Acute Obstetric Coagulopathy and postpartum haemorrhage

Professor Peter Collins

On behalf of Obstetric Bleeding Study collaborators

SFOAI Spring 2025

Disclosures for Peter Collins

Research Support/P.I.	NIHR, OAA, NIAA, CSL Behring, Haemonectics, Werfen
Employee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	No relevant conflicts of interest to declare
Scientific Advisory Board	CSL Behring, Haemonectics, Werfen

Overview

	Study	Outcome
2008-2010	Clinical observation	Case reports All Wales audit
2010-2011	Retrospective observational study PPH over 3 years	Fibrinogen is first coagulation factor to fall
2012-2013	Prospective observational study of moderate/severe PPH	Fibrinogen and Fibtem biomarkers for predicting progression of PPH
2013-2015	Prospective double blind RCT of Fibtem guided fibrinogen	1. Intervention trigger for fibrinogen replacement identified: 2 g/L 2. Safe to withhold FFP
2016-2018	National quality improvement programme introducing OBSUK care bundle	Red cell transfusions and massive PPH reduced

OBSCYMRU
Obstetric Bleeding Strategy for Wales

NIHR | National Institute for Health Research

Stepped wedge randomised control trial

Introducing the OBS care bundle using quality improvement methodology

Primary endpoint the proportion of women transfused red blood cells

Causes of bleeding during childbirth

- **Uterine Atony**
- **Trauma; lacerations, inversions, rupture**
- **Retained tissue, invasive placentation**
- **Coagulopathy, low fibrinogen**

OBS Cymru/UK

care bundle

Risk assessment

Measured cumulative real time blood loss

Escalation to more senior clinicians

Causes of bleeding during childbirth

- **Uterine Atony**
- **Trauma; lacerations, inversions, rupture**
- **Retained tissue, invasive placentation**
- **Coagulopathy, low fibrinogen – 5%**

OBS Cymru/UK

care bundle

Risk assessment

Measured cumulative real time blood loss

Escalation to more senior clinicians

Point of coagulation tests
Early replacement of low fibrinogen

Why is coagulopathy important?

- 27% of maternal deaths in UK result from PPH
  - Equal 2nd leading direct cause of maternal death[1]
- Death rate has not improved in 25 years[1]
  - 0.55/100,000 (1996)
  - 0.89/100,000 (2020-2022)
- Most women who died of bleeding had inadequately treated coagulopathy
- UK Obstetric Surveillance System (UKOSS): PPH and fibrinogen <2 g/L
  - Maternal deaths 2/114 (1.8%)[2]
    - 150-fold higher death rate
  - Fetal neonatal deaths 25/103 (24.3%) [2]

1. MBBRACE 2023, 2024
2. Diguisto et al AOGS 103:1339, 2024

Arresting obstetric bleeding

Clot formation

Platelets

FBC

Platelets

FFP

PT/aPTT

Clotting factors

Fibrinogen / Cryoprecipitate

Clauss fibrinogen

Fibrinogen

Factor XIII

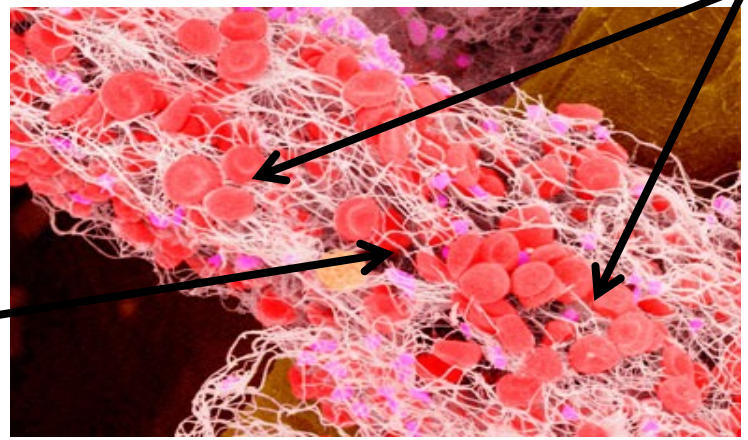
Physiological
Pharmacological
Surgical/radiological

Control of bleeding vessels
Uterine contraction

Platelet plug
Fibrin clot

Tranexamic acid

Fibrinolysis



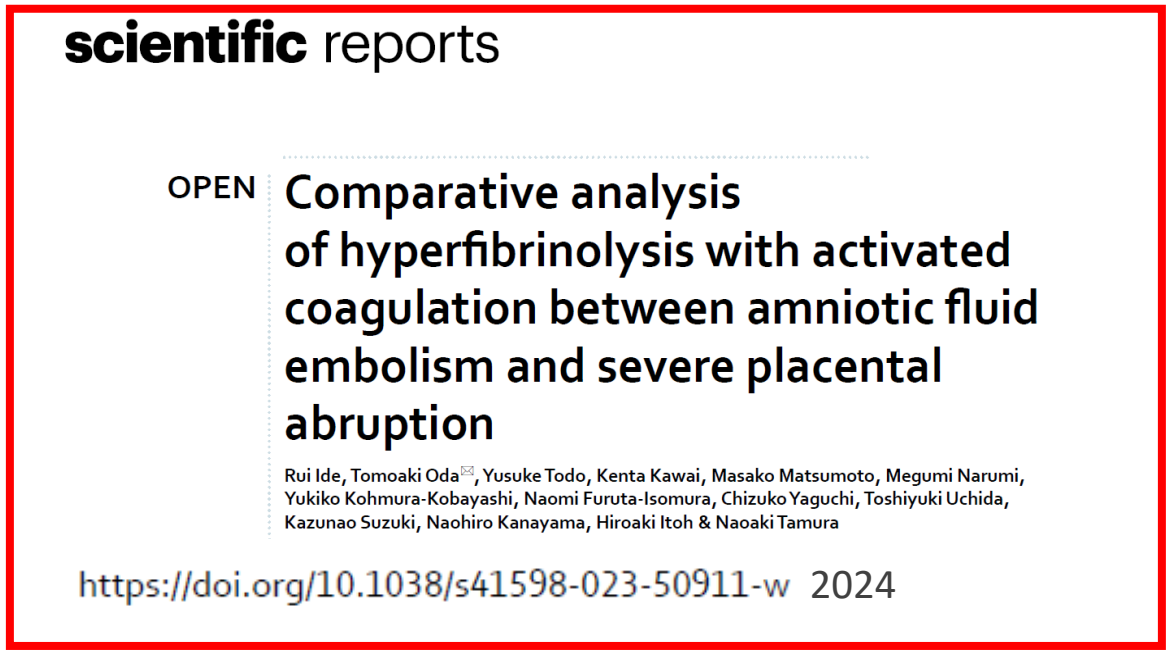
Fibrinogen and postpartum haemorrhage

- **Fibrinogen may fall to critically low levels early during PPH**
  - **Other clotting factors rarely low**
- **Fibrinogen >2 g/L is adequate for haemostasis during PPH**
- **RCOG/AAGBI/BSH and FIGO guidelines**
  - **Recommend maintaining fibrinogen >2 g/L during PPH**
- **Rotem/TEG**
  - **Detects fibrinogen <2 g/L**
  - **Can be used to guide blood product replacement during PPH**
- **Why does fibrinogen fall during PPH?**

De Lloyd et al IJOA 20:135, 2011
Collins BJA 119:411, 2017
Mavrides BJOG 124:e106-e149, 2016 and Escobar IJOG 157(S1):3-50
Roberts et al IJOA 47, 2021

Haemostatic impairment during childbirth

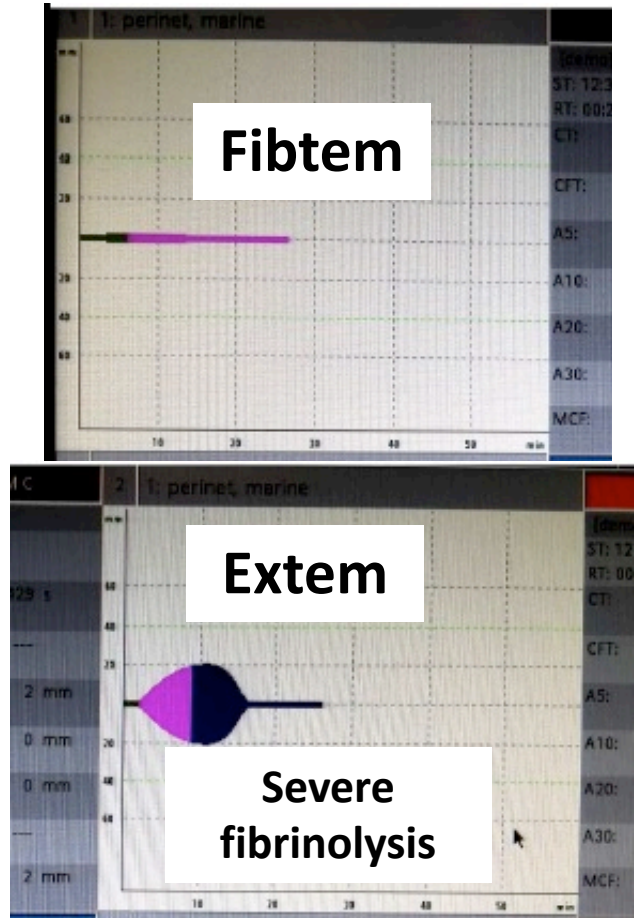
- **Limited knowledge about the mechanisms of coagulopathy associated with childbirth**
- **An early, severe coagulopathy is well recognised often associated with:**
  - **Amniotic fluid embolism**
  - **Placental abruption**



Amniotic fluid embolism

- **Rare disorder: incidence about 1/50000 deliveries**
  - **Severe coagulopathy >90%[1]**
  - **Mortality about 66%[2]**

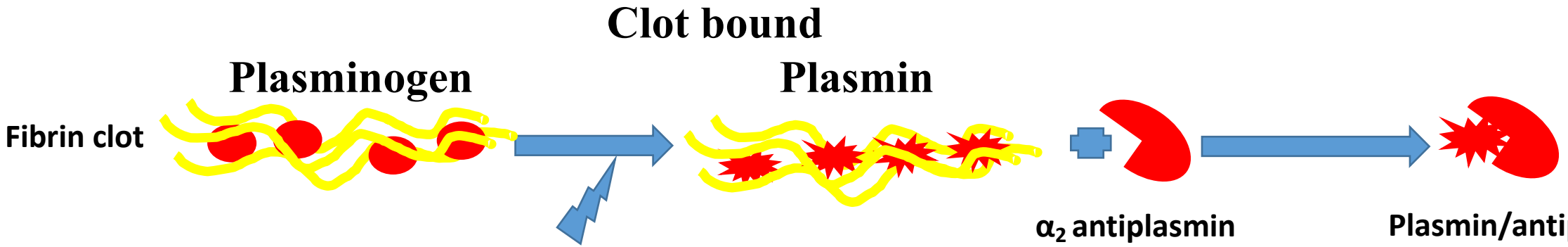
- **Data on coagulopathy from case reports and case series[3]**
  - **Early and rapid onset**
  - **Very low fibrinogen (often unmeasureable)**
  - **Very high D-dimer**
    - **Massive fibrinolysis**
  - **Initially low FV and other coagulation factors normal**
  - **Platelets low but usually adequate (>50 x10^9/L)**

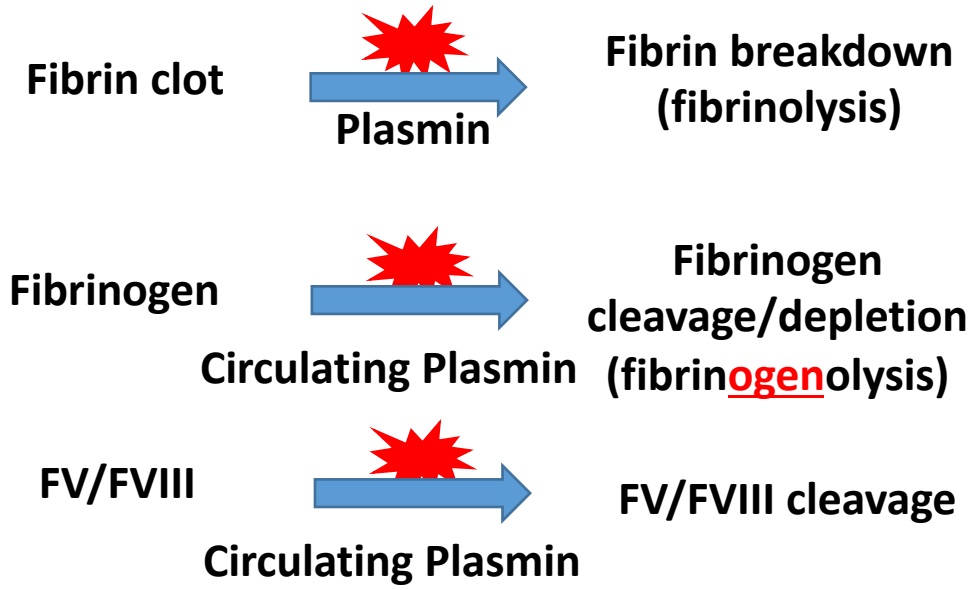


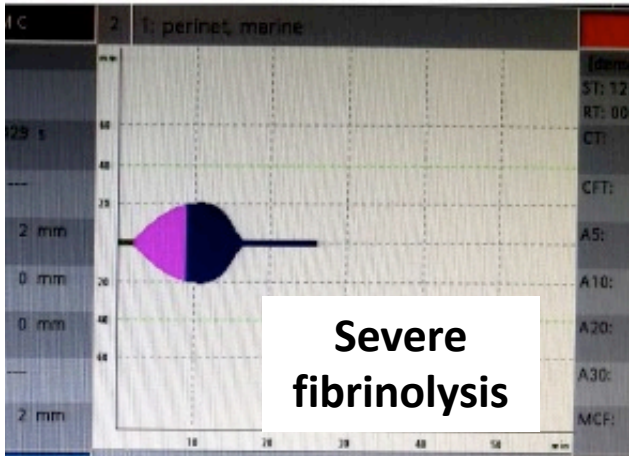
Provided by Anne-Sophie Ducloy-Bouthers (prior to tranexamic acid)

1. Stafford et al Am J Obstet Gynecol 2020
2. Schroder et al Arch Gynecol Obstet 2020 301:923-929
3. Ide et al Scientific Reports 14:272, 2024

Fibrinolysis mediated by plasmin







A description of the coagulopathy characteristics in amniotic fluid embolism: a case report

International Journal of Obstetric Anesthesia 51 (2022) 103573

C. Oliver [a,*], J. Freyer [a], M. Murdoch [a], L. De Lloyd [a], P.V. Jenkins [b], R. Collis [a], P.W. Collins [b]

Fibrinogen inhibition: dysfibrinogenaemia

Parameter	Amniotic fluid embolus	
Clauss fibrinogen (g/L) function	1.6	
Antigenic fibrinogen (g/L) amount	2.9	
Ratio	0.56	

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Clauss fibrinogen (g/L) function	1.6	0.8
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Ratio	0.56	0.26

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D-dimer (ng/mL)	282,190	1,400,000
Factor V (IU/dL)	32	11

Obstetric Bleeding Study plus

Acute obstetric coagulopathy during postpartum hemorrhage is caused by hyperfibrinolysis and dysfibrinogenemia: an observational cohort study

Lucy de Lloyd[1] | Peter V. Jenkins[2,3] | Sarah F. Bell[1] | Nicola J. Mutch[4] | Julia Freyer Martins Pereira[1] | Pilar M. Badenes[5] | Donