NHS Blood and Transplant
North East Regional Transfusion Committee

SHOP – Serious Hazards of Pregnancy

The Durham Centre, Belmont
Wednesday 17th October 2018

Clinical research in obstetric haemorrhage – SALVO, WOMAN & COPE

Kim Hinshaw
Consultant Obstetrician & Gynaecologist
Director of Research & Innovation

City Hospitals Sunderland NHS
NHS Foundation Trust

Presentation

- Research in clinical obstetrics…..
- What do we mean by PPH?
- The SALVO and WOMAN trials
- The COPE trial
- Consent in emergency research

NIHR Clinical Research Network NE & N Cumbria

NHS National Institute for Health Research
Clinical Research Network North East and North Cumbria

- One of 15 large research networks in England

Research drives high quality care

RESEARCH ARTICLE

Research Activity and the Association with Mortality

Baris A. Ozdemir[1]*, Alan Karthikesalingam[1], Sidhartha Sinha[1], Jan D. Poloniecki[1], Robert J. Hinchliffe[1], Matt M. Thompson[1], Jonathan D. Gower[2], Annette Boaz[3], Peter J. E. Holt[1]

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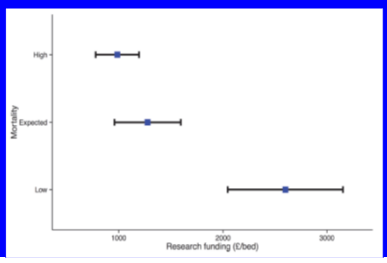
PLOS ONE
2015

Research drives high quality care



Conclusions

Research active Trusts appear to have key differences in composition than less research active Trusts. Research active Trusts had lower risk-adjusted mortality for acute admissions, which persisted after adjustment for staffing and other structural factors.

… confirmed in women's health

BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14528
www.bjog.org

Systematic review

Participation in clinical trials improves outcomes in women's health: a systematic review and meta-analysis

SK Nijjar,[a] MI D'Amico,[a] NA Wimalaweera,[b] NAM Cooper,[a] J Zamora,[a,c] KS Khan[d]

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… confirmed in women's health

21 relevant RCTs
n = 20,160 women

Conclusions

- Trial participants, compared with non-participants had **25% better odds of improved outcomes**
  RR = 0.75 95%CI(0.64 – 0.87)
- 'High quality' RCTs = **38% odds of better outcomes**
- 'Low quality' RCTs = **8% odds of better outcomes**

Relevance of PPH

What do we mean by PPH?

The Impact of PPH

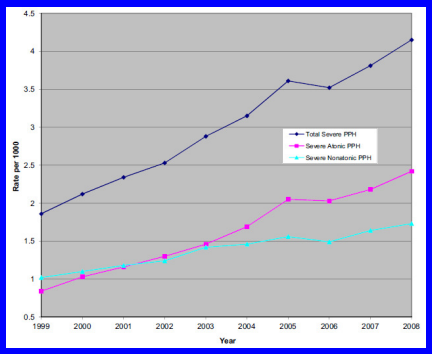
PPH is often defined as the loss of more than 500ml or 1,000ml of blood within the first 24 hours following childbirth. It is a common maternity emergency affecting 40,000 British women each year. Although it can usually be treated in the UK, it can lead to long-lasting complications.

Globally, however, it remains a major cause of death and is responsible for around 25% of the 289,000 maternal deaths annually. It is estimated that somewhere in the world a woman dies from PPH every 6 minutes.

"One woman dies from PPH every 6 minutes"

Temporal trends in severe PPH

USA - 8.5 million deliveries 1999-2008



Kramer MS et al AJOG 2013;209:449.e1-7

Protocols for Massive Haemorrhage

258 UK maternity units - 81% returns

- **lack of agreement on definitions**
- **lack of agreement on interventions for massive PPH**
- **majority used oxytocin, ergometrine & carboprost as '1st line'**
- **hysterectomy – commonest surgical intervention**

Mousa & Alfiveric, Acta Obstet Gynecol Scand 2002

Protocols for Massive Haemorrhage

"There is an urgent need to identify protocols that will reduce the need for hysterectomy in women with major haemorrhage who are unresponsive to conventional medical therapy… "

Mousa & Alfirevic, Acta Obstet Gynecol Scand 2002

The Four 'T's

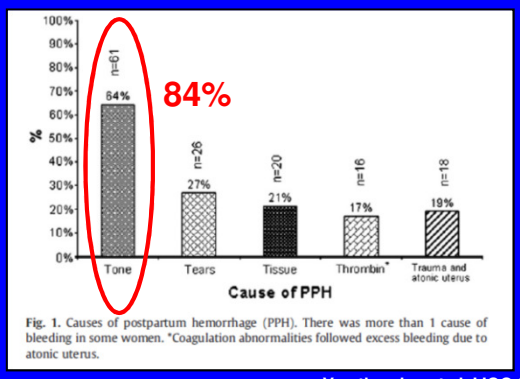


Fig. 1. Causes of postpartum hemorrhage (PPH). There was more than 1 cause of bleeding in some women. *Coagulation abnormalities followed excess bleeding due to atonic uterus.

Varatharajan et al. IJOG 2011

Variable medical prophylaxis….

- Oxytocin
- Misoprostol
- Syntometrine
- Ergometrine
- Carbetocin
- Carboprost

Variable 1st line treatment for PPH…

- Oxytocin bolus
- Misoprostol
- Ergometrine
- Carboprost
- Oxytocin infusion

What do we mean by PPH?

DOI: 10.1111/1471-0528.14417
www.bjog.org

Commentary

Postpartum haemorrhage: a single definition is no longer enough

RS Kerr, AD Weeks

Sanyu Research Unit, Department of Women's and Children's Health, University of Liverpool, Liverpool Women's Hospital, Liverpool, UK
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- Volume?
- Rate of bleeding?
- Mode of delivery?
- Physiological change?

Postpartum hemorrhage: new insights for definition and diagnosis

A. Borovac-Pinheiro, PhD, R. C. Pacagnella, PhD, J. G. Cecatti, PhD, S. Miller, PhD, A. M. El Ayadi, ScD, MPH, I. P. Souza, PhD, J. Durocher, MA, P. D. Blumenthal, MD, MPH, B. Winikoff, MD, MPH

TABLE 1
Summary of blood loss thresholds and vital sign changes for diagnosis of postpartum hemorrhage according to international clinical guidelines

Guideline	Vaginal/cesarean delivery	Vital signs	Comments
International Federation of Gynecology and Obstetrics, 2012[19]	Loss >500 mL/>1000 mL	For clinical purposes, any blood loss that has the potential to produce hemodynamic instability should be considered a postpartum hemorrhage.	Clinical estimates of blood loss are often inaccurate.
American College of Obstetricians and Gynecologists, 2017[20]	Cumulative blood loss ≥1000 mL, regardless of route of delivery	Signs or symptoms of hypovolemia; important to recognize that the signs or symptoms of considerable blood loss often do not present or do not present until blood loss is substantial	Excess of 500 mL after vaginal delivery is an alert; when postpartum bleeding exceeds expected volumes (500 mL in a vaginal delivery or 1,00 mL in a cesarean delivery), a careful and thorough evaluation should be undertaken.
Royal College of Obstetricians and Gynaecologists, 2016[21]	Estimated blood loss of 500–1000 mL (minor PPH) and >1000 mL (major PPH) with no clinical signs of shock	Pulse and blood pressure normal until blood loss exceeds 1000 mL; tachycardia, tachypnea slight fall in systolic blood pressure with blood loss of 1000–1500 mL; >1500 mL systolic blood pressure <80 mm Hg, worsening tachycardia, tachypnea, and altered mental state	A blood loss of >40% of total blood volume (approximately 2800 mL) is generally regarded as "life-threatening."
Society of Obstetricians and Gynaecologists of Canada, 2010[22]	Loss >500 mL/>1000 mL	Any blood loss that has the potential to produce hemodynamic instability should be considered PPH.	The amount of blood loss required to cause hemodynamic instability will depend on the preexisting condition of the woman.
Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2016[23]	Estimated blood loss 500 mL: severe PPH after blood loss of 1000 mL	Clinical signs of shock or tachycardia, which includes an accurate appraisal of blood loss (both concealed and revealed), should prompt a thorough assessment of the mother.	It is important to consider both the patient's previous hemoglobin level and her total blood volume for the assessment of the severity of PPH.

Physiological changes

TABLE 2
Maternal hemorrhage classification systems

Hemorrhage class	Acute blood loss, mL	Lost, %	Blood pressure, mm Hg	Clinical signs
Benedetti[27]				
1	900	15	—	—
2	1200–1500	20–25	—	—
3	1800–2100	30–35	—	—
4	2400	40	—	—
Bonnar[28]				
	500–1000		Normal	Palpitations, dizziness, tachycardia
	1000–15000		Slightly low	Weakness, sweating, tachycardia
	1500–2000		70–80	Restlessness, pallor, oliguria
	2000–3000		50–70	Collapse, air hunger, anuria
Coker and Oliver[29]				
0	<500	<10	—	None
1	500–1000	15	—	Minimal
2	1200–1500	20–25	—	Decreased urine output, increased pulse rate, increased postural hypotension, narrow pulse pressure
3	1800–2100	30–35	—	Hypotension, tachycardia, cold clammy skin, tachypnea
4	>2400	>40	—	Profound shock

- ?? 'Shock Index' = HR / SBP ??
- SI >0.9 = need for transfusion
- …but normal SI postpartum = 0.52 – 0.89
- 20% 'normal' have SI >0.9……

This is relevant in clinical trials

- Who do we include to allow valid comparisons?

CHS - when do we give ergometrine?

n=101

Up to 500 (250-450)	32	31.7%
500 up to 999ml	45	
1000 up to 1499ml	10	
1500 up to 1999ml	6	
2000 up to 2499ml	6	
2500ml (exactly!)	2	

So… the rate of bleeding is relevant….

SALVO - cell SALVage in Obstetrics

A Randomised Controlled Trial of Intra-Operative Cell Salvage during Caesarean Section in Women at Risk of Haemorrhage

CI = Professor Khalid Khan, Bart's, London

Objectives

Primary Objective:

- To determine if the routine use of IOCS during CS, in women at risk of haemorrhage, reduces the need for donor blood transfusion in comparison to current practice.

Secondary Objectives:

- To determine the effect of IOCS on secondary outcomes including the number of units of donor blood transfused, mean fall in serum haemoglobin level and maternal morbidity resulting from post-operative anaemia (time to first mobilisation, duration of hospital stay, and immediate multidimensional fatigue inventory.
- To determine if the routine use of IOCS during CS, in women at risk of haemorrhage, is cost effective in comparison to current practice.

Objectives

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- To determine if the routine use of IOCS during CS, in women at risk of haemorrhage, is cost effective in comparison to current practice.

Inclusion criteria

Inclusion Criteria

Women who are admitted to a participating labour ward who fulfil all the following criteria will be eligible to be randomised:

- 16 years of age or older
- Delivery by elective or emergency caesarean section with an identifiable increased risk of haemorrhage.
- Ability to provide informed consent

Exclusion criteria

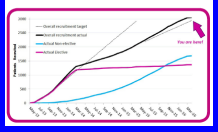
- Elective first Caesarean section for maternal request or breech presentation
- Sickle cell disease
- Active malignancy contraindicated to CS e.g. abdominal cancer
- Cultural or social beliefs contraindicating blood transfusion e.g. Jehovah's Witnesses.
- Significant antibodies making it difficult to find cross matched blood for transfusion
- Unable to understand written and spoken English

Recruitment – June 2014 – April 2016

Salvo Sites	April 2016 recruitment	Total recruitment since 1.4.2014	Total recruitment since start of study
Sunderland Royal Hospital	2	238	383
James Cook University Hospital		188	219
Singleton Hospital, Swansea		172	173
Royal Victoria Infirmary, Newcastle	1	144	241
Barts Health, London		138	231
Hinchingbrooke Hospital		133	168
Royal Hallamshire Hospital, Sheffield	1	109	281
Royal United Hospital, Bath	1	100	176
Royal Stoke University Hospital		89	145
Whiston Hospital		40	40
West Middlesex University Hospital		66	101
Queen's Hospital Romford		66	119
Simpsons Centre, Edinburgh		58	98
Croydon University Hospital	5	46	97
St Michael's Hospital, Bristol	1	33	47
Leicester University Hospitals	1	31	165
Birmingham Heartlands Hospital		27	85
Norfolk and Norwich University Hospital		10	10
Derriford Hospital, Plymouth		18	116
Nottingham University Hospitals		15	59
Torbay Hospital		12	58
Northwick Park Hospital		10	29
Birmingham Women's Hospital		0	13

3054!

Our 3054th and final participant was recruited by our team in Sunderland. What a journey this has been – it's almost 3 years since participant No. 1 was recruited in Sheffield, back in June 2013. Well done on making the study a success and rising to the challenges of recruiting in the emergency obstetric setting. Look at what you've achieved:



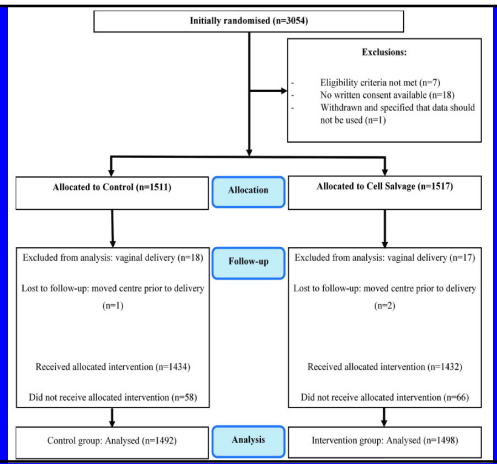
n = 26 units

Outcomes
– PLOS December 2017

RESEARCH ARTICLE

Cell salvage and donor blood transfusion during cesarean section: A pragmatic, multicentre randomised controlled trial (SALVO)

Khalid S. Khan[1]*, Philip A. S. Moore[2], Matthew J. Wilson[3], Richard Hooper[4], Shubha Allard[5], Ian Wrench[6], Lee Beresford[4], Tracy E. Roberts[7], Carol McLoughlin[7], James Geoghegan[2], Jane P. Daniels[8], Sue Catling[9], Vicki A. Clark[10], Paul Ayuk[11], Stephen Robson[12], Fang Gao-Smith[13], Matthew Hogg[14], Doris Lanz[1], Julie Dodds[1], on behalf of the SALVO study group¶



Outcomes
– PLOS December 2017

n= 3028 (n= 2099 analysed)

- 95.6% of 1,498 allocated had IOCS deployed
- 50.8% (n=792) received salvaged blood
- Mean 259.9 [149.7] ml
- IOCS deployed in 3.9% of 1,492 controls

Outcomes
– PLOS December 2017

	IOCS		Control	
Blood transfusion	2.5%	vs	3.5%	OR 0.65 [0.42-1.01]
Emergency CS	3.0%		4.5%	OR 0.58 [0.34-0.99]
Elective CS	2.2%		1.8%	OR 0.83 [0.38-1.83]
Fetomaternal Haem	25.6%	vs	10.5%	OR 5.63 [1.43-22.14]

Serious adverse outcomes
– PLOS December 2017

With transfused cell salvaged blood

- x1 patient – tachycardia & difficulty breathing
- x1 patient – sudden hypotension after 600ml salvaged blood
- ?due to LDF? (*leucocyte depletion factor*)
- No cases of AFE

Economics
– PLOS December 2017

- Incremental cost-effectiveness ratio (ICER) of £8,110 per transfusion avoided for cell salvage
- Sensitivity analysis = 'uncertain cost difference'
- "If willing to pay £50,000 to avoid transfusion, probability of cell salvage being cost-effective was 62%"

Conclusion
– PLOS December 2017

The overall reduction observed in donor blood transfusion associated with the routine use of cell salvage during cesarean section was not statistically significant.

- While donor blood transfusion rates were lower in the cell salvage group than in the control group (2.5% versus 3.5%, meaning that, on average, 1 in every 100 mothers given cell salvage avoided a donor blood transfusion), the difference between the groups was not statistically significant.
- Additionally, the study showed that in women with RhD-negative blood type who gave birth to RhD-positive babies, cell salvage was associated with increased maternal exposure to fetal blood.

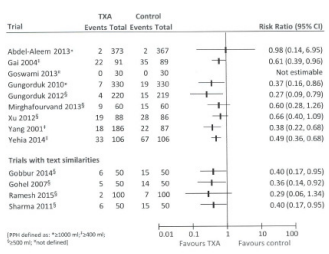
WOMAN Trial Collaborators

CLINICAL TRIALS UNIT

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials

K Ker, H Shakur, I Roberts



Conclusions There is no reliable evidence that TXA prevents postpartum haemorrhage during childbirth. Many of the trials conducted to date are small, low quality and contain serious flaws.

CLINICAL TRIALS UNIT

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WOMAN trial

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

Published Online April 26, 2012 http://dx.doi.org/10.1016/S0140-6736(17)30638-4

See Online/Editorial http://dx.doi.org/10.1016/S0140-6736(17)31111-X

*Collaborators listed at end of the report

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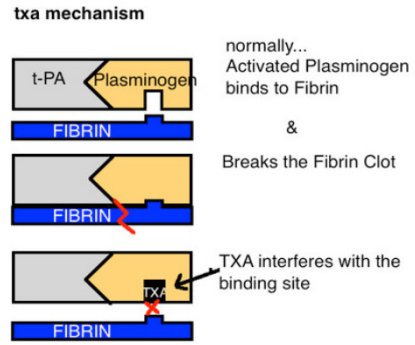
CLINICAL TRIALS UNIT

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Tranexamic acid in PPH – WOMAN results

- ↓ death due to bleeding overall by one fifth (19%)
- ↓ death due to bleeding within 3 hours by ≅ one third (1.2% vs 1.7%)
- No effect on other causes of death
- Did not reduce hysterectomy
- ↓ laparotomy for bleeding by over 35% (0.8% vs 1.3%)
- No evidence of adverse effects

TXA – mechanism of action



Aims and objectives

A randomised, double blind, placebo controlled trial among 20,060 women with a clinical diagnosis of postpartum haemorrhage.

AIMS

To determine the effect of early administration of TXA on mortality, hysterectomy and other morbidities in women with clinically diagnosed PPH.

OBJECTIVES

To provide reliable evidence as to whether TXA reduces mortality, hysterectomy and other morbidities in women with clinically diagnosed PPH; thromboembolic effects on breastfed babies also assessed.

Eligibility

Legally adult women with clinically diagnosed PPH following vaginal delivery or caesarean section (minimum age 16 years).

Excluded if

- clear indication for tranexamic acid
- clear contraindication for tranexamic acid

Consent

- Women given advance information at maternity clinics
- Consent obtained from woman when possible
- If woman unable to provide consent, obtained from Personal or Professional Representative
- If neither available, enrolment by the investigator and a health professional not associated with the trial
- The woman and/or her representative informed as soon as possible and consent sought for continuation in the trial

Randomisation and treatment

RANDOMISATION

- Eligibility assessed by completing the Entry form
- The next consecutively numbered treatment pack from a box of eight packs selected

TREATMENT

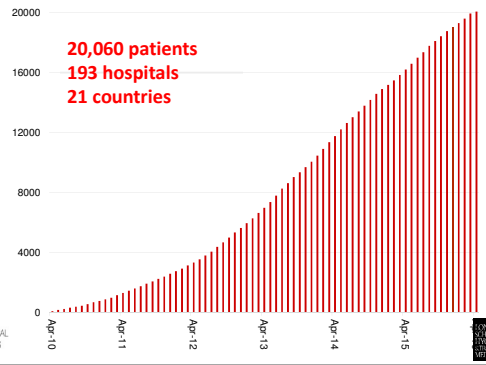
- Dose 1; 1 gram of tranexamic acid by intravenous injection, or placebo (sodium chloride 0.9%)
- Dose 2; if after 30 minutes bleeding continues, or if it stops and restarts within 24 hours after dose 1

Follow-up

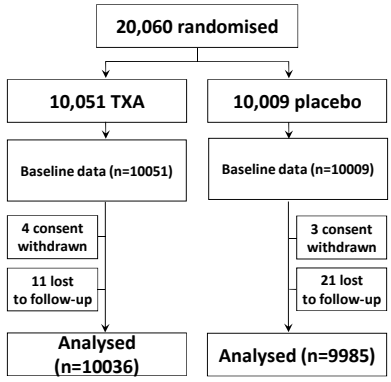
FOLLOW-UP

- Outcome form completed 42 days after randomisation or at discharge or at death, whichever occurs first
- Adverse events reported up to 42 days after randomisation

Patient enrolment



The WOMAN trial



Baseline characteristics

	TXA n (%)	Placebo n (%)
Age at randomisation		
<16	1 (<1)	3 (<1)
16–25	3445 (34)	3407 (34)
26–33	4580 (46)	4608 (46)
≥34	2022 (20)	1987 (20)
Unknown	3 (<1)	4 (<1)
Baby delivered in the randomising hospital		
Yes	8869 (88)	8756 (88)
No	1181 (12)	1251 (13)
Unknown	1 (<1)	2 (<1)
Type of delivery		
Vaginal	7093 (71)	7126 (71)
Caesarean section	2957 (29)	2879 (29)
Unknown	1 (<1)	4 (<1)

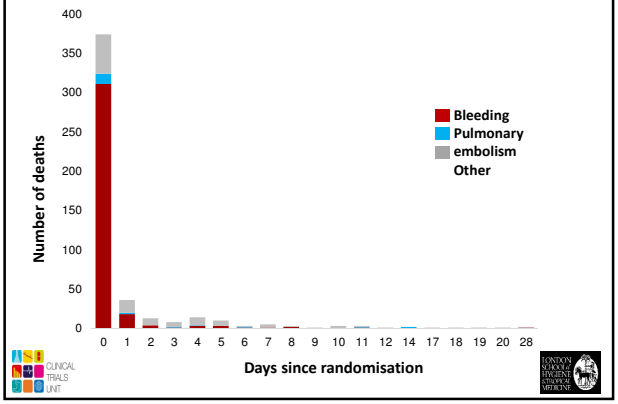
Baseline characteristics

	TXA n (%)	Placebo n (%)
Time between delivery and randomisation (h)		
≤1	4852 (48)	4733 (47)
>1 to ≤3	2678 (27)	2691 (27)
>3	2517 (25)	2574 (26)
Unknown	4 (<1)	11 (<1)
Placenta fully delivered		
Yes	9089 (90)	9016 (90)
No	962 (10)	990 (10)
Primary cause of haemorrhage		
Uterine atony	6437 (64)	6347 (63)
Placenta praevia or accreta	943 (9)	935 (9)
Surgical trauma or tears	1834 (18)	1857 (19)
Other	720 (7)	737 (7)
Unknown	117 (1)	133 (1)
Systolic blood pressure (mmHg)		
≥90	8138 (81)	8065 (81)
<90	1908 (19)	1929 (19)
Unknown	5 (<1)	15 (<1)

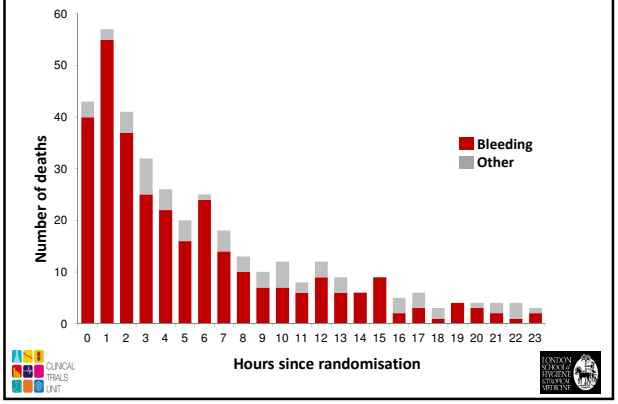
Baseline characteristics

	TXA n (%)	Placebo n (%)
Estimated volume of blood loss (mL)		
≤500	295 (3)	313 (3)
>500 to ≤1000	4949 (49)	4861 (49)
>1000 to ≤1500	2832 (28)	2882 (29)
>1500	1973 (20)	1953 (20)
Not known	2 (<1)	0
Uterotonic prophylaxis given		
Yes	9687 (96)	9618 (96)
No	131 (1)	139 (1)
Unknown	233 (2)	252 (3)
Clinical signs of haemodynamic instability		
Yes	5961 (59)	5898 (59)
No	4090 (41)	4110 (41)

Death by days since randomisation (n = 483)



Death by hours since randomisation (n=483)



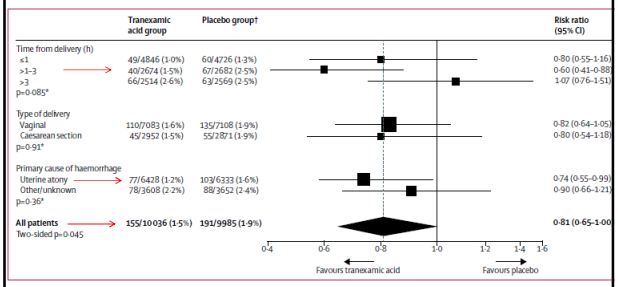
Maternal Death (n =483)

	Tranexamic acid group (n=10 036)	Placebo group (n=9985)	RR (95% CI)	p value (two-sided)
Bleeding	155 (1·5%)	191 (1·9 %)	0·81 (0·65–1·00)	0·045
Pulmonary embolism	10 (0·1%)	11 (0·1)	0·90 (0·38–2·13)	0·82
Organ failure	25 (0·3%)	18 (0·2%)	1·38 (0·75–2·53)	0·29
Sepsis	15 (0·2%)	8 (0·1%)	1·87 (0·79–4·40)	0·15
Eclampsia	2 (0·02%)	8 (0·1%)	0·25 (0·05–1·17)	0·057
Other	20 (0·2%)	20 (0·2%)	0·99 (0·54–1·85)	0·99
Any cause of death	227 (2·3%)	256 (2·6%)	0·88 (0·74–1·05)	0·16

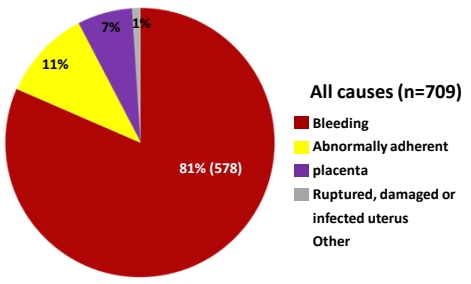
Data are n (%), unless otherwise indicated. RR=risk ratio.

Table 2: Effect of tranexamic acid on maternal death

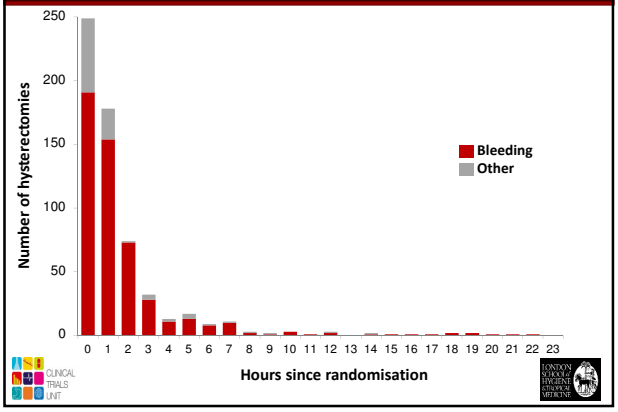
Effect of TXA on death due to bleeding: subgroups



Cause of hysterectomy



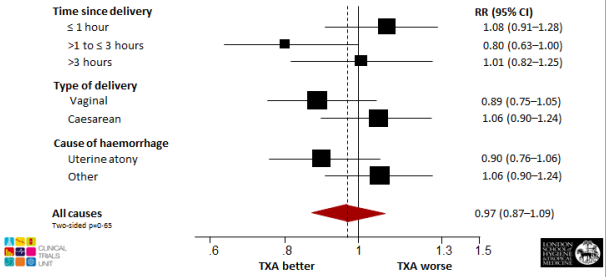
Hysterectomy by hours since randomisation



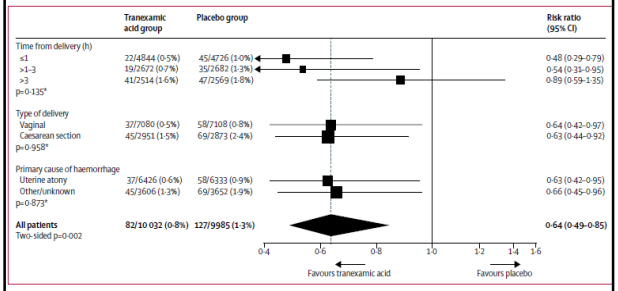
Hysterectomy

Outcome	TXA (N=10036) n (%)	Placebo (N=9985) n (%)	Risk ratio (95% CI)	P-value
Hysterectomy (all causes)	358 (3.6)	351 (3.5)	1.02 (0.88–1.17)	0.84
Hysterectomy (bleeding)	283 (2.8)	295 (3.0)	0.95 (0.81–1.12)	0.57

Death or hysterectomy



Laparotomy for bleeding



Thromboembolic events

	Tranexamic acid group	Placebo group	RR (95% CI)	p value
Thromboembolic events*	10 033	9985	..	
Any event	30 (0·3%)	34 (0·3%)	0·88 (0·54–1·43)	0·603
Venous events	20 (0·2%)	25 (0·3%)	0·80 (0·44–1·43)	0·446
Deep vein thrombosis	3 (0·03%)	7 (0·07%)	0·43 (0·11–1·65)	0·203
Pulmonary embolism	17 (0·2%)	20 (0·2%)	0·85 (0·44–1·61)	0·611
Arterial events	10 (0·1%)	9 (0·09%)	1·11 (0·45–2·72)	0·827
Myocardial infarction	2 (0·02%)	3 (0·03%)	0·66 (0·11–3·97)	0·651
Stroke	8 (0·08%)	6 (0·06%)	1·33 (0·46–3·82)	0·599

Complications

	Tranexamic acid group	Placebo group	RR (95% CI)	p value
Complications*	10 033	9985	..	..
Renal failure	129 (1·3%)	118 (1·2%)	1·09 (0·85–1·39)	0·505
Cardiac failure	110 (1·1%)	115 (1·2%)	0·95 (0·73–1·23)	0·710
Respiratory failure	108 (1·1%)	124 (1·2%)	0·87 (0·67–1·12)	0·274
Hepatic failure	29 (0·3%)	30 (0·3%)	0·96 (0·58–1·60)	0·882
Sepsis	180 (1·8%)	185 (1·9%)	0·97 (0·79–1·19)	0·756
Seizure	33 (0·3%)	43 (0·4%)	0·76 (0·49–1·20)	0·242

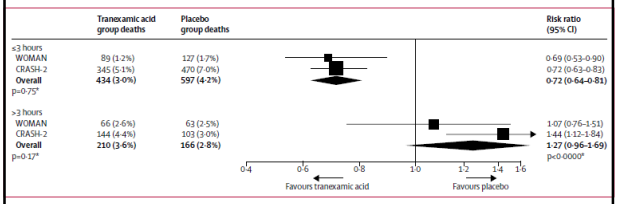
Use of uterotonics for PPH treatment

	Tranexamic acid group	Placebo group	RR (95% CI)	p value
Use of uterotonics	10 034	9984	..	..
Received at least one type	9996 (99·6%)	9930 (99·5%)	1·00 (1·00–1·00)	0·090
Oxytocin	9940 (99·1%)	9865 (98·8%)	1·00 (1·00–1·01)	0·079
Ergometrine	4326 (43·1%)	4314 (43·2%)	1·00 (0·97–1·03)	0·891
Misoprostol	6707 (66·8%)	6717 (67·3%)	0·99 (0·97–1·01)	0·513
Prostaglandin	689 (6·9%)	722 (7·2%)	0·95 (0·86–1·05)	0·313

Quality of life

	Tranexamic acid group	Placebo group	RR (95% CI)	p value
ED-5Q+	9805	9728	..	..
Mobility	30 (0·3%)	31 (0·3%)	0·96 (0·58–1·58)	0·874
Self-care	39 (0·4%)	31 (0·3%)	1·25 (0·78–2·00)	0·355
Usual activities	38 (0·4%)	44 (0·5%)	0·86 (0·56–1·32)	0·484
Pain/discomfort	13 (0·1%)	18 (0·2%)	0·72 (0·35–1·46)	0·357
Anxiety/depression	30 (0·3%)	29 (0·3%)	1·03 (0·62–1·71)	0·920

Death due to bleeding



Tranexamic acid in PPH – WOMAN results

- ↓ death due to bleeding overall **by one fifth (19%)**
- ↓ death due to bleeding within 3 hours by ≅ **one third (1.2% vs 1.7%)**
- **No effect on other causes of death**
- **Did not reduce hysterectomy**
- ↓ **laparotomy for bleeding by over 35% (0.8% vs 1.3%)**
- **No evidence of adverse effects**

WOMAN results – subsequent analysis

RESEARCH ARTICLE Open Access

The impact of early outcome events on the effect of tranexamic acid in post-partum haemorrhage: an exploratory subgroup analysis of the WOMAN trial

Amy Brenner[1*], Haleema Shakur-Still[1], Rizwana Chaudhri[2], Bukola Fawole[3], Sabaratnam Arulkumaran[4], Ian Roberts[1] and on behalf of the WOMAN Trial Collaborators

Brenner *et al. BMC Pregnancy and Childbirth* (2018) 18:215
https://doi.org/10.1186/s12884-018-1855-5

Impact of deaths due to early bleeding on effectiveness of TA

Exclusion interval (hours from randomisation)	Exclusions[a]		N		Death due to bleeding		
	TXA (%)	Placebo (%)	TXA	Placebo	TXA (%)	Placebo (%)	Risk ratio (99% CI)
None	–	–	7518	7405	89 (1.2)	127 (1.7)	0.69 (0.48–0.98)
1	14 (0.2)	15 (0.2)	7504	7390	76 (1.0)	114 (1.5)	0.66 (0.45–0.96)
2	30 (0.4)	38 (0.5)	7488	7367	61 (0.8)	92 (1.3)	0.65 (0.43–1.00)
3	42 (0.6)	57 (0.8)	7476	7348	50 (0.7)	75 (1.0)	0.66 (0.41–1.05)
4	53 (0.7)	70 (1.0)	7465	7335	42 (0.6)	64 (0.9)	0.64 (0.39–1.07)
5	62 (0.8)	77 (1.0)	7456	7328	33 (0.4)	59 (0.8)	0.55 (0.31–0.96)
6	66 (0.9)	85 (1.2)	7452	7320	29 (0.4)	53 (0.7)	0.54 (0.30–0.97)
7	73 (1.0)	94 (1.3)	7445	7311	23 (0.3)	44 (0.6)	0.51 (0.26–0.99)
8	80 (1.1)	97 (1.3)	7438	7308	18 (0.2)	41 (0.6)	0.43 (0.21–0.89)
9	83 (1.1)	101 (1.4)	7435	7304	16 (0.2)	38 (0.5)	0.41 (0.19–0.89)
10	84 (1.1)	104 (1.4)	7434	7301	16 (0.2)	37 (0.5)	0.42 (0.20–0.91)

Impact of deaths due to early bleeding on effectiveness of TA

	IOCS		Control	
Death (bleeding)	16/7435	vs	38/7403	OR 0.41 [0.19-0.81]

ie – a potentially greater effect of TA masked by early deaths

COPE

The Carboprost or Oxytocin Postpartum haemorrhage Effectiveness Study

Chief Investigator – Professor Andrew Weeks
Liverpool

Background

- PPH affects 1 in 20 births
- Leading cause of maternal mortality worldwide
- 13 direct maternal deaths in UK 2012-2014

- Best 1st line treatment for PPH?
- Limited evidence from RCTs
  - Unpredictable
  - Emergency consent
- Guidance from PPH prevention studies, observational studies, expert opinions

What do you use for 1st line prophylaxis?

- Oxytocin
- Misoprostol
- Syntometrine
- Ergometrine
- Carbetocin
- Carboprost

What do you use for 1st line <u>treatment</u>?

- Oxytocin bolus
- Misoprostol
- Ergometrine
- Carboprost
- Oxytocin infusion

Rationale

OXYTOCIN	CARBOPROST
• Effective uterotonic • Used as 1st line treatment • Low cost - 91p • Side effects: headache, nausea vomiting • **BUT** less effective in women already on oxytocin during labour (saturation of receptors) and potential hypotension, water retention	• Prostaglandin F2α • Reserved for 2nd/3rd line tx • Higher cost £18.20 • Side effects in 15%: diarrhoea, vomiting • **BUT** PPH prevention studies suggest use of PG may be associated with less mean blood loss than oxytocin (-224 ml MD; 95% CI -420 to -27)

NICE: need for an RCT to ascertain both the effectiveness of carboprost and its optimal position in a PPH treatment pathway

COPE

Published:
JUNE 20, 2017
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£1.8m for major new study into bleeding after childbirth

The University's Institute of Translational Medicine has been awarded £1.8m funding from the UK National Institute of Health Research (NIHR) to run a large study into the drug treatment of bleeding after childbirth (also called postpartum haemorrhage or PPH).

COPE Team

UNIVERSITY OF LIVERPOOL

NIHR grant: £1.8 million

Sponsor: University of Liverpool

Chief Investigator: Prof Andrew Weeks

Trial Management Group:

- Liverpool CTU: Helen Hickey, Carrol Gamble, Kerry Woolfall
- Zarko Alfirevic, Gill Gyte (Liverpool)
- Shireen Meher (Birmingham)
- Kim Hinshaw (Sunderland)
- Dyfrig Huges (Bangor)
- Dimitrios Siassakos (Bristol)
- Annette Briley (St Thomas' London)
- Tina Lavender (Manchester)

Co-applicants

- Dilly Anumba (Sheffield)
- Peter Collins (Cardiff)
- Rachel Collis (Cardiff)
- Nina Johns (Birmingham)
- Steve Robson (Newcastle)
- Andy Shennan (St Thomas' London)
- Nigel Simpson (Leeds)
- Jim Thornton (Nottingham)

Objectives

- **Primary**
  - To compare carboprost 250 mcg IM with oxytocin 10 IU for the initial treatment of women with clinically diagnosed PPH
- **Secondary**
  - To assess the relative cost-effectiveness of carboprost and oxytocin as initial treatments for PPH
  - To explore the views of participants and their carers about their experiences of the two treatments and the consent process.

CHS - how often do we use ergometrine?

Total deliveries for calendar year 2015 = 3138

Normal	1937 (61.7%)	Ergometrine	68 (3.5%)
Forceps	285 (9.1%)	Ergometrine	20 (7.0%)
Vacuum	160 (5.1%)	Ergometrine	11 (6.9%)
Vaginal breech	21 (0.7%)		
Total CS	735 (23.4%)		
Elective CS – Cat 4	321 (10.2%)	Ergometrine	1
Emergency – Cat 1	112 (3.6%)	Ergometrine	1
Emergency – Cat 2	192 (6.1%)		
Emergency – Cat 3	110 (3.5%)		

CHS - when do we give ergometrine?

n=101

Up to 500 (250-450)	32	31.7%
500 up to 999ml	45	
1000 up to 1499ml	10	
1500 up to 1999ml	6	
2000 up to 2499ml	6	
2500ml (exactly!)	2	

Methods

- **Study design**
  - Double blind placebo controlled RCT (phase IV study)
  - Randomised in a 1:1 ratio using random variable block size, stratified by mode of birth (caesarean section or vaginal birth)
- **Participants**
  - Women >16 yrs requiring medical treatment for primary PPH
  - Exclusions: known contraindications/hypersensitivity to oxytocin or carboprost, active cardiac / pulmonary disease, stillbirth, declined participation antenatally
- **Intervention**
  - Intervention: Carboprost 250 mcg IM inj and 1ml placebo IV inj
  - Control: Oxytocin 10 IU slow IV inj and 1ml placebo IM inj

Outcomes

Based on PPH Core Outcome Set Liverpool 2016

Primary outcome

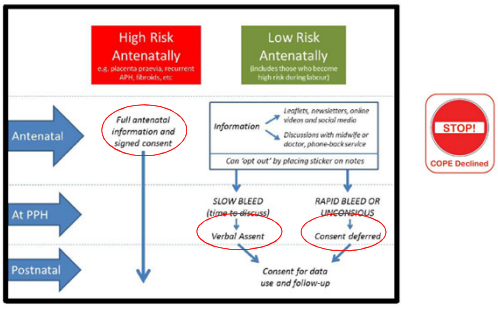
Blood transfusion.

Secondary outcomes

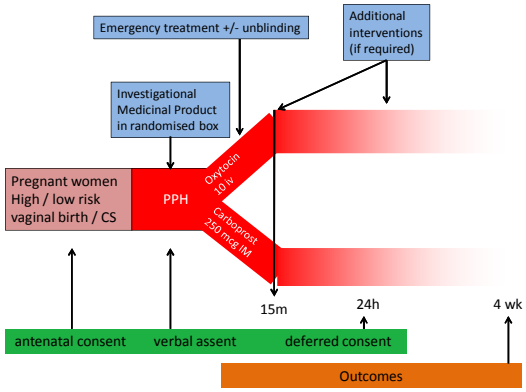
- Mean estimated blood loss
- Morbidity: Any organ dysfunction, shock, coagulopathy, hysterectomy
- Maternal death
- Use of additional uterotonics
- Transfer to a higher level of care
- Breastfeeding
- Side effects
- Resource use, costs and QALYs to estimate incremental cost effectiveness ratio
- Patient reported outcomes (CEQ)
- Qualitative research: views / experiences of women, partners and practitioners involved in recruitment and consent

Consent process - COPE

- RCOG Guidelines for intrapartum consent to research in acute situations
- Informed by PPI input and previous studies conducted in this setting.



Study procedures



Sample size and recruitment

- **Sample size**
  - 3948 women
  - Based on 2.3% reduction in a 5.8% transfusion rate (relative risk 0.60) with 90% power (alpha 0.05) and 5% loss to follow up: 1974 women per group.
- **Recruitment**
  - 40 UK NHS hospital maternity units
  - Internal pilot for 6 months in 5 UK hospitals: Liverpool, Birmingham, Sunderland, Bristol, Guy's & St Thomas', London
  - Commence recruitment March 2018
  - Trial duration 4 years (Sept 2021)
  - 4.5 recruits/month/centre

COPE
The Carboprost or Oxytocin Postpartum haemorrhage Effectiveness Study

Watch this space.....

For further information contact smeher@nhs.net

Consent in emergency obstetric trials

What women think about consent to research at the time of an obstetric emergency: a qualitative study of the views of a cohort of World Maternal Antifibrinolytic Trial participants

G Houghton,[a,*] C Kingdon,[b] M Dower,[a] H Shakur-Still,[c] Z Alfirevic[d]

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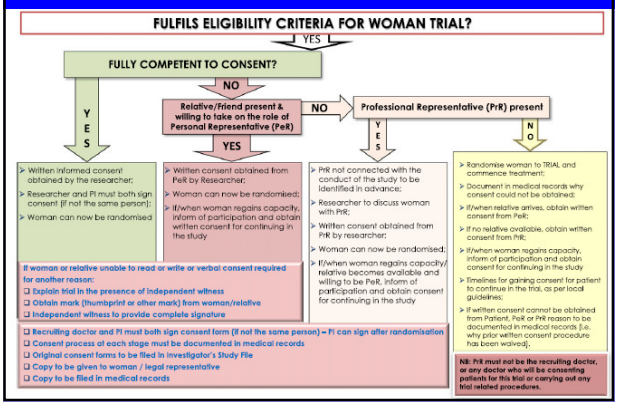
Email gillian.houghton@lwh.nhs.uk

Accepted 4 June 2018. Published Online 31 July 2018.

Consent in WOMAN trial



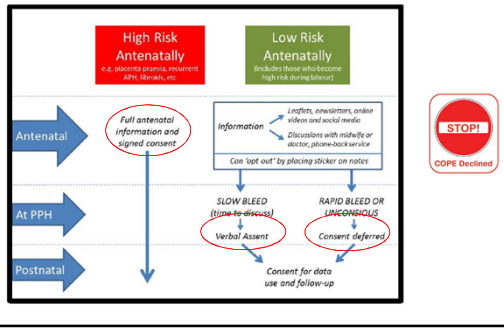
Consent in emergency obstetric trials

What were the main findings?

Women understood how difficult it was for their doctors and midwives to ask them about the research study. They were pleased to have been included in the research and were mostly happy with the way they gave consent. Women's views were similar whether they were asked about the research at the time of the bleeding or after they had recovered. The most important thing was that doctors and midwives carefully thought about the situation the woman found herself in and how this might make her feel, so they could tailor their approach accordingly.

Consent process - COPE

- RCOG Guidelines for intrapartum consent to research in acute situations
- Informed by PPI input and previous studies conducted in this setting.



Summary

- Cell salvage is not of benefit in routine emergencies
- Early use of tranexamic acid for PPH
- Carboprost as 1st line for PPH – watch this space!
- Flexible approaches to consent required in emergency obstetrics

Thank you….