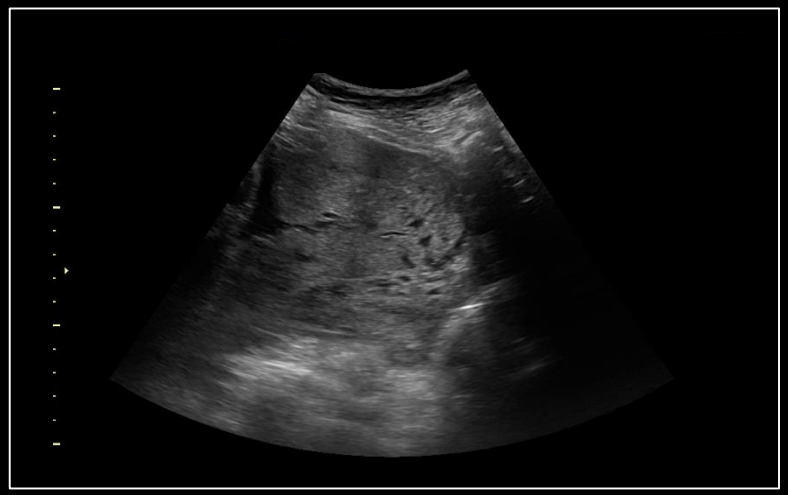

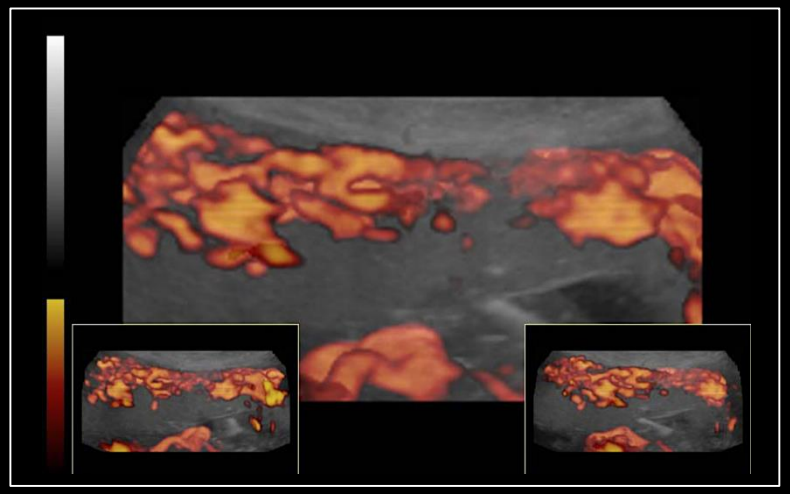

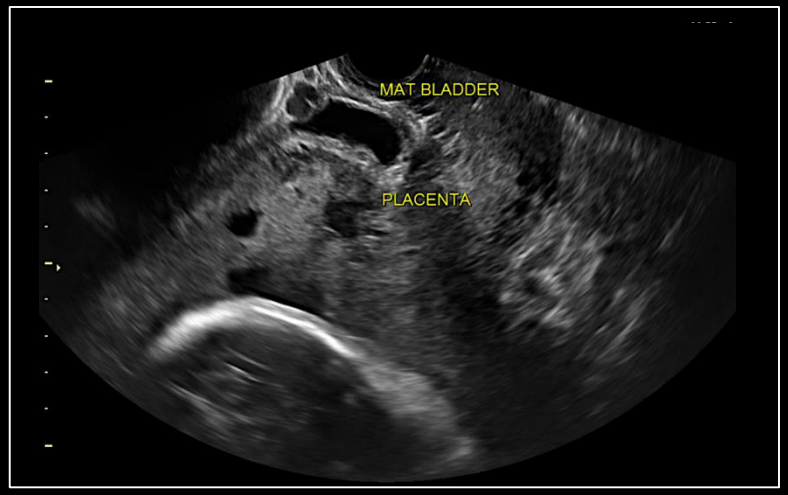

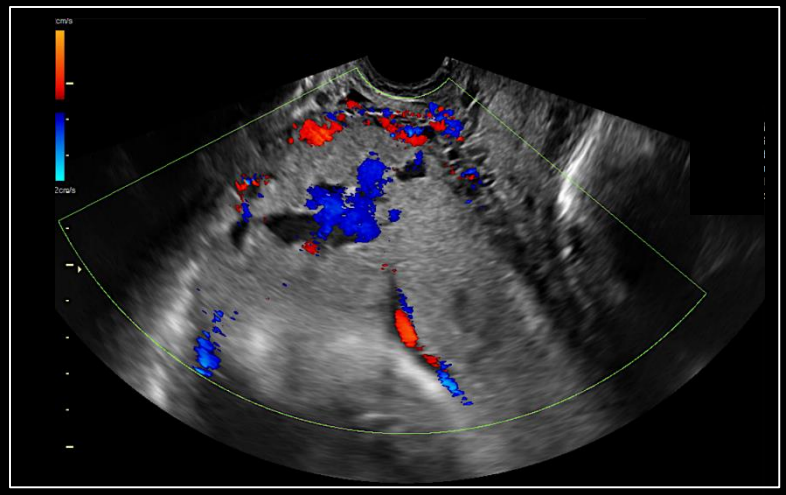

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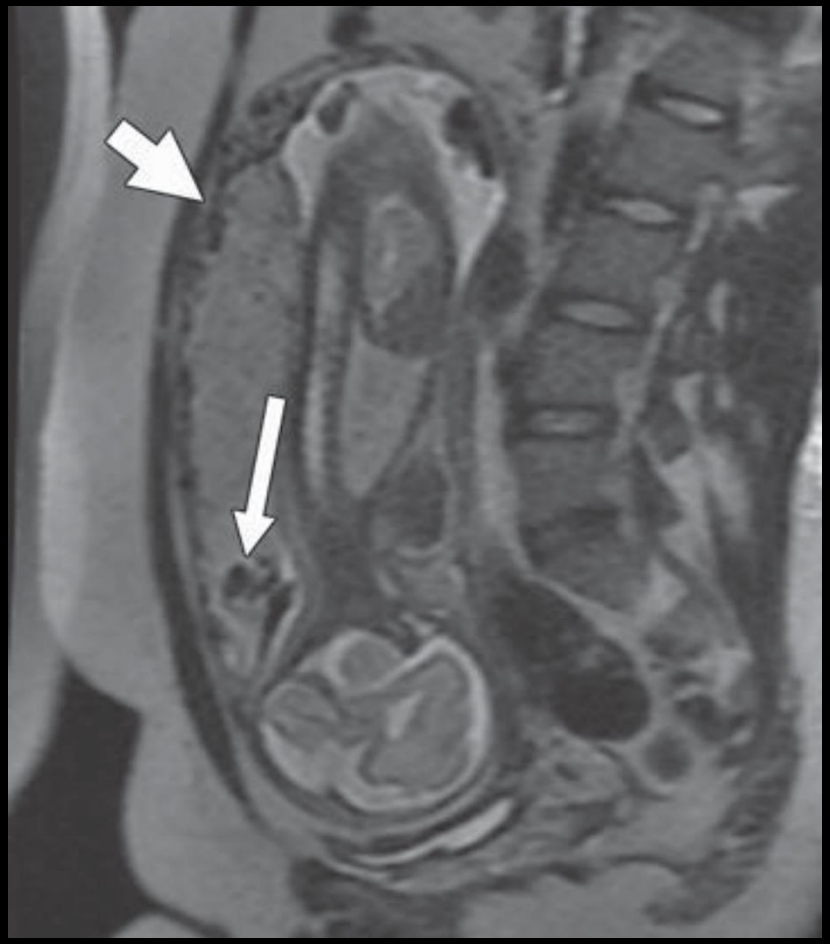

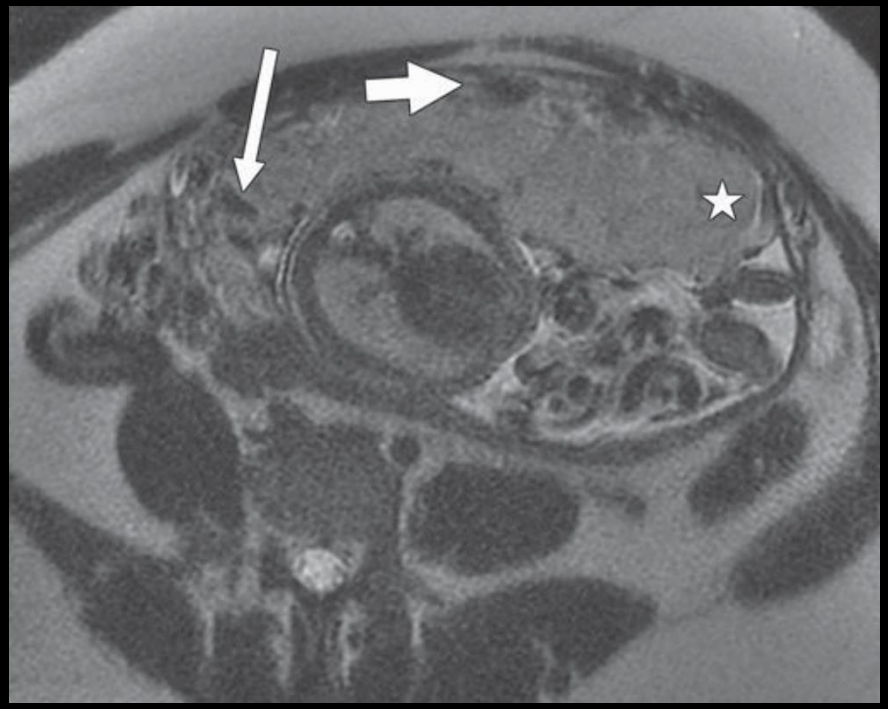

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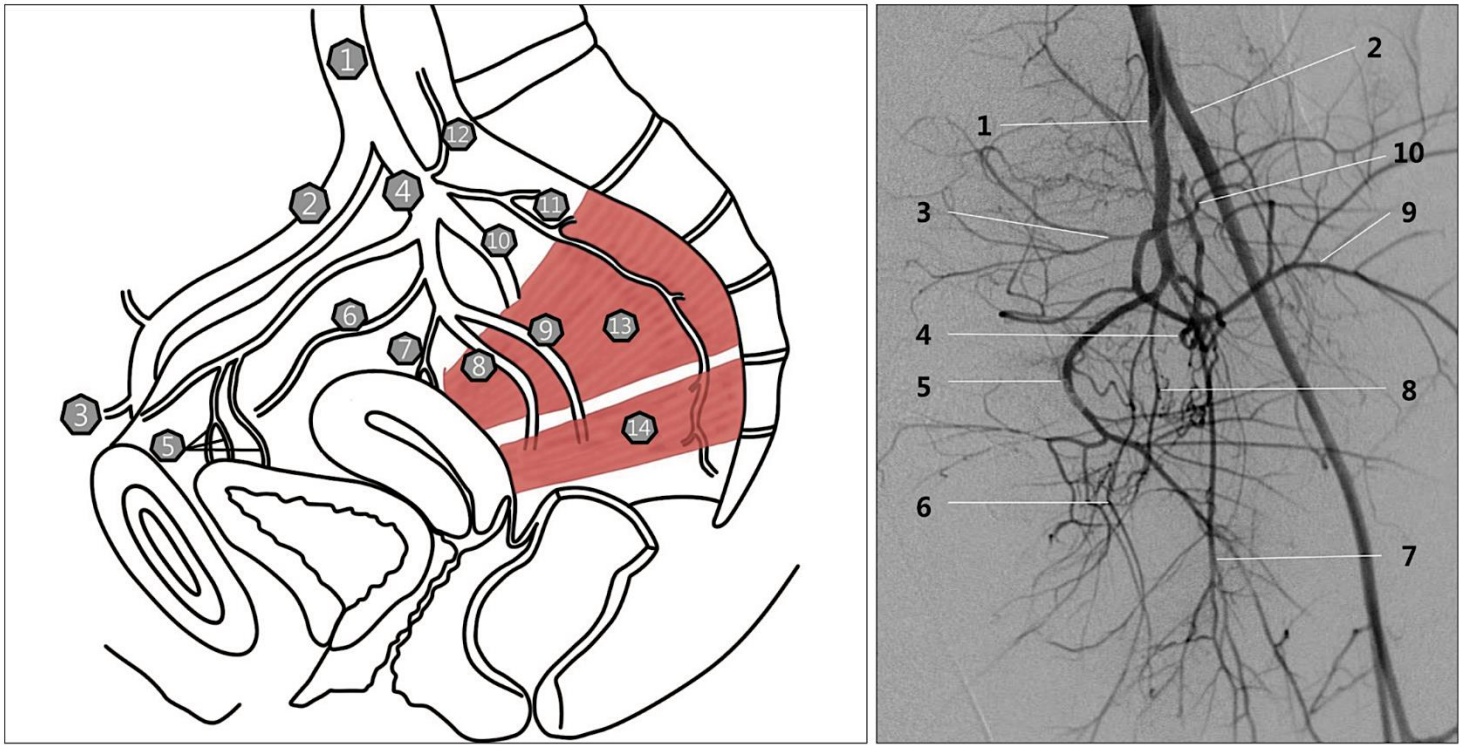
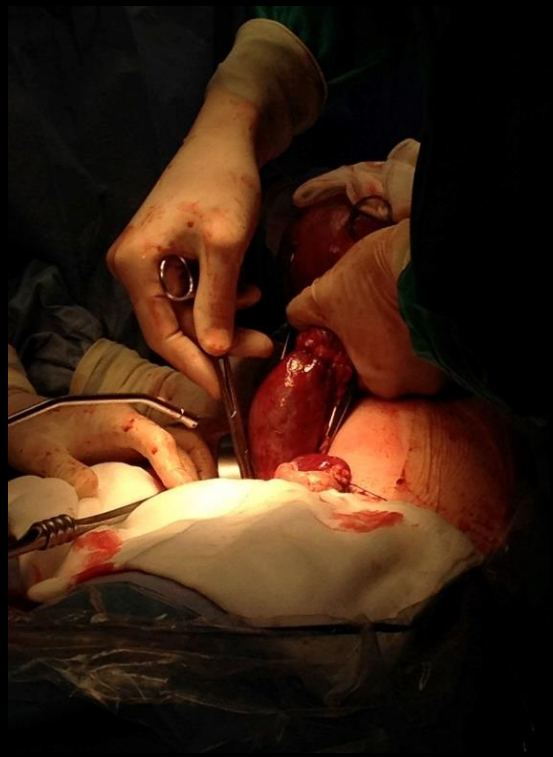
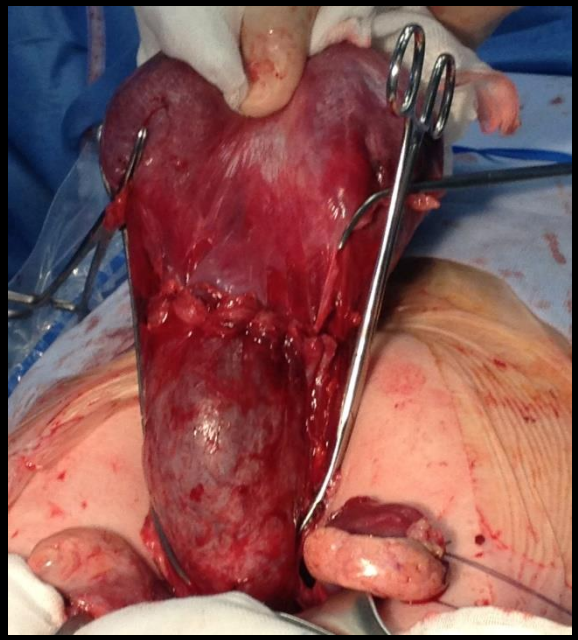


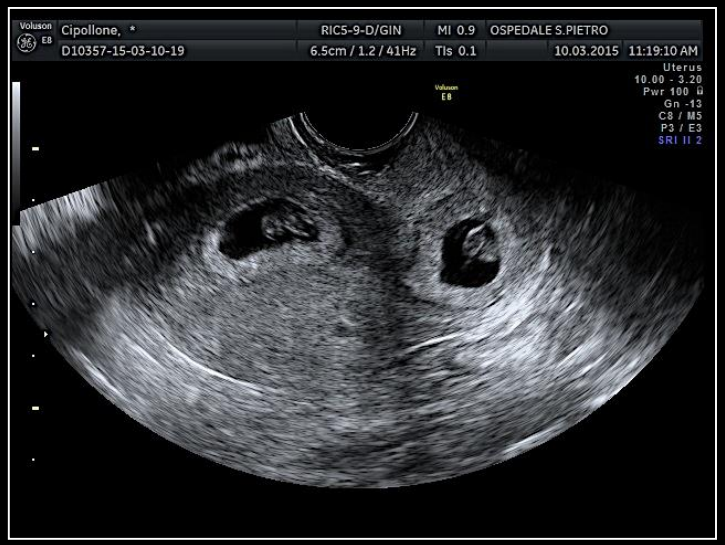
Fig. 1. Vascular anatomy relevant to PPH.

A. Schema of IIA and its branches. 1, common iliac artery; 2, external iliac artery; 3, inferior epigastric artery; 4, IIA; 5, superior vesical artery; 6, obturator artery; 7, UA; 8, internal pudendal artery; 9, inferior gluteal artery; 10, superior gluteal artery; 11, lateral sacral artery; 12, iliolumbar artery; 13, piriformis muscle; and 14, sacrospinous ligament. **B.** Left IIA arteriogram in right anterior oblique projection (20°). 1, IIA; 2, external iliac artery; 3, lateral sacral artery; 4, UA; 5, inferior gluteal artery; 6, internal pudendal artery; 7, obturator artery; 8, vesical artery; 9, superior gluteal artery; and 10, iliolumbar artery. IIA = internal iliac artery, PPH = postpartum hemorrhage, UA = uterine artery

Chren C et al, 2019



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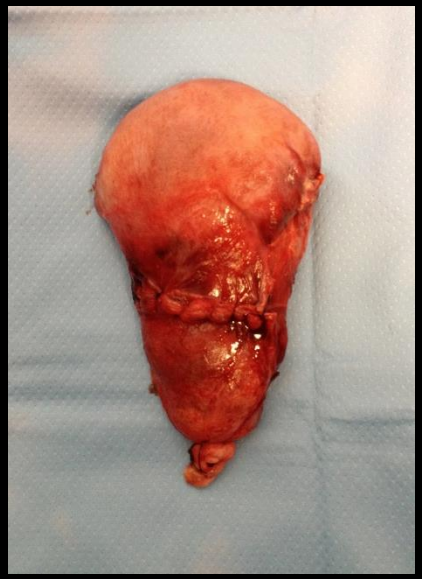

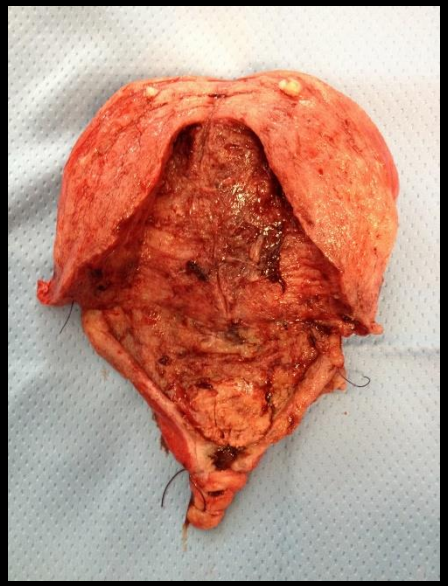

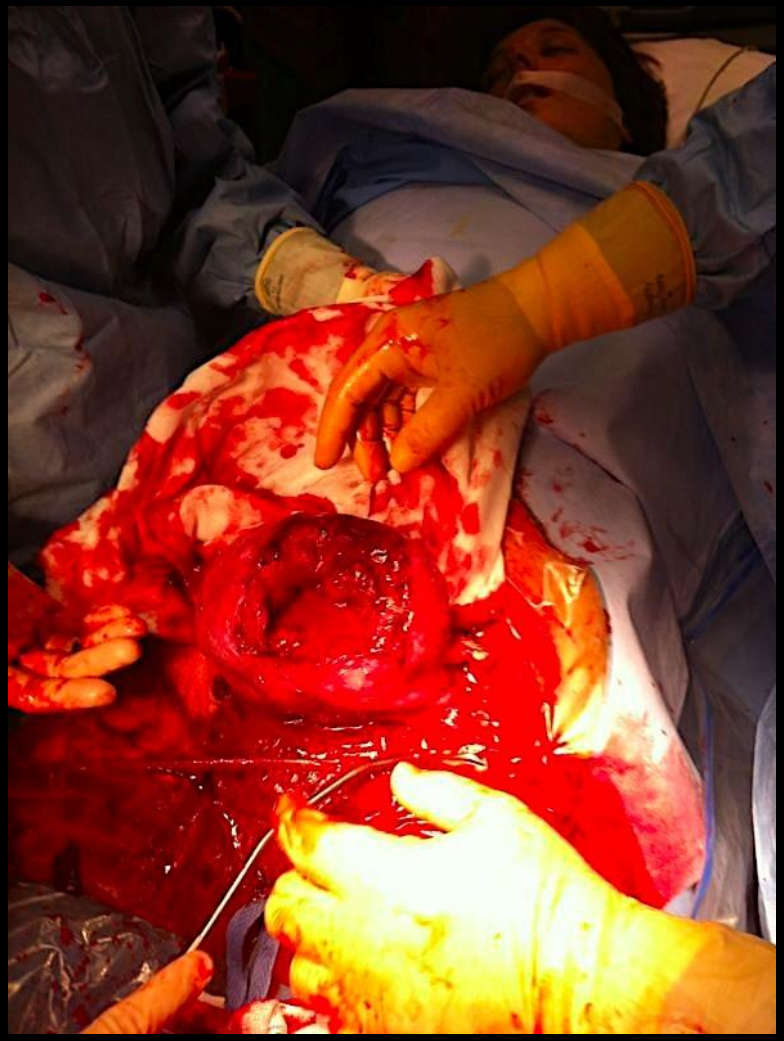

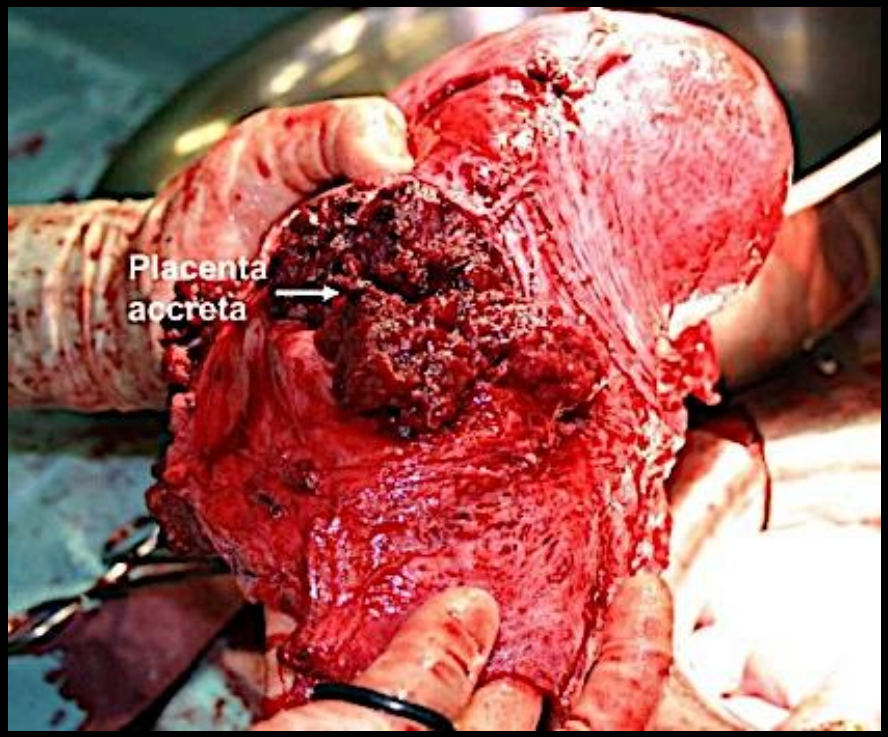
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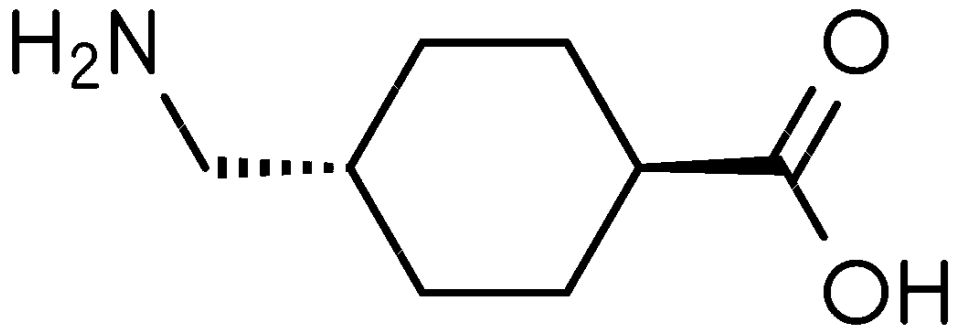
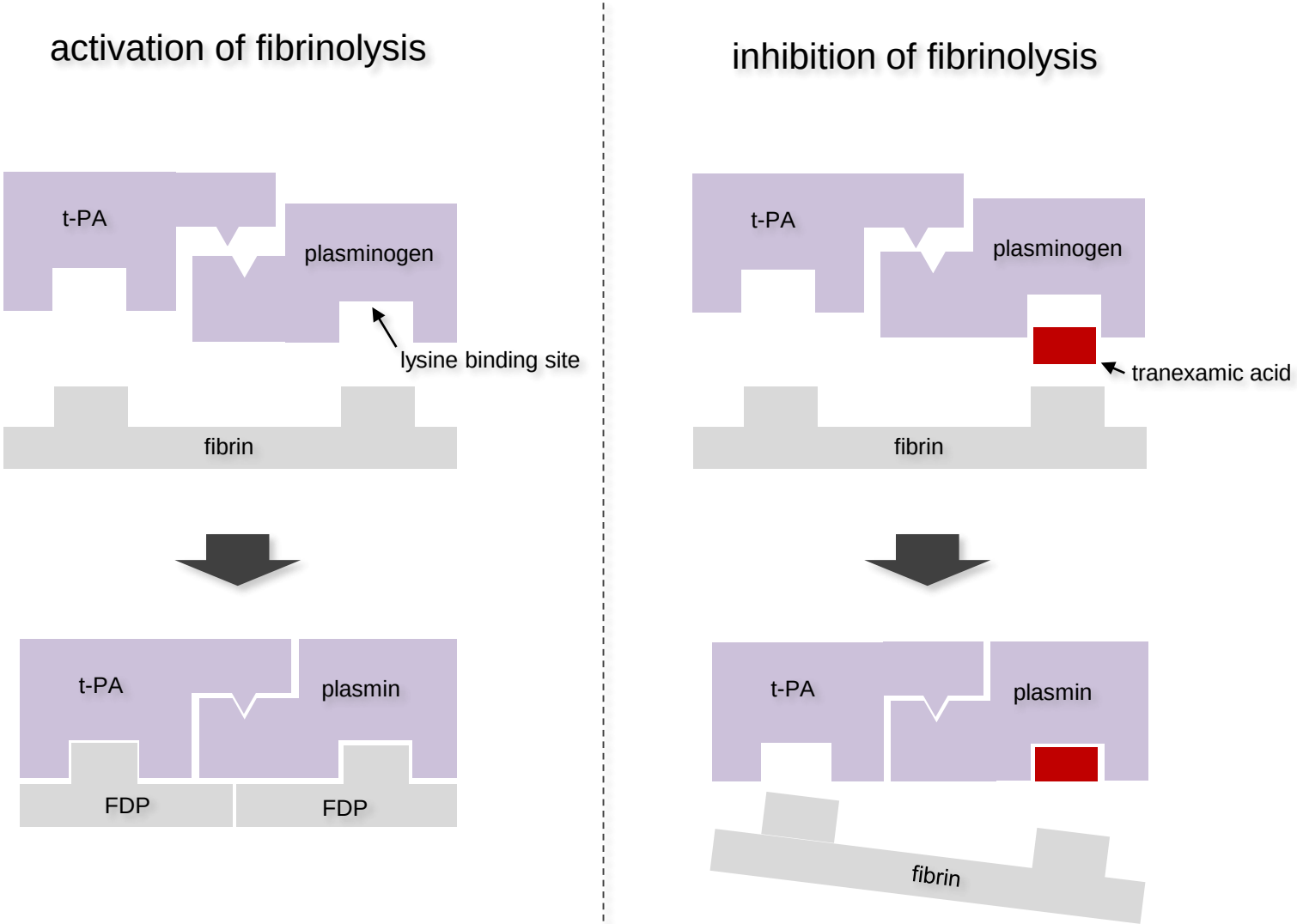


tranexamic acid



t-PA: tissue plasminogen activator FDP: fibrin degradation products

Utako Okamoto
(1918 - 2014)

Agenti emostatici

Acido tranexamico

L'acido tranexamico (AT) è un agente antifibrinolitico che si è mostrato in grado di ridurre l'emorragia e il bisogno di trasfusioni in vari contesti di chirurgia elettiva e che, somministrato entro otto ore da un trauma alla dose di carico di 1 g in 10 minuti, seguita da infusione di 1 g in otto ore, è risultato associato a una riduzione della mortalità intraospedaliera per tutte le cause e per emorragia (Henry 2011, Crash-2 2010 e 2011).

Interpretazione delle prove

È stato incluso un RCT multicentrico di qualità molto bassa, realizzato in Francia tra il 2005 e il 2008, che ha valutato l'efficacia e la sicurezza del trattamento con AT ad alte dosi (dose di carico 4 g endovena in un'ora, poi infusione di 1 g/ora per 6 ore) in 144 donne con EPP insorta dopo parto vaginale. Il trattamento di seconda linea con AT è risultato associato a una ridotta perdita ematica e a un minore decremento della concentrazione emoglobinica in donne con EPP a seguito di parto vaginale. Si tratta del primo studio che dimostra che l'AT può avere un ruolo nel ridurre la perdita ematica in donne con EPP, e tuttavia non fornisce prove sufficienti sull'efficacia del trattamento con AT nel controllare l'EPP senza necessità di ricorrere ad altre procedure assistenziali. Inoltre le prove disponibili non consentono di raccomandare uno specifico dosaggio di AT da utilizzare per il trattamento dell'EPP. Il trattamento adiuvante di seconda linea con AT è risultato associato a una maggiore incidenza di effetti avversi lievi e transitori, come nausea o vomito. Non è possibile trarre conclusioni definitive relativamente al rischio di complicanze tromboemboliche dopo somministrazione di AT in questo setting specifico.

RACCOMANDAZIONE

In presenza di EPP non responsiva ai trattamenti farmacologici di prima e seconda linea valutare il ricorso a opzioni terapeutiche adiuvanti tra cui la somministrazione di acido tranexamico.

raccomandazione debole, prove di qualità bassa

Cochrane Library

Tranexamic acid for preventing postpartum haemorrhage (Review)

Novikova N, Hofmeyr GJ, Cluver C

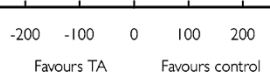
Analysis 1.3. Comparison 1 Tranexamic acid versus placebo/no treatment, Outcome 3 Mean blood loss (mL).

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 1 Tranexamic acid versus placebo/no treatment

Outcome: 3 Mean blood loss (mL)

Study or subgroup	TA N	TA Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Tranexamic acid in vaginal birth							
Gungorduk 2013	220	261.5 (146.8)	219	349.98 (188.8)		40.6 %	-88.48 [-120.13, -56.83]
Mirghafourvand 2013	60	310.2 (188.7)	60	371.8 (243.7)		6.7 %	-61.60 [-139.59, 16.39]
Yang 2001	186	243.1 (140.4)	87	314.8 (180.9)		21.9 %	-71.70 [-114.74, -28.66]
Subtotal (95% CI)	**466**		**366**			**69.2 %**	**-80.56 [-104.80, -56.33]**
Heterogeneity: $Chi^2 = 0.63$, df = 2 (P = 0.73); $I^2 = 0.0\%$							
Test for overall effect: Z = 6.52 (P < 0.00001)							
2 Tranexamic acid in caesarean section							
Gai 2004	91	359.3 (152)	89	439.4 (191.5)		15.9 %	-80.10 [-130.68, -29.52]
Xu 2013	88	379.2 (160.1)	86	441.7 (189.5)		14.9 %	-62.50 [-114.68, -10.32]
Subtotal (95% CI)	**179**		**175**			**30.8 %**	**-71.57 [-107.89, -35.26]**
Heterogeneity: $Chi^2 = 0.23$, df = 1 (P = 0.64); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.86 (P = 0.00011)							
Total (95% CI)	**645**		**541**			**100.0 %**	**-77.79 [-97.95, -57.64]**
Heterogeneity: $Chi^2 = 1.02$, df = 4 (P = 0.91); $I^2 = 0.0\%$							
Test for overall effect: Z = 7.56 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.16$, df = 1 (P = 0.69), $I^2 = 0.0\%$							



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Tranexamic acid for preventing postpartum haemorrhage (Review)

Novikova N, Hofmeyr GJ, Cluver C

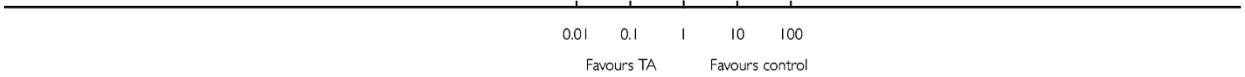
Analysis 1.4. Comparison 1 Tranexamic acid versus placebo/no treatment, Outcome 4 Use of additional medical interventions to control PPH.

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 1 Tranexamic acid versus placebo/no treatment

Outcome: 4 Use of additional medical interventions to control PPH

Study or subgroup	TA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Tranexamic acid in vaginal birth					
Gungorduk 2013	6/220	19/219		22.2 %	0.31 [0.13, 0.77]
Mirghafourvand 2013	3/60	7/60		8.2 %	0.43 [0.12, 1.58]
Subtotal (95% CI)	**280**	**279**		**30.4 %**	**0.35 [0.16, 0.72]**
Total events: 9 (TA), 26 (Control)					
Heterogeneity: Chi^2 = 0.15, df = 1 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 2.82 (P = 0.0048)					
2 Tranexamic acid in caesarean section					
Abdel-Aleem 2013	1/373	1/367		1.2 %	0.98 [0.06, 15.67]
Goswami 2013	5/60	8/30		12.4 %	0.31 [0.11, 0.87]
Gungorduk 2011	28/330	48/330		56.0 %	0.58 [0.38, 0.91]
Subtotal (95% CI)	**763**	**727**		**69.6 %**	**0.54 [0.36, 0.81]**
Total events: 34 (TA), 57 (Control)					
Heterogeneity: Chi^2 = 1.39, df = 2 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 3.02 (P = 0.0025)					
Total (95% CI)	**1043**	**1006**		**100.0 %**	**0.48 [0.34, 0.68]**
Total events: 43 (TA), 83 (Control)					
Heterogeneity: Chi^2 = 2.56, df = 4 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 4.09 (P = 0.000043)					
Test for subgroup differences: Chi^2 = 1.11, df = 1 (P = 0.29), I^2 =10%					



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Tranexamic acid for preventing postpartum haemorrhage (Review)

Novikova N, Hofmeyr GJ, Cluver C

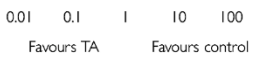
Analysis 1.6. Comparison 1 Tranexamic acid versus placebo/no treatment, Outcome 6 Blood transfusion.

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 1 Tranexamic acid versus placebo/no treatment

Outcome: 6 Blood transfusion

Study or subgroup	TA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Tranexamic acid in vaginal birth					
Gungorduk 2013	1/220	3/219		10.7 %	0.33 [0.03, 3.17]
Subtotal (95% CI)	**220**	**219**		**10.7 %**	**0.33 [0.03, 3.17]**
Total events: 1 (TA), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.96 (P = 0.34)					
2 Tranexamic acid in CS					
Goswami 2013	0/60	2/30		11.8 %	0.10 [0.01, 2.05]
Gungorduk 2011	2/330	7/330		24.9 %	0.29 [0.06, 1.37]
Senturk 2013	0/101	0/122			Not estimable
Shahid 2013	3/38	12/36		43.8 %	0.24 [0.07, 0.77]
Yehia 2014	0/106	2/106		8.9 %	0.20 [0.01, 4.12]
Subtotal (95% CI)	**635**	**624**		**89.3 %**	**0.23 [0.10, 0.54]**
Total events: 5 (TA), 23 (Control)					
Heterogeneity: Chi^2 = 0.37, df = 3 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 3.38 (P = 0.00073)					
Total (95% CI)	**855**	**843**		**100.0 %**	**0.24 [0.11, 0.53]**
Total events: 6 (TA), 26 (Control)					
Heterogeneity: Chi^2 = 0.46, df = 4 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 3.50 (P = 0.00046)					
Test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.76), I^2 =0.0%					



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Tranexamic acid for preventing postpartum haemorrhage (Review)

Novikova N, Hofmeyr GJ, Cluver C

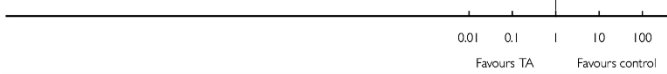
Analysis 1.9. Comparison 1 Tranexamic acid versus placebo/no treatment, Outcome 9 Thromboembolic events.

Review: Tranexamic acid for preventing postpartum haemorrhage

Comparison: 1 Tranexamic acid versus placebo/no treatment

Outcome: 9 Thromboembolic events

Study or subgroup	TA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Tranexamic acid in vaginal birth					
Gungorduk 2013	0/220	0/219			Not estimable
Minghafourvand 2013	0/60	0/60			Not estimable
Subtotal (95% CI)	**280**	**279**			**Not estimable**
Total events: 0 (TA), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Tranexamic acid for caesarean section					
Abdel-Aleem 2013	0/373	0/367			Not estimable
Gai 2004	0/91	0/89			Not estimable
Goswami 2013	0/60	0/30			Not estimable
Gungorduk 2011	0/330	0/330			Not estimable
Movafegh 2011	0/50	0/50			Not estimable
Senturk 2013	0/101	0/122			Not estimable
Shahid 2013	0/38	0/36			Not estimable
Xu 2013	2/88	2/86		100.0 %	0.98 [0.14, 6.78]
Yehia 2014	0/106	0/106			Not estimable
Subtotal (95% CI)	**1237**	**1216**		**100.0 %**	**0.98 [0.14, 6.78]**
Total events: 2 (TA), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
Total (95% CI)	**1517**	**1495**		**100.0 %**	**0.98 [0.14, 6.78]**
Total events: 2 (TA), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
Test for subgroup differences: Not applicable					



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Tranexamic acid for preventing postpartum haemorrhage (Review)

Novikova N, Hofmeyr GJ, Cluver C

Authors' conclusions

TA (in addition to uterotonic medications) decreases postpartum blood loss and prevents PPH and blood transfusions following vaginal birth and CS in women at low risk of PPH based on studies of mixed quality. There is insufficient evidence to draw conclusions about serious side effects, but there is an increase in the incidence of minor side effects with the use of TA. Effects of TA on thromboembolic events and mortality as well as its use in high-risk women should be investigated further.

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

*WOMAN Trial Collaborators**

Summary

Background Post-partum haemorrhage is the leading cause of maternal death worldwide. Early administration of tranexamic acid reduces deaths due to bleeding in trauma patients. We aimed to assess the effects of early administration of tranexamic acid on death, hysterectomy, and other relevant outcomes in women with post-partum haemorrhage.

Methods In this randomised, double-blind, placebo-controlled trial, we recruited women aged 16 years and older with a clinical diagnosis of post-partum haemorrhage after a vaginal birth or caesarean section from 193 hospitals in 21 countries. We randomly assigned women to receive either 1 g intravenous tranexamic acid or matching placebo in addition to usual care. If bleeding continued after 30 min, or stopped and restarted within 24 h of the first dose, a second dose of 1 g of tranexamic acid or placebo could be given. Patients were assigned by selection of a numbered treatment pack from a box containing eight numbered packs that were identical apart from the pack number. Participants, care givers, and those assessing outcomes were masked to allocation. We originally planned to enrol 15 000 women with a composite primary endpoint of death from all-causes or hysterectomy within 42 days of giving birth. However, during the trial it became apparent that the decision to conduct a hysterectomy was often made at the same time as randomisation. Although tranexamic acid could influence the risk of death in these cases, it could not affect the risk of hysterectomy. We therefore increased the sample size from 15 000 to 20 000 women in order to estimate the effect of tranexamic acid on the risk of death from post-partum haemorrhage. All analyses were done on an intention-to-treat basis. This trial is registered with ISRCTN76912190 (Dec 8, 2008); ClinicalTrials.gov, number NCT00872469; and PACTR201007000192283.

Findings Between March, 2010, and April, 2016, 20 060 women were enrolled and randomly assigned to receive tranexamic acid (n=10 051) or placebo (n=10 009), of whom 10 036 and 9985, respectively, were included in the analysis. Death due to bleeding was significantly reduced in women given tranexamic acid (155 [1·5%] of 10 036 patients *vs* 191 [1·9%] of 9985 in the placebo group, risk ratio [RR] 0·81, 95% CI 0·65–1·00; p=0·045), especially in women given treatment within 3 h of giving birth (89 [1·2%] in the tranexamic acid group *vs* 127 [1·7%] in the placebo group, RR 0·69, 95% CI 0·52–0·91; p=0·008). All other causes of death did not differ significantly by group. Hysterectomy was not reduced with tranexamic acid (358 [3·6%] patients in the tranexamic acid group *vs* 351 [3·5%] in the placebo group, RR 1·02, 95% CI 0·88–1·07; p=0·84). The composite primary endpoint of death from all causes or hysterectomy was not reduced with tranexamic acid (534 [5·3%] deaths or hysterectomies in the tranexamic acid group *vs* 546 [5·5%] in the placebo group, RR 0·97, 95% CI 0·87-1·09; p=0·65). Adverse events (including thromboembolic events) did not differ significantly in the tranexamic acid versus placebo group.

Interpretation Tranexamic acid reduces death due to bleeding in women with post-partum haemorrhage with no adverse effects. When used as a treatment for postpartum haemorrhage, tranexamic acid should be given as soon as possible after bleeding onset.

Funding London School of Hygiene & Tropical Medicine, Pfizer, UK Department of Health, Wellcome Trust, and Bill & Melinda Gates Foundation.

Lancet 2017; 389: 2105–16

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This online publication has been corrected. The corrected version first appeared at thelancet.com on May 5, 2017

See Editorial page 2081

*Collaborators listed at end of the report

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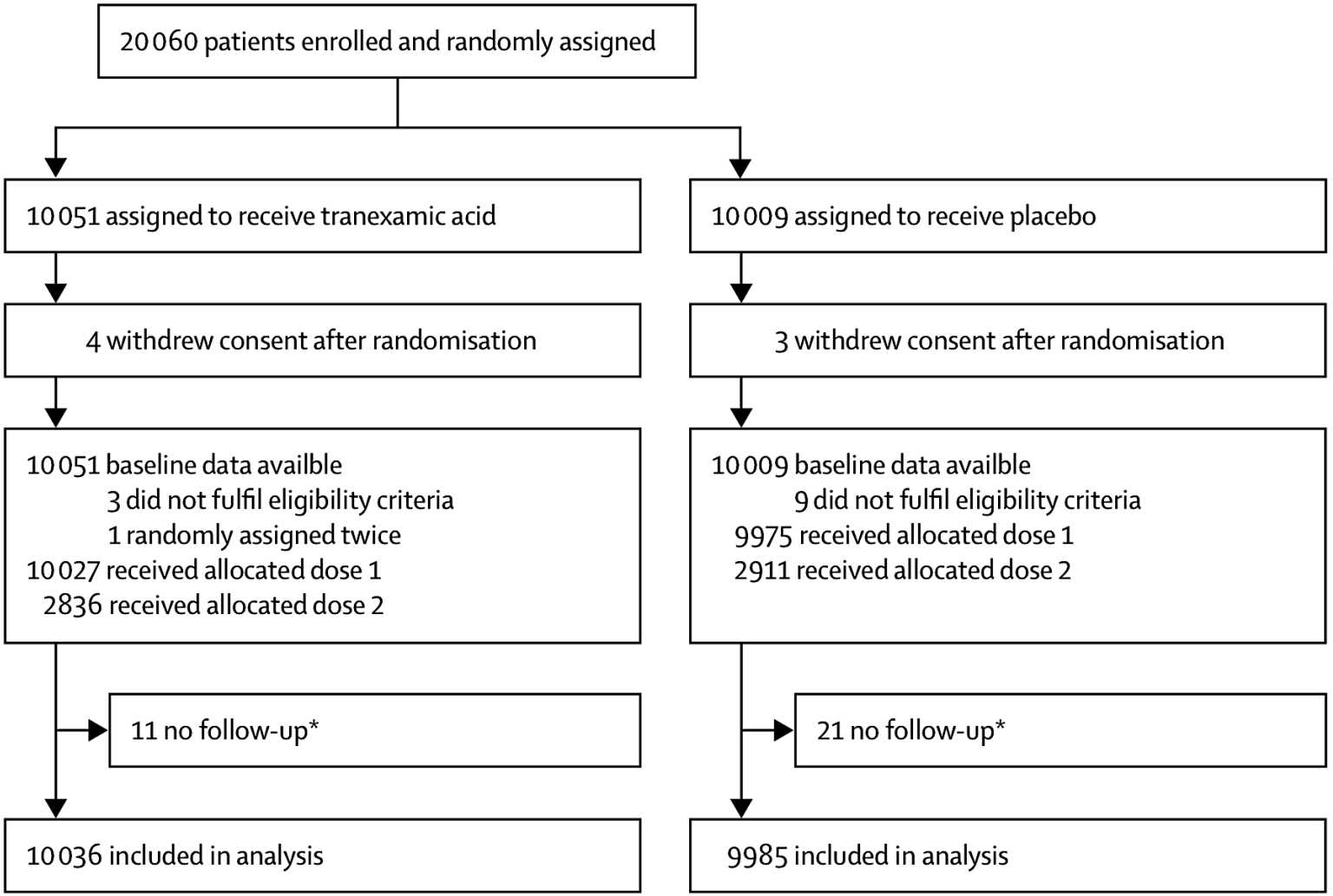
20 060 patients enrolled and randomly assigned
10 051 assigned to receive tranexamic acid
10 009 assigned to receive placebo
4 withdrew consent after randomisation
3 withdrew consent after randomisation
10 051 baseline data availble
3 did not fulfil eligibility criteria
1 randomly assigned twice
10 027 received allocated dose 1
2836 received allocated dose 2
10 009 baseline data availble
9 did not fulfil eligibility criteria
9975 received allocated dose 1
2911 received allocated dose 2
11 no follow-up*
21 no follow-up*
10 036 included in analysis
9985 included in analysis

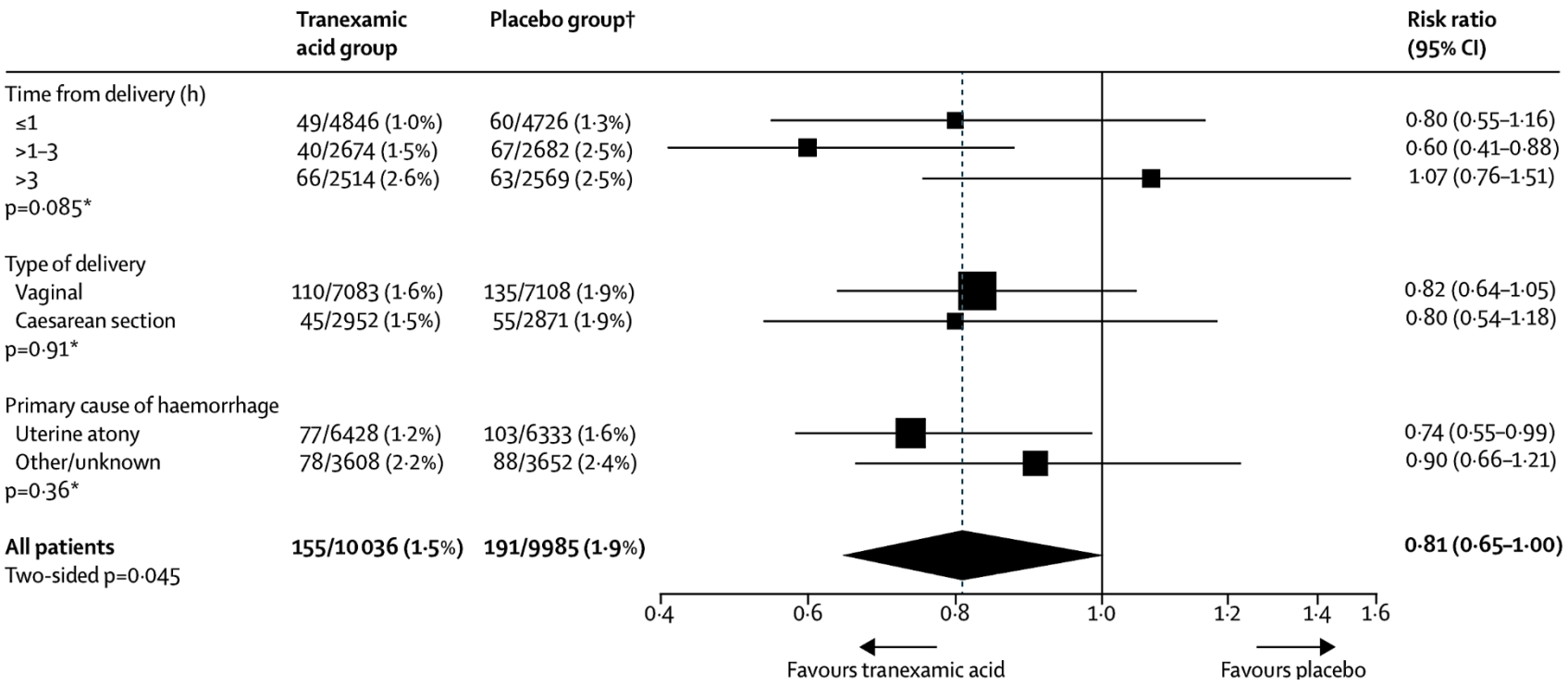

Figure 3: **Death from bleeding by subgroup**

*Heterogeneity p value. †One patient excluded from subgroup analysis because of missing baseline data.

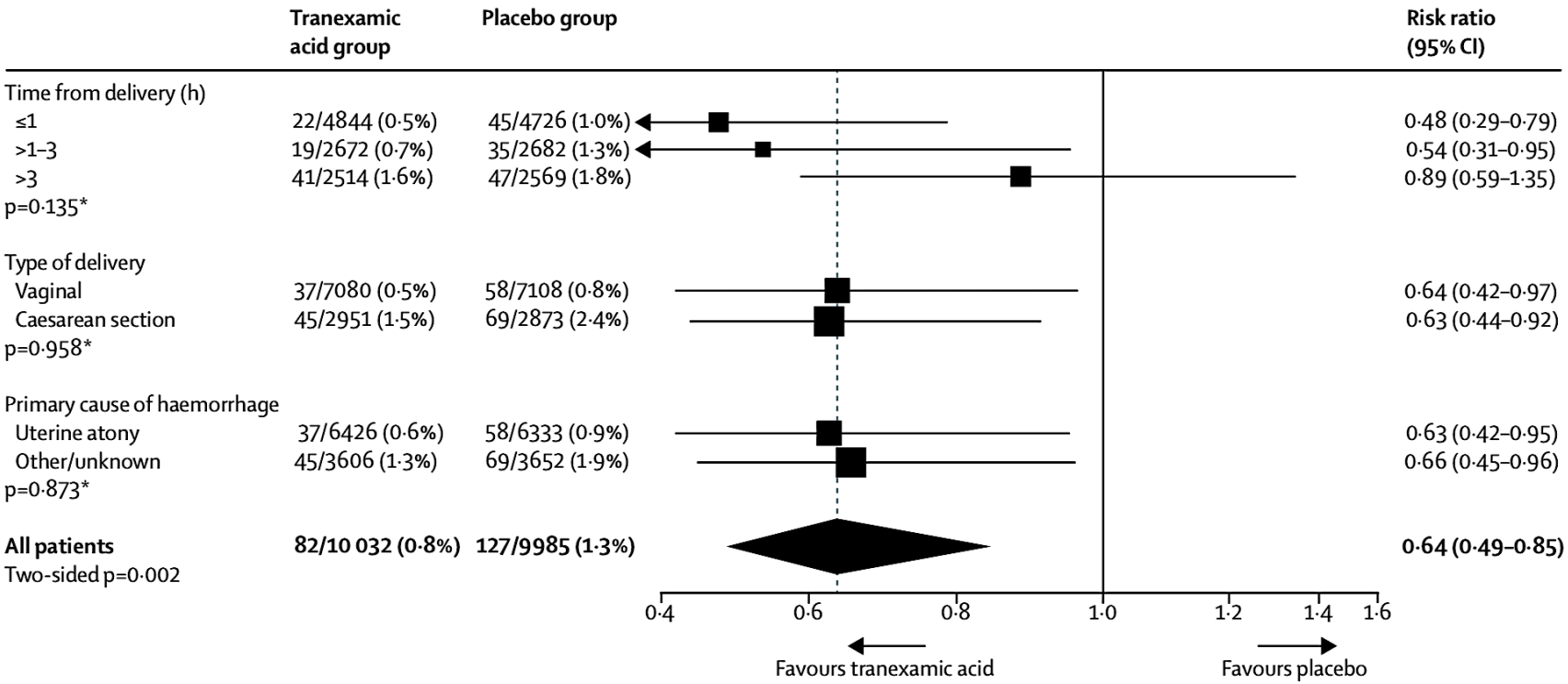

Figure 4: **Laparotomy for bleeding by subgroup**

*Heterogeneity p value.

Tranexamic acid for post-partum haemorrhage in the WOMAN trial

We read with interest the WOMAN trial (May 27, p 2105).[1] Tranexamic acid is an antifibrinolytic drug used to reduce haemorrhage complications in trauma and elective surgery. The WOMAN trial originally planned to enrol 1 prima all cau 42 da increas to mo that t power partun study signific from b to 155 reduct tranex of givir Reduct was no the tra placeb Trial ("when partun should after bleeding onset".[1]

We strongly believe that such a conclusion is premature and might be misleading to health-care professionals and the public. Moreover, the following statement is cited on the chief investigator's institutional website and also appears in videos and on social media platforms: "tranexamic acid could save the lives of one in three mothers who would otherwise bleed to death after childbirth". We believe that such statements seem to misrepresent the data.

How is tranexamic acid known to reduce death from post-partum haemorrhage and how is p=0·008 (or p=0·045) interpreted when the cutoff value to reject the null hypothesis is p=0·05? Statistically, it means that eight in 1000 chances exist for being wrong, which sounds compelling, but there are limits. In the WOMAN trial, p=0·008 denotes a 0·8% probability of observing a mortality difference of 0·5% (1·7–1·2%) under the null hypothesis, and would indicate that the null hypothesis should be rejected. However, establishment of the magnitude of difference between

This study was mainly done in low-income and middle-income countries; thus, we have concerns about its generalisability. Many differences probably exist in the health-care systems (and disease burdens) between many countries included in the trial. Therefore, we do not think the results are immediately translatable to high-income countries.

between groups, which are completely clinically irrelevant. However, with proper marketing, billions can be made from results of dubious clinical importance". Judgments about clinical importance should be formed on the basis of the size of the effect and CIs instead of the p value, because the p value is strongly affected by the size of the study.[3,4] If the study kept its original sample size of 15 000, would the results be different?

Finally, the WOMAN trial does not adequately address clinical issues about optimum timing and dose. What laboratory tests are recommended to drive the clinical use of tranexamic acid? Similar questions emerged from the CRASH-2 trial,[5] which continues to generate controversy. Although we agree that global action for maternal health should be accelerated and not diminished, the results of the WOMAN trial are only the beginning stages towards this goal. Tranexamic acid should not constitute all approach to treat provide a basis for based discussions to mortality and morbid ce. competing inte etson, *Geof bson@jcu.e and Sepsis Rese dicine and Denti wnsville City, QL Trial Collaborat ic acid administ tomy, and other t-partum haem ational, randor controlled trial. 5–16. Stump DA. Sta inical significanc rdiothorac Vasc A TJ. Clinical trials: pretation of the erap 2004; 11: 3 olles BM, Porche hypothesis testi archers. Clin Orth 5–92. Shreve J, Thom a: "myth," "reali ". Semin Thromb 12.

We read with intere trial[1] and commend t on this important international, plac trial. For a study tc validity, its conditions need to be representative of a larger population. This study was mainly done in low-income and middle-income countries; thus, we have concerns about its generalisability. Many differences probably exist in the health-care systems (and disease burdens) between many countries included in the trial. Therefore, we do not think the results are immediately translatable to high-income countries.

In the trial, the incidence of death from post-partum haemorrhage (but not overall mortality) was 1·9% and reduced to 1·4% with tranexamic acid. Based on the data, the number needed to treat was 250 women. In Australia, 11 deaths from haemorrhage occurred over a 5-year period.[2] If the post-partum haemorrhage incidence was 5% and the same relative risk and risk reduction as the WOMAN trial was used, the number needed to treat in this setting is approximately 35 587 women.[3]

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should not be routinely included in the management of obstetric haemorrhage in women from high-income countries.

We declare no competing interests.

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1 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: 2105–16.
2 Humphrey MD, Bonello MR, Chughtai A, Macaldowie A, Harris K, Chambers GM, for Australian Institute of Health and Welfare. 12. 2015.

Science Photo

For more on the **institutional website** see http://womantrial.lshtm.ac.uk/

Submissions should be made via our electronic submission system at http://ees.elsevier.com/thelancet/

Authors' reply

Alicia Therese Dennis and James D Griffiths believe that women in high-income countries with post-partum haemorrhage should not receive tranexamic acid for the following reasons: the WOMAN trial[1] was mostly done in middle-income countries and so the results are not generalisable and death from bleeding is rare in high-income countries where women more often die from the complications of bleeding.

International differences in obstetric care do not necessarily mean that the results of the WOMAN trial[1] are not generalisable. To generalise results, the mechanism by which the treatment improves health outcomes and factors that might be relevant to this mechanism should be considered.[2] This point draws on the wider body of evidence about how tranexamic acid works. Dichotomising results according to whether the upper limit of the CI includes the null, as suggested by Hayley L Letson and Geoffrey P Dobson, is unhelpful in this respect. Furthermore, apart from the fact that the absolute risk reduction (and number needed to treat) is not a generalisable measure,[2] their indifference to a 0·5% mortality reduction is surprising. We would want our daughters to be treated.

Tranexamic acid reduces bleeding by inhibiting the breakdown of fibrin blood clots.[3] Studies[4,5] in high-income countries show that tranexamic acid reduces surgical bleeding without increasing vascular occlusive events. Tranexamic acid reduces death from bleeding after trauma and the WOMAN trial shows it reduces death from bleeding and the need for laparotomy to control bleeding.[6] The effects of tranexamic acid and treatment-time interaction were similar in traumatic bleeding and post-partum bleeding. From this finding, we can conclude that tranexamic acid reduces bleeding and its adverse effects, and thus its effects are widely generalisable.

If tranexamic acid reduces bleeding, we should expect some reduction in the non-fatal consequences of bleeding that are common in high-income countries. Why expose women to invasive and expensive treatments like radiology and surgery when a simple, inexpensive treatment is available? And when an untreated mother dies from post-partum bleeding, the argument that few women die will be hard to defend.

We agree that tranexamic acid should not replace another effective intervention and that our results do not support the prophylactic use of tranexamic acid in all women who deliver. We did not record the timing of blood product administration but we can reassure Yuto Maeda and colleagues that in a large trial, differences in transfusion policies should not cause confounding outcomes. Finally, Letson and Dobson ask about the optimal timing of tranexamic acid use. Optimal timing is being investigated in an individual patient data meta-analysis and will be reported on later.

IR and HS report grants from Wellcome Trust, Department of Health, Bill & Melinda Gates Foundation, and Pfizer during the conduct of the study.

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1 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:** 2105–16.

2 Roberts I, Prieto D. Applying results from clinical trials: tranexamic acid in trauma patients. *J Intensive Care* 2014; **2:** 56.

3 Cesarman-Maus G, Hajjar K. Molecular mechanisms of fibrinolysis. *Br J Haematol* 2005; **129:** 307–21.

4 Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; **344:** e3054.

5 Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med* 2017; **376:** 136–48.

6 The CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; **377:** 1096–101.

If tranexamic acid reduces bleeding, we should expect some reduction in the non-fatal consequences of bleeding that are common in high-income countries. Why expose women to invasive and expensive treatments like radiology and surgery when a simple, inexpensive treatment is available? And when an untreated mother dies from post-partum bleeding, the argument that few women die will be hard to defend.

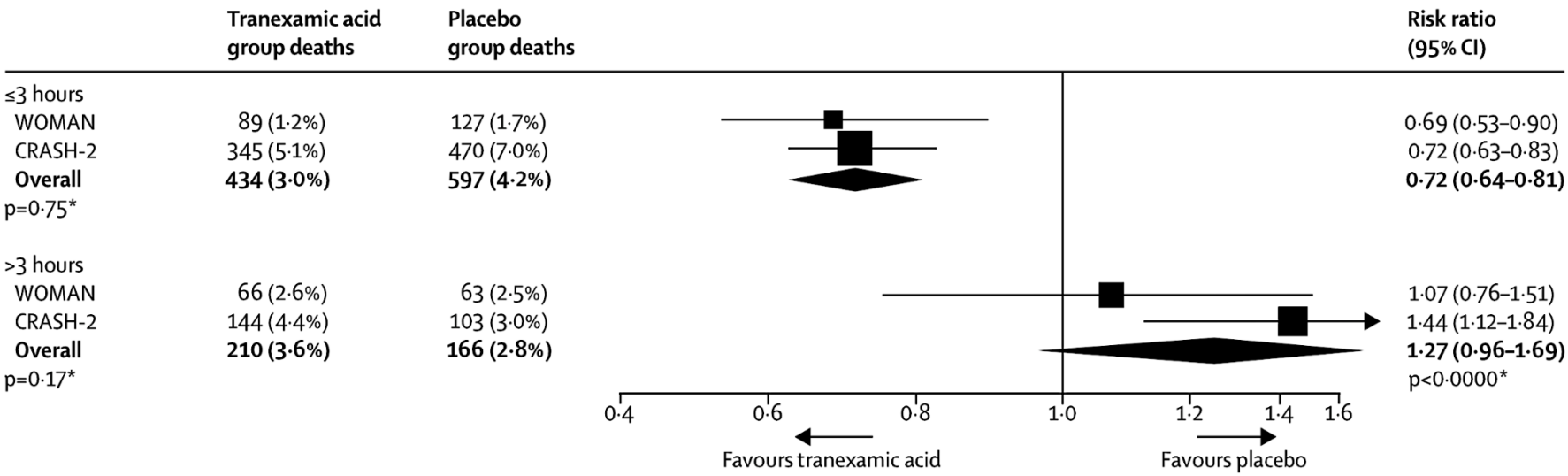

Figure 5: **Time to treatment**
*Heterogeneity p value.

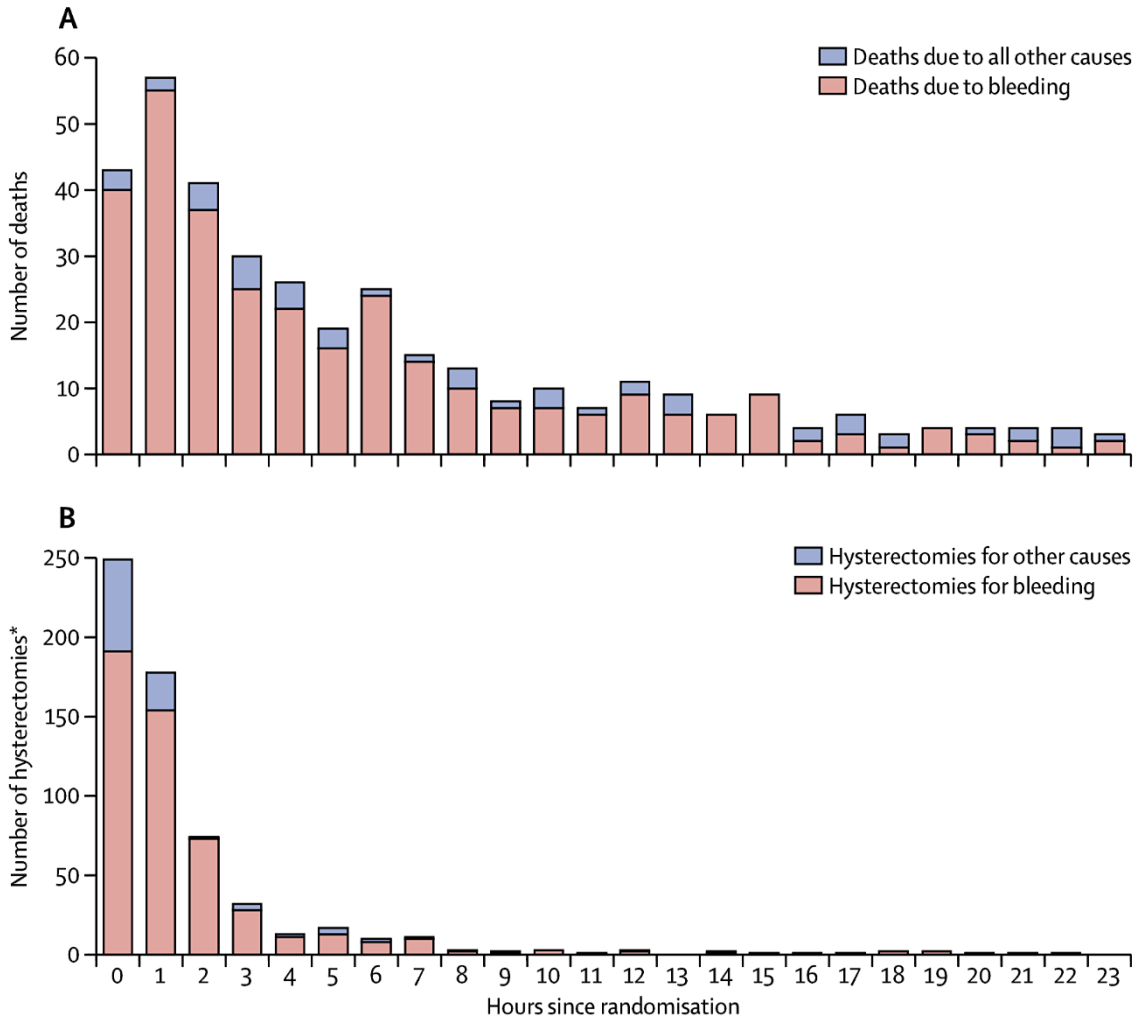

Figure 2: **Cause of death by hours since randomisation (A) and cause of hysterectomy by hours since randomisation (B)**

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Antifibrinolytic drugs for treating primary postpartum haemorrhage (Review)

Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA

Comparison 1. Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Maternal mortality due to bleeding (subgroup time from birth)	1	20011	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.01]
3.1 Less than 1 hour	1	9572	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.55, 1.16]
3.2 1-3 hours	1	5356	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.41, 0.88]
3.3 More than 3 hours	1	5083	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.76, 1.51]
6 Maternal mortality (all cause) (subgroup time from birth)	1	20011	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
6.1 Less than 1 hour	1	9572	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.72, 1.33]
6.2 1-3 hours	1	5356	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.49, 0.96]
6.3 More than 3 hours	1	5083	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]

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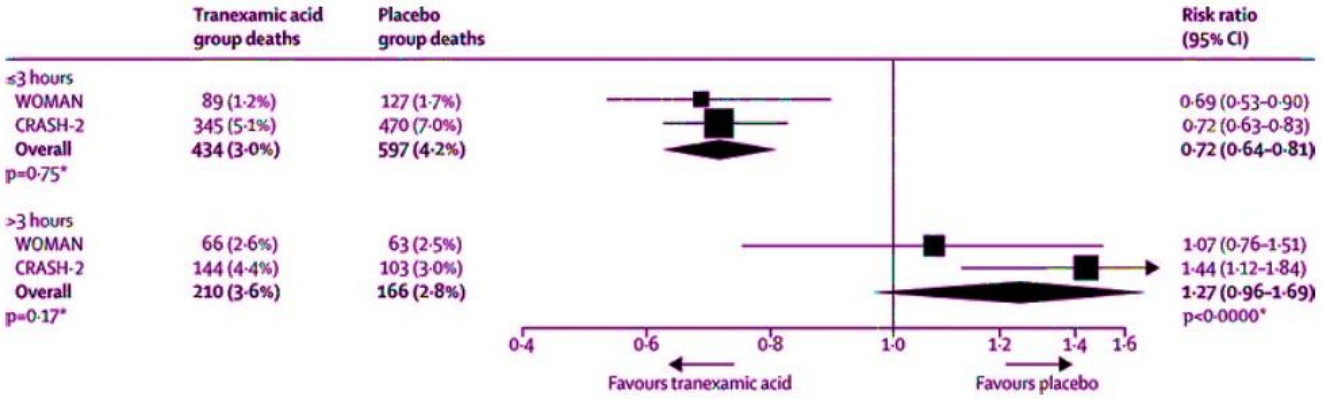
Antifibrinolytic drugs for treating primary postpartum haemorrhage (Review)

Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA

Figure 4. Time to treatment. Effect of TXA on death due to bleeding by time to treatment in the WOMAN and CRASH-2 trials (reproduced from http://dx.doi.org/10.1016/S0140-6736(17)30638-4)



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Antifibrinolytic drugs for treating primary postpartum haemorrhage (Review)

Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA

Comparison 1. Standard care plus IV tranexamic acid versus placebo or standard care alone for the treatment of PPH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29 Side effects of the intervention: any maternal vascular occlusive event	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.54, 1.43]
30 Side effects of the intervention: maternal vascular occlusive events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 DVT	2	20169	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.20, 1.88]
30.2 Pulmonary embolism	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.44, 1.61]
30.3 Myocardial infarction	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.11, 3.97]
30.4 Stroke	1	20018	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.46, 3.82]

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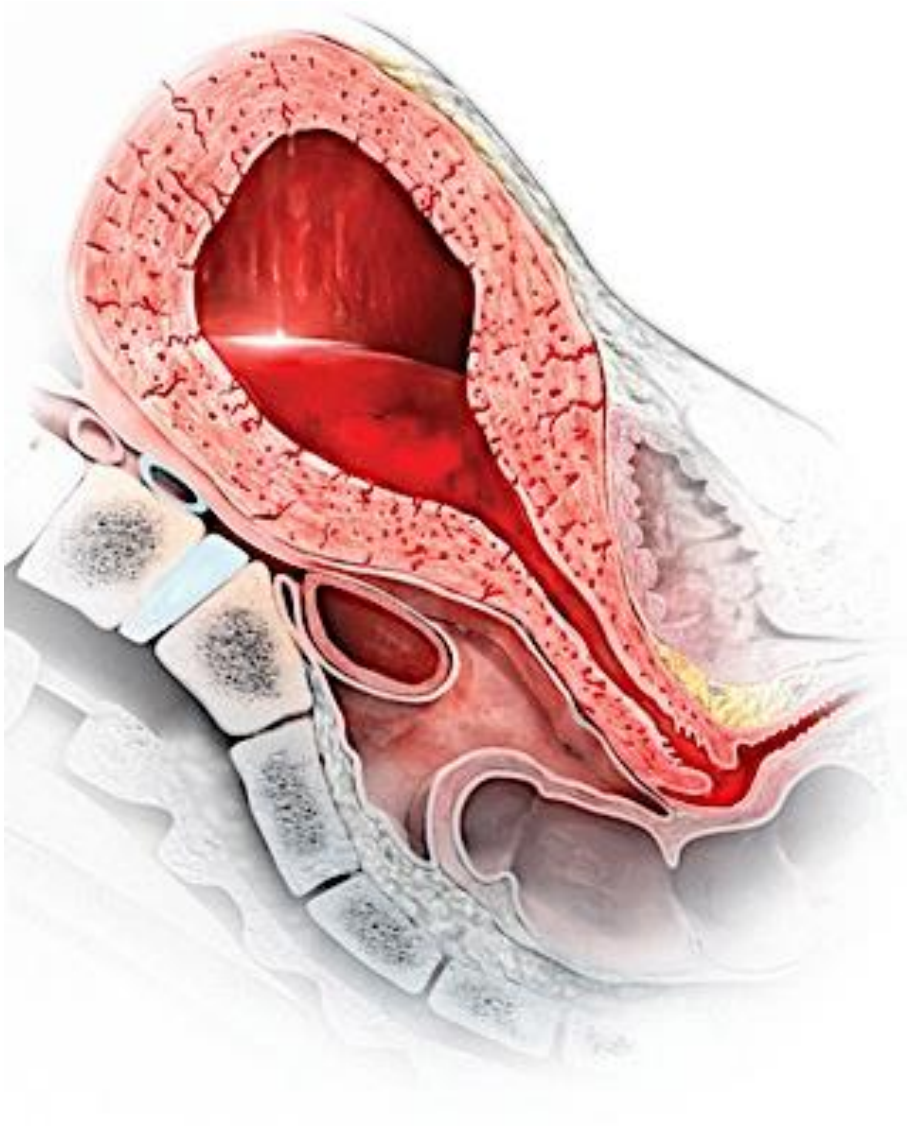
Antifibrinolytic drugs for treating primary postpartum haemorrhage (Review)

Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA

Authors' conclusions

TXA when administered intravenously reduces mortality due to bleeding in women with primary PPH, irrespective of mode of birth, and without increasing the risk of thromboembolic events. Taken together with the reliable evidence of the effect of TXA in trauma patients, the evidence suggests that TXA is effective if given as early as possible.

tone



Ridurre la perdita ematica nel parto vaginale

• Quesito 5 •

Quali interventi sono efficaci nel ridurre l'incidenza di EPP (>500 ml) in donne che partoriscono per via vaginale?

Il trattamento attivo del terzo stadio

La profilassi maggiormente efficace dell'EPP nel parto vaginale è stata a lungo identificata con il trattamento attivo del terzo stadio.

Il trattamento attivo, rappresentato dalla somministrazione contestuale di tre distinti interventi (iniezione di uterotonici, clampaggio immediato del funicolo e trazione controllata del cordone ombelicale), è risultato associato a una riduzione del rischio di EPP >1.000 ml (RR: 0,34, IC 95%: 0,14-0,87) clinicamente rilevante (Begley 2015). Successivamente è stato analizzato il contributo intrinseco di ciascuno dei tre interventi compresi nel trattamento attivo. Sulla base di nuove conoscenze, l'intervento per la prevenzione dell'EPP con il miglior rapporto beneficio/danno risulta attualmente essere: la

① somministrazione di 10 UI di ossitocina per via intramuscolare (IM) dopo l'espulsione della spalla anteriore; la

② trazione controllata del cordone ombelicale viene considerata opzionale; il

③ taglio immediato del cordone ombelicale risulta invece controindicato per motivi diversi dalla prevenzione dell'EPP.

Cochrane Library

Active versus expectant management for women in the third stage of labour (Review)

Begley CM, Gyte GML, Devane D, McGuire W, Weeks A, Biesty LM

Authors' conclusions

Although the data appeared to show that active management reduced the risk of severe primary PPH greater than 1000 mL at the time of birth, we are uncertain of this finding because of the very low-quality evidence. Active management may reduce the incidence of maternal anaemia (Hb less than 9 g/dL) following birth, but harms such as postnatal hypertension, pain and return to hospital due to bleeding were identified.

In women at low risk of excessive bleeding, it is uncertain whether there was a difference between active and expectant management for severe PPH or maternal Hb less than 9 g/dL (at 24 to 72 hours). Women could be given information on the benefits and harms of both methods to support informed choice. Given the concerns about early cord clamping and the potential adverse effects of some uterotonics, it is critical now to look at the individual components of third-stage management. Data are also required from low-income countries.

It must be emphasised that this review includes only a small number of studies with relatively small numbers of participants, and the quality of evidence for primary outcomes is low or very low.

Ridurre la perdita ematica nel taglio cesareo

• Quesito 6 •

Quali interventi sono efficaci nel ridurre l'incidenza di EPP (>1.000 ml) in donne che hanno partorito mediante taglio cesareo?

RACCOMANDAZIONI

Si raccomanda l'ossitocina come farmaco di prima scelta per la prevenzione dell'EPP nel taglio cesareo.

raccomandazione forte, prove di moderata qualità perché indirette

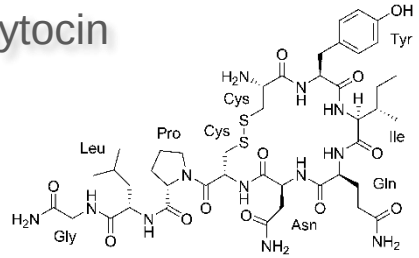
Si raccomanda in donne a basso rischio di emorragia post partum dopo taglio cesareo una dose di 3-5 UI di ossitocina in bolo endovenoso lento (non meno di 1-2 minuti; non meno di 5 minuti in donne con rischio cardiovascolare), seguita da un'infusione lenta di 8-10 UI/ora in soluzione isotonica per 2-4 ore.

raccomandazione debole, prove di bassa qualità

Si raccomanda la trazione controllata del cordone per la rimozione della placenta nel taglio cesareo.

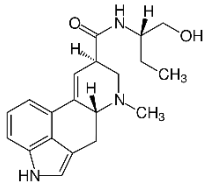
raccomandazione forte, prove di moderata qualità

oxytocin



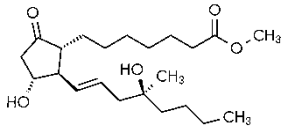
short half-life: 3-5 min
latent phase: 2-5 min
uterine contraction for 2-3 hrs
heat instability
side-effects: severe hypotension (large *ev* bolus), water intossication (anti-diuretic effect, mild nausea and vomiting

ergometrine



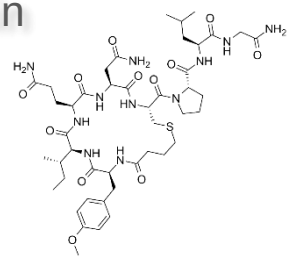
ergot alkaloids
plasma half-life: 30 to 120 min
latent phase: 2-5 min
heat instability
side-effects: hypertension (vasoconstrictive action), pain after birth, nausea and vomiting

misoprostol



PGE_1 analogue
half-life: 20-40 min
latent phase: 9-15 min (oral and sublingual routes have the advantage of rapid onset of action, while the vaginal and the rectal routes result in prolonged activity and greater bioavailability)
uterine contraction for 2-3 hrs
heat stable and water soluble
side-effects: diarrhoea, abdominal pain, shivering, nausea and vomiting

carbetocin



synthetic OXY analogue
latent phase: 6 min (*ev*) and 11 min (*im*)
uterine contraction for 1 hr (*ev*) and 2 hrs (*im*)
heat stable
side-effects: similar to OXY

TABLE 1 Cochrane reviews comparing uterotonic drugs for preventing PPH

Cochrane review (first author and date of publication)	Included trials (number of participants)	Latest search update	Available comparisons	Trials awaiting classification (number of participants)	Active trials to be completed by December 2015 (number of participants)
Liabsuetrakul *et al.*,[16] 2007	6 ($n = 1996$)	30 April 2011	Ergometrine vs. placebo or no treatment	2 ($n = 340$)	0
McDonald *et al.*,[22] 2004	6 ($n = 9332$)	30 April 2007	Oxytocin plus ergometrine vs. oxytocin	4 ($n = 946$)	3 ($n = 6860$)
Su *et al.*,[21] 2012	11 ($n = 2635$)	1 March 2011	Carbetocin vs. oxytocin	20 ($n = 5898$)	17 ($n = 41,583$)
			Carbetocin vs. oxytocin plus ergometrine		
Tunçalp *et al.*,[17] 2012	72 ($n = 52,678$)	7 January 2011	Misoprostol vs. oxytocin	24 ($n = 10,666$)	15 ($n = 8067$)
			Misoprostol vs. ergometrine		
			Misoprostol vs. placebo or no treatment		
			Misoprostol vs. oxytocin plus ergometrine		
			Misoprostol vs. oxytocin plus misoprostol		
Westhoff *et al.*,[13] 2013	20 ($n = 10,806$)	21 May 2013	Oxytocin vs. placebo or no treatment	8 ($n = 4221$)	8 ($n = 6816$)
			Oxytocin vs. ergometrine		
			Oxytocin plus ergometrine vs. ergometrine		
Total	115 ($n = 77,447$)			58 ($n = 22,071$)	43 ($n = 63,326$)

Cochrane Library

Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage (Review)

Salati JA, Leathersich SJ, Williams MJ, Cuthbert A, Tolosa JE

Authors' conclusions

Prophylactic oxytocin compared with no uterotonics may reduce blood loss and the need for additional uterotonics. The effect of oxytocin compared to ergot alkaloids is uncertain with regards to blood loss, need for additional uterotonics, and blood transfusion. Oxytocin may increase the risk of a prolonged third stage compared to ergot alkaloids, although whether this translates into increased risk of manual placental removal is uncertain. This potential risk must be weighed against the possible increased risk of side effects associated with ergot alkaloids. Oxytocin-ergometrine may reduce blood loss compared to ergot alkaloids, however the certainty of this conclusion is low. More high-quality trials are needed to assess optimal dosing and route of oxytocin administration, with inclusion of important outcomes such as maternal mortality, shock, and transfer to a higher level of care. A network meta-analysis of uterotonics for PPH prevention plans to address issues around optimal dosing and routes of oxytocin and other uterotonics.

Professor Archibald Leman Cochrane, *CBE, FRCP, FFCM*
(1909 - 1988)

Cochrane Library

Cochrane Database of Systematic Reviews

Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review)

Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, Moorthy V, Tobias A, Deeks JJ, Widmer M, Tunçalp Ö, Gülmezoglu AM, Hofmeyr GJ, Coomarasamy A

Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, Moorthy V, Tobias A, Deeks JJ, Widmer M, Tunçalp Ö, Gülmezoglu AM, Hofmeyr GJ, Coomarasamy A.

Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis.

Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD011689.

DOI: 10.1002/14651858.CD011689.pub2.

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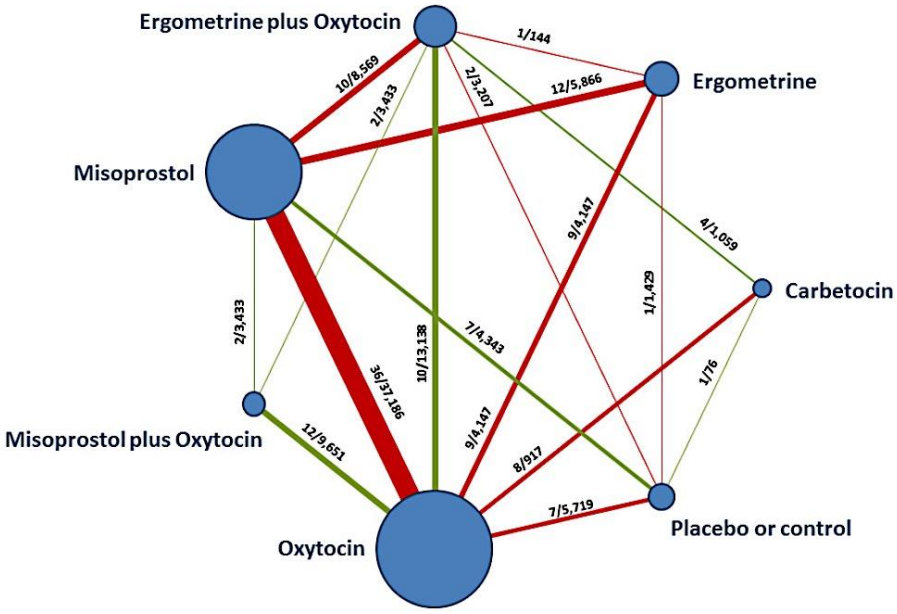
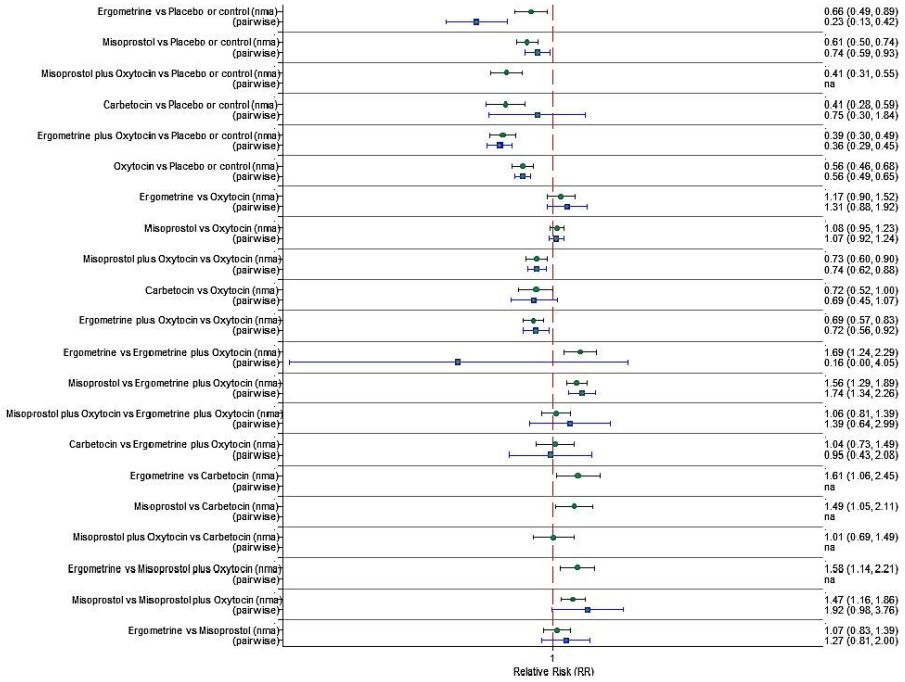
PPH ≥ 500 mL



Network diagram



Forest plot with relative risk ratios and 95% CIs

Cochrane Library

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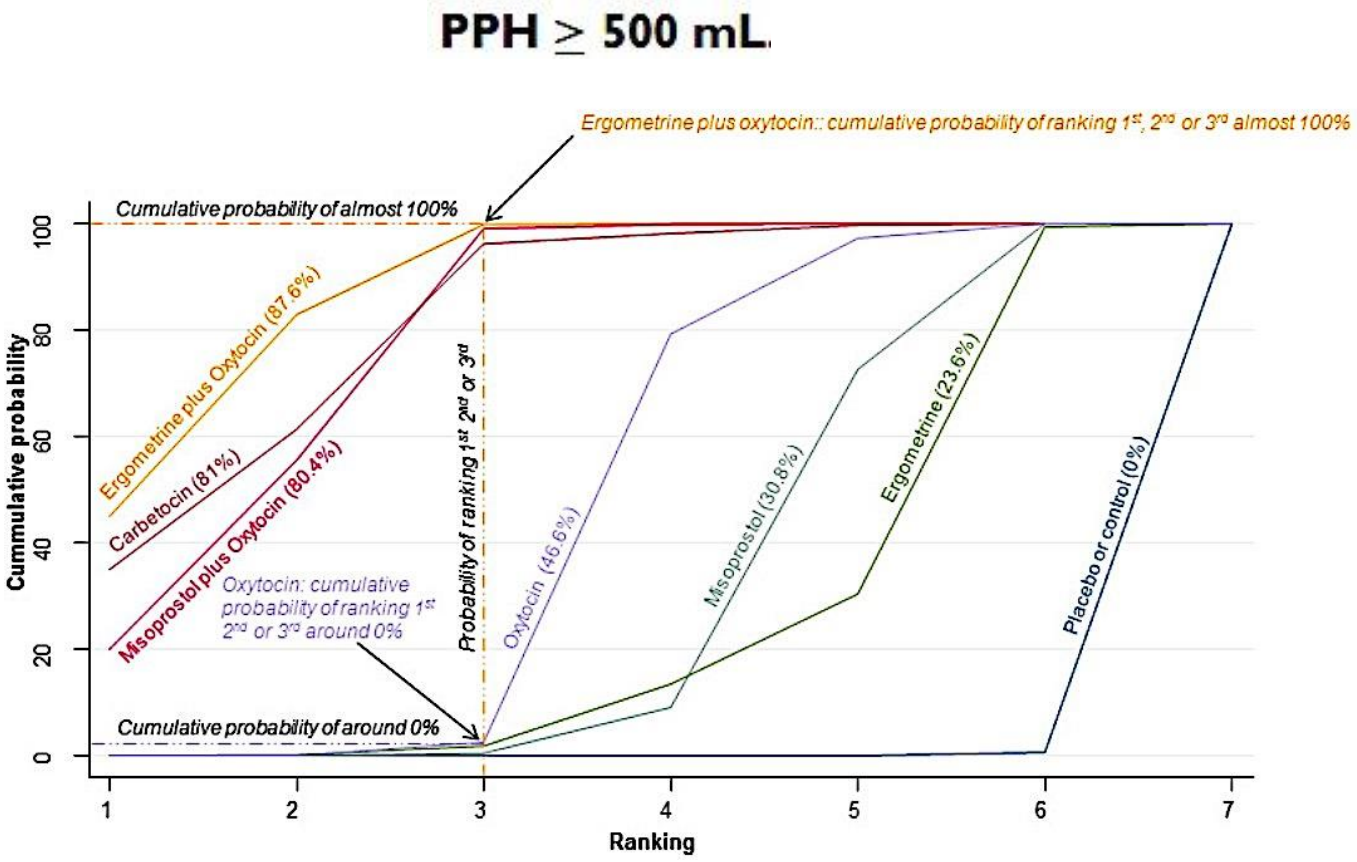

SUrface underneath this Cumulative RAnking line (SUCRA)

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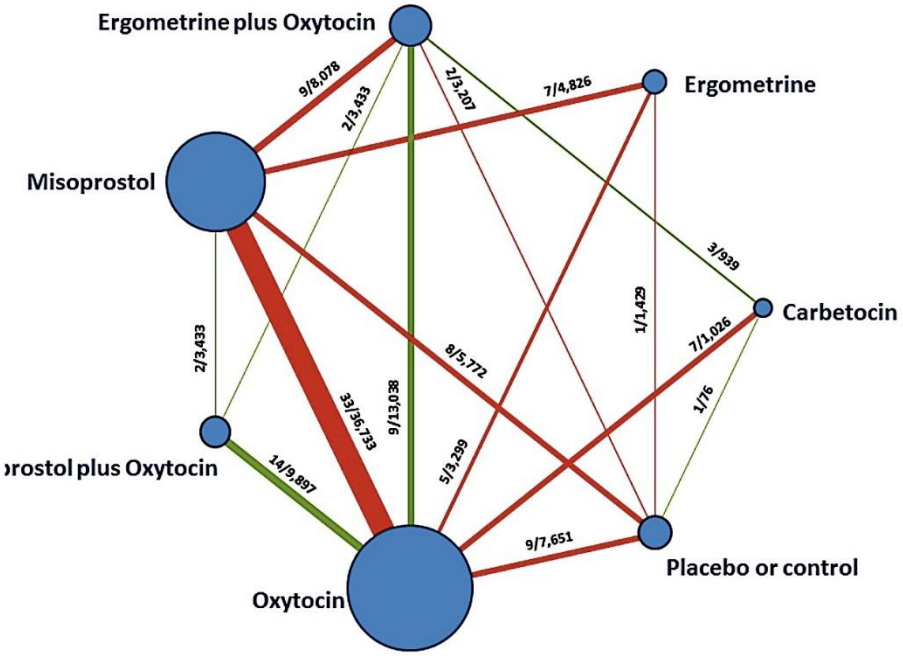
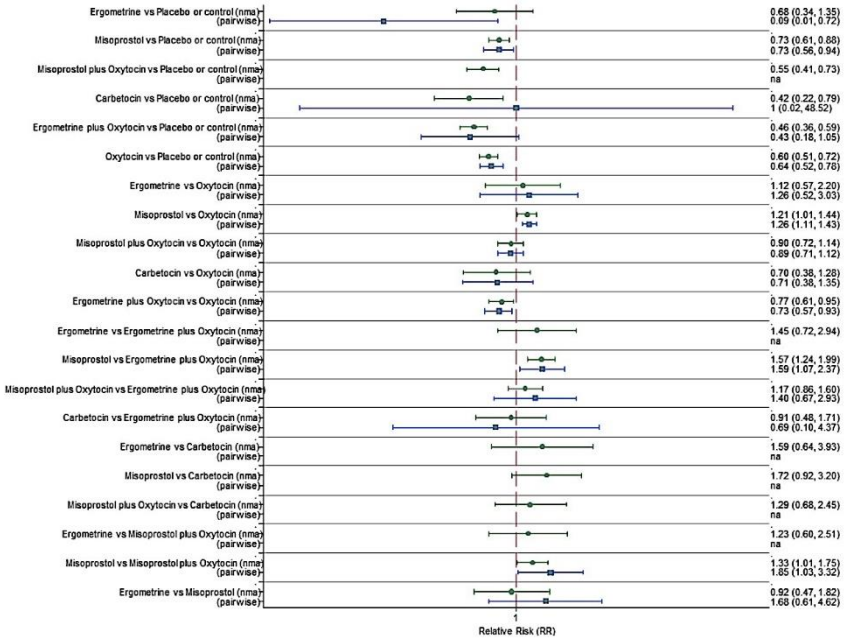
PPH ≥ 1000 mL.



Network diagram



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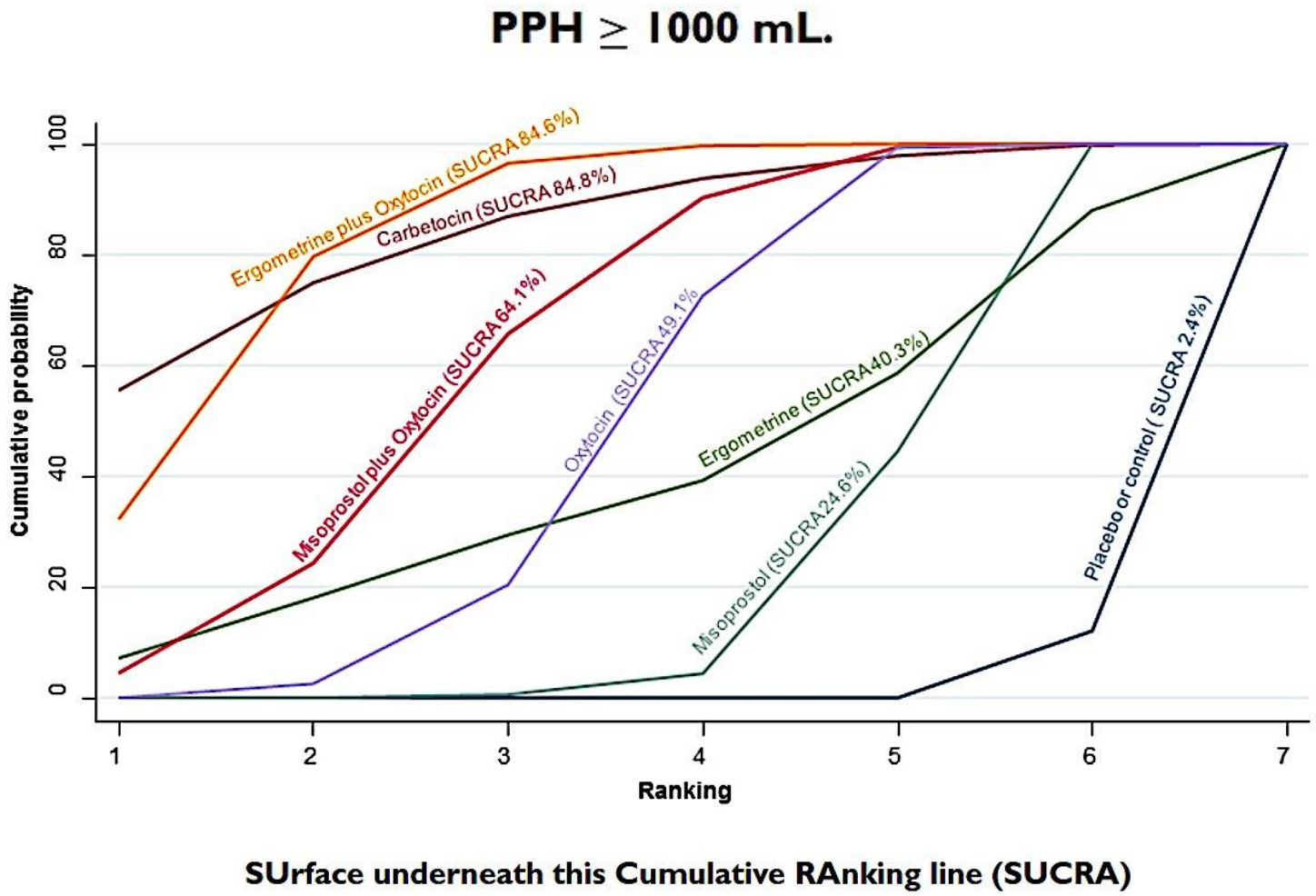

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Authors' conclusions

Ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination were more effective for preventing PPH $\geq$ 500 mL than the current standard oxytocin. Ergometrine plus oxytocin combination was more effective for preventing PPH $\geq$ 1000 mL than oxytocin. Misoprostol plus oxytocin combination evidence is less consistent and may relate to different routes and doses of misoprostol used in the studies. Carbetocin had the most favourable side-effect profile amongst the top three options; however, most carbetocin trials were small and at high risk of bias.

Cochrane Library

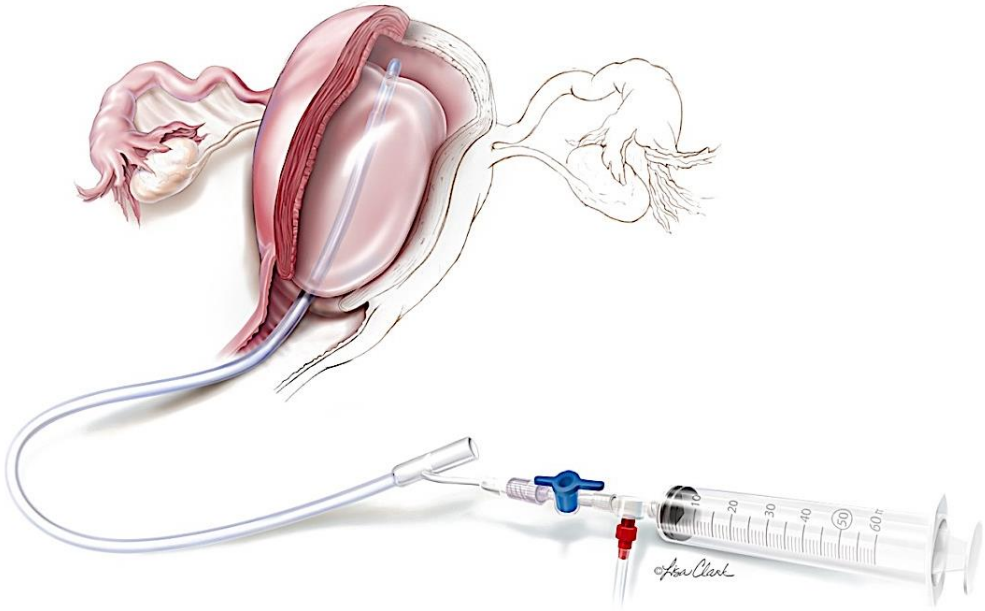
Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review)

Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, Moorthy V, Tobias A, Deeks JJ, Widmer M, Tunçalp Ö, Gülmezoglu AM, Hofmeyr GJ, Coomarasamy A

Implications for practice

The current WHO recommendation for preventing PPH is 10 IU of intramuscular or intravenous oxytocin (WHO 2012). Oxytocin should be kept refrigerated (2 °C to 8 °C) or stored at room temperature (25 °C or lower). Several studies have demonstrated that oxytocin loses potency if stored at room temperature for too long or at higher temperatures, making its use difficult in low-resource countries (Hogerzeil 1993; WHO 1993). Since we have shown that oxytocin is ranked fourth in effectiveness, and and ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination are more effective, our results could have important implications for clinical practice. Ergometrine plus oxytocin combination is the only agent that significantly reduces PPH ≥ 500 mL and PPH ≥ 1000 mL compared with oxytocin on both network and pairwise estimates. Misoprostol plus oxytocin combination evidence is less consistent and this may be related to the different routes and doses of misoprostol used in the studies. Carbetocin is more effective compared with oxytocin with a similar side-effect profile to oxytocin. However, when we restricted our analysis to trials with low risk of bias, the ranking of carbetocin changed and it did not appear to be more effective than oxytocin.

The manufacturer of carbetocin (Ferring Pharmaceuticals) has recently developed a room temperature stable (RTS) formulation, which makes it an attractive option for countries where maintaining the cold chain is problematic. Therefore, we conclude that there is an urgent need for a high-quality large trial comparing the current standard of oxytocin with carbetocin, and especially RTS carbetocin, to confirm or reject the findings of small and at high risk of bias trials that have involved carbetocin to date.

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Costs to the National Health Service

Treatment of PPH costs the NHS £32–180M per year. The National Institute for Health and Care Excellence (NICE) recently estimated the costs of treating PPH to be between £488 and £2700 for each woman, depending on the severity of PPH.[23] Treating PPH also has societal implications, as it can reduce economic productivity by causing physical disability or a psychological burden to parents and families. A relative risk reduction of 34% in PPH occurrence can represent a saving of £10–60M per year for the NHS, with important benefits for public health.

NHS
National Institute for Health Research

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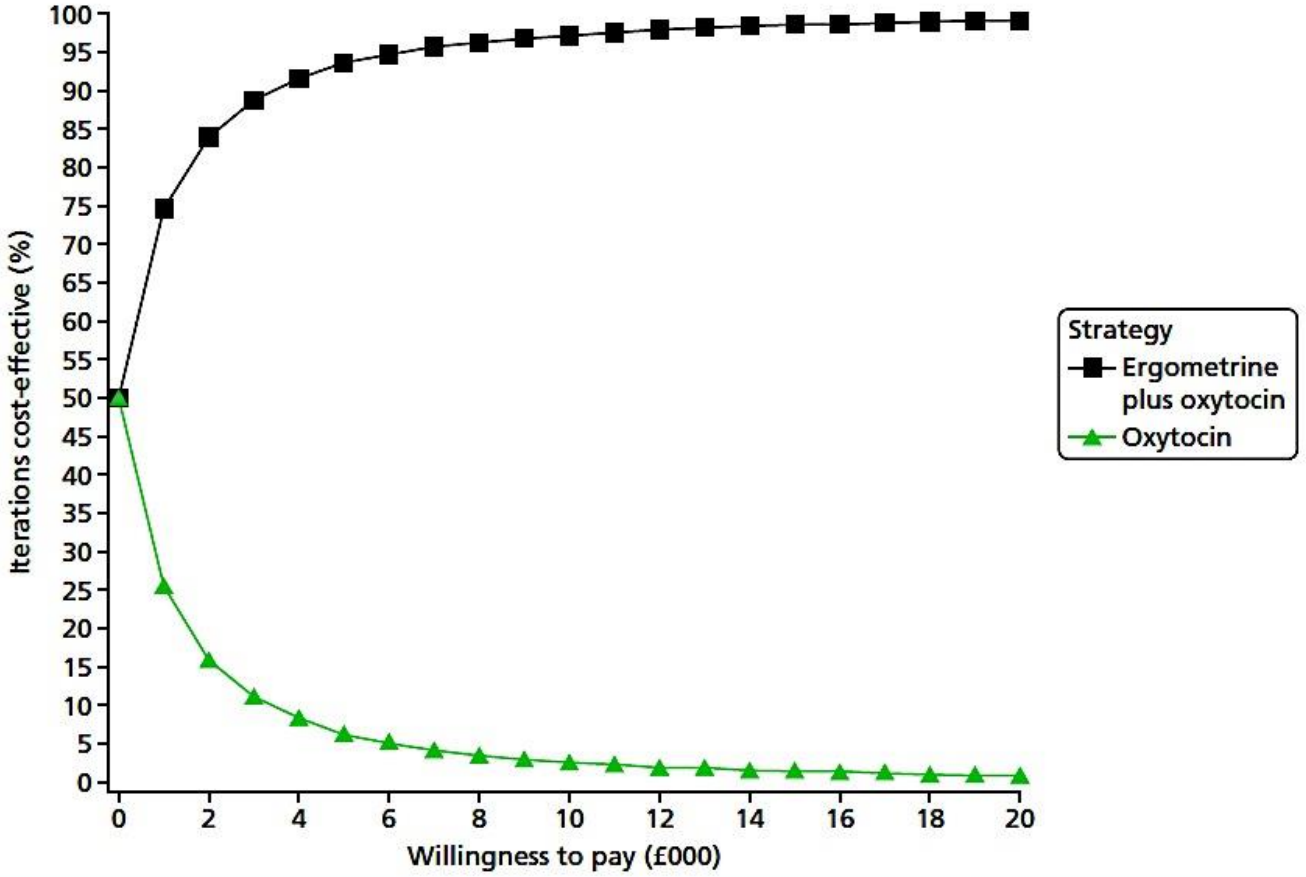

FIGURE 111 Cost-effectiveness acceptability curve between prevention strategies ergometrine plus oxytocin, and oxytocin, for caesarean section birth, using distributions around the accuracy data.

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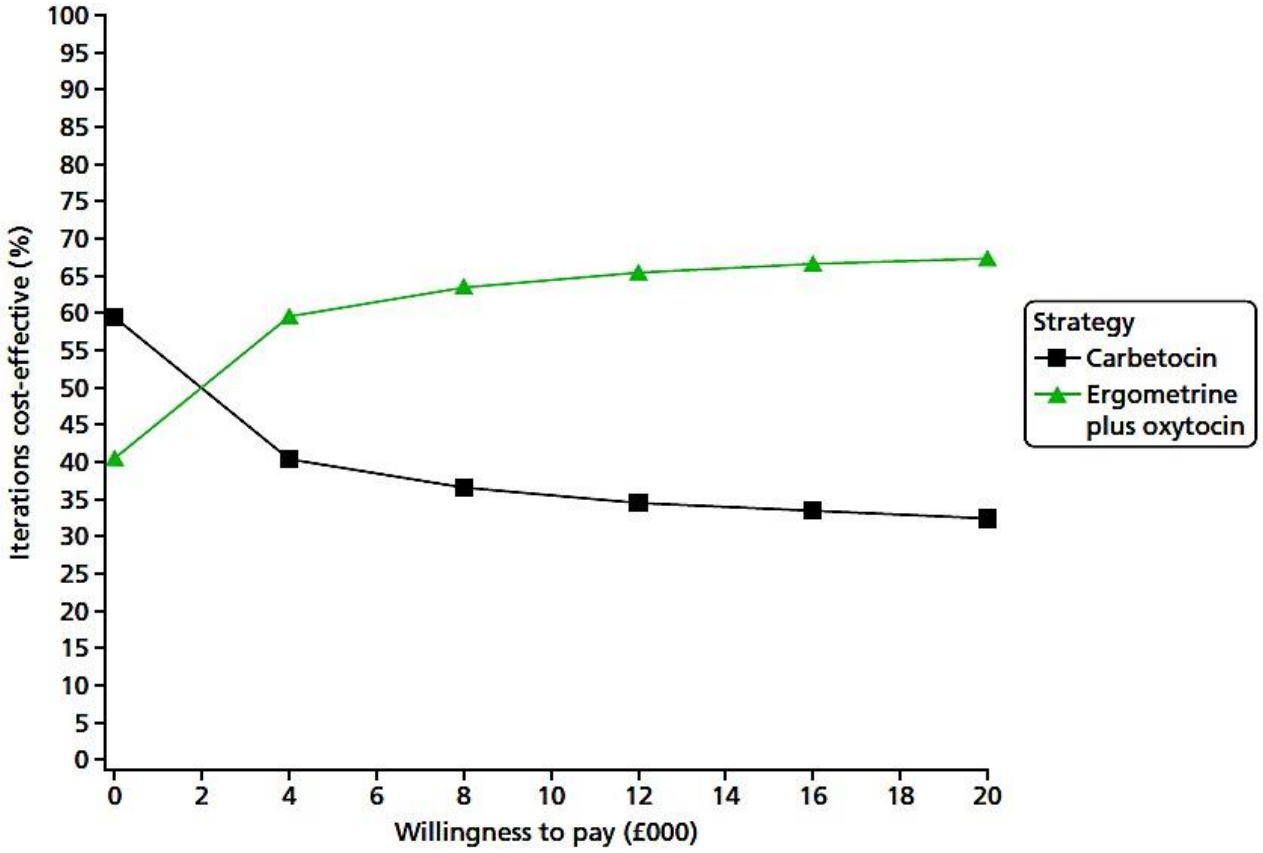

FIGURE 112 Cost-effectiveness acceptability curve between prevention strategies carbetocin and ergometrine plus oxytocin, for caesarean section birth, using distributions around the accuracy data.

cause mortalità materna

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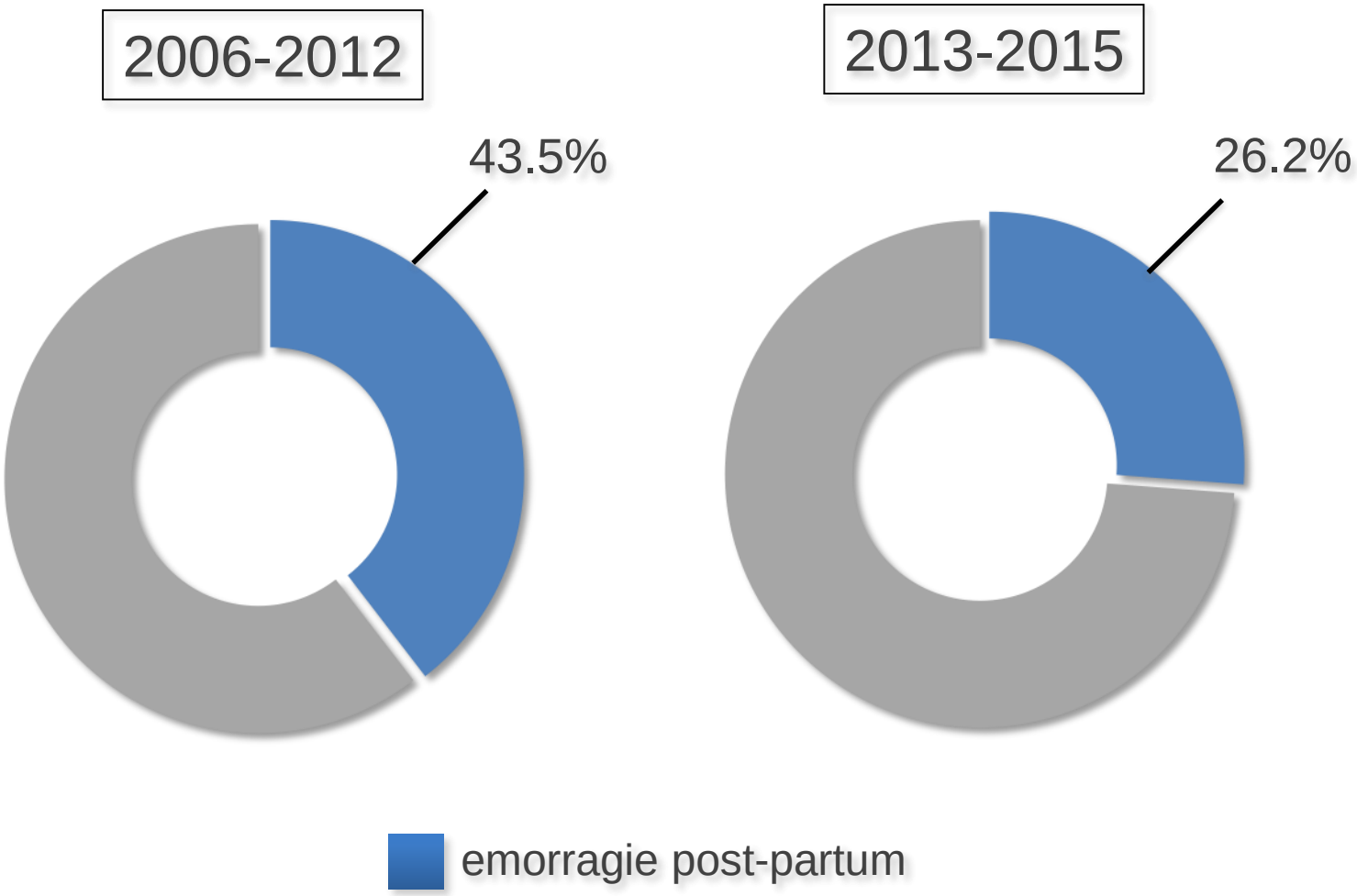


managing maternal hemorrhage

NYC Health — New York City Department of Health and Mental Hygiene

Important phone numbers:

_____

_____

_____

_____

_____

_____

The American College of Obstetricians and Gynecologists/District II (ACOG)

Vital Signs
Normal vitals don't guarantee patient stability

- **Airway—intubate**
  If inadequate ventilation or to assist airway protection
- **Breathing**
  Supplemental O2, 5-7 L/min by tight face mask to assist O2 carrying capacity
- **Circulation**
  Pallor, delayed capillary refill and decreased urine output can indicate compromised blood volume without change in BP or HR.

  Late signs of compromise are: decreased urine output, low BP and tachycardia.

Infusions

- **Start 2nd large bore (16 gauge or larger)**
- **RL or NS replaces blood loss at 3:1**
- **Volume expanders 1:1 (albumin, hetastarch, dextran)**
- **Transfusion (PRBC, Coagulation factors)**
- **Warm blood products and infusions to prevent hypothermia, coagulopathy and arrhythmias**

Medication for uterine atony

- **Oxytocin**
  10-40* units in 1 liter NS or RL IV rapid infusion
  *30-40 units/liter most commonly used dose for hemorrhage
- **Methylergonovine (Methergine)**
  0.2 milligrams intramuscular q 2-4 hrs maximum 5 doses; avoid with hypertension
- **Prostaglandin F2 Alpha (Hemabate)**
  250 micrograms intramuscular, intramyometrial, repeat q 20-90 minutes, maximum 8 doses; avoid with asthma or hypertension
- **Prostaglandin E2 suppositories (Dinoprostone, Prostin E2)**
  20 milligrams per rectum q 2 hrs; avoid with hypotension
- **Misoprostol (Cytotec)**
  1000 micrograms per rectum or sublingual (ten 100 microgram tabs or five 200 microgram tabs)
- **Surgical interventions**
  May be a life-saving measure and should not be delayed

www.nyc.gov/health/maternity

Figure 1

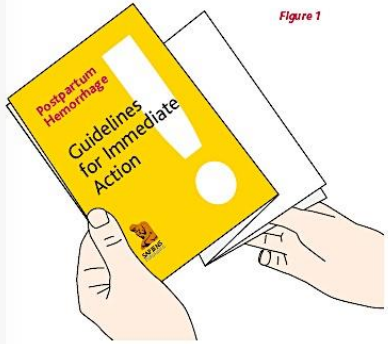


Figure 2

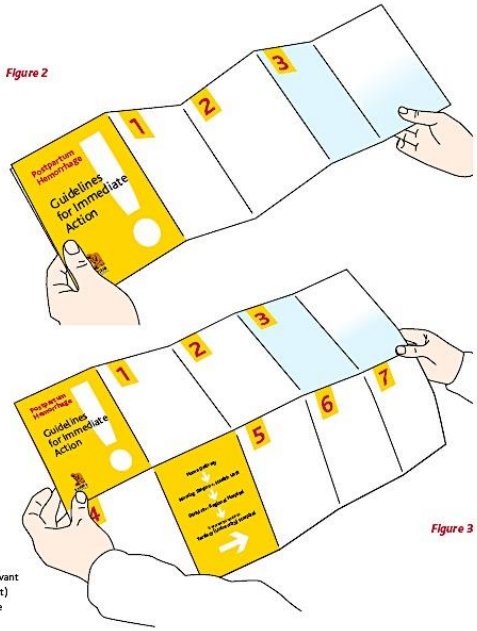


Figure 3

Postpartum Hemorrhage

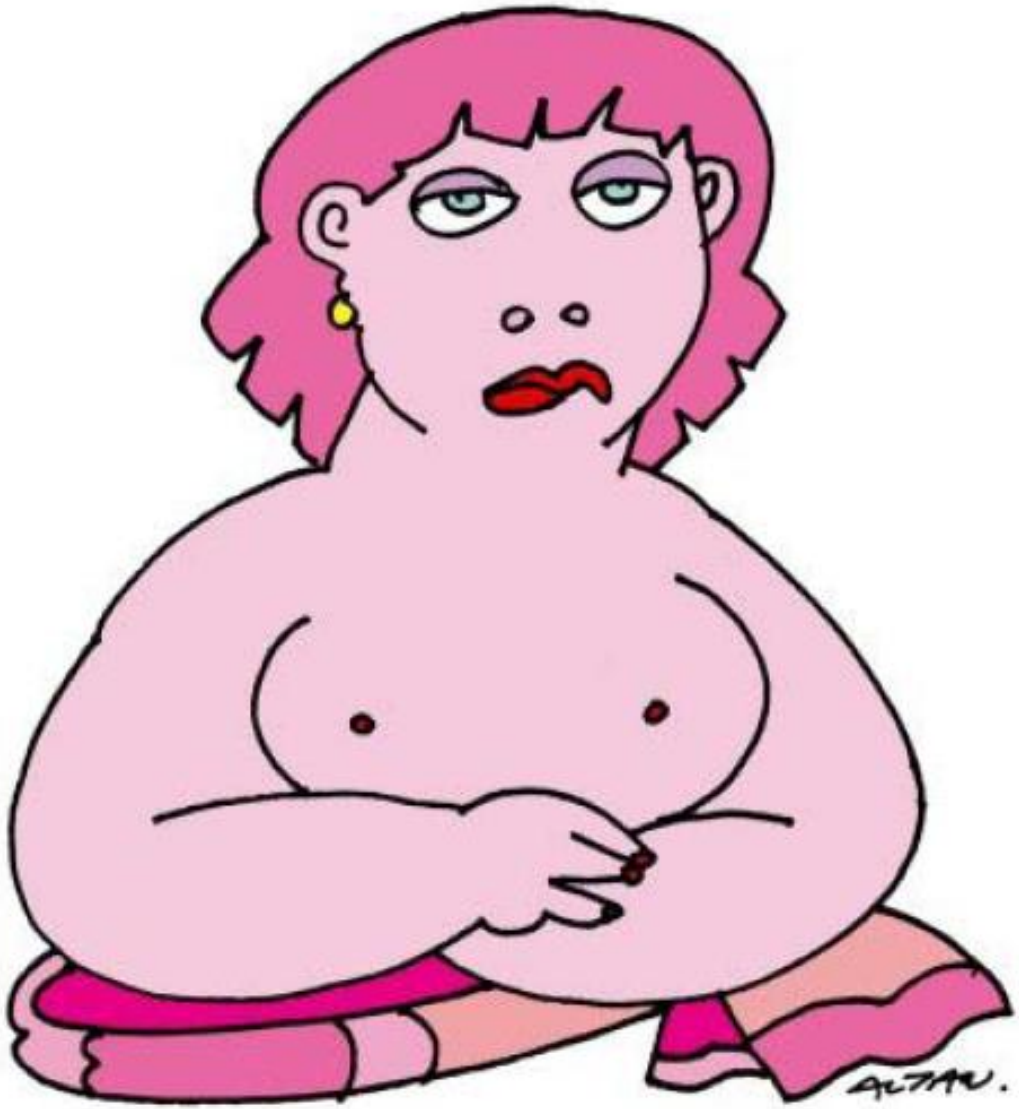
Guidelines for Immediate Action

How this leaflet works – first as a ordinary leaflet, and then as a ready-reference wallchart

Ten-panel A5-format leaflet, concertina-folded. Folds out horizontally to view Steps 1–3 (*Figs.1 & 2*), flip over to view Steps 4–7 or fold down to view all the steps (*Fig. 3*) and/or use as a wallchart. On the reverse face is further detail on each of the steps with references to relevant pages in *A Textbook of Postpartum Hemorrhage*. This reverse face (with a light yellow tint over it) is optional reading for those who want to know more. The front face, with the seven immediate action steps shown on a white background, is designed as the basic reading for most users.

$$\frac{A4}{3M} = 0$$

NON VORREI AVER COMMESSO
UN'IMPRUDENZA,
A NASCERE DONNA.



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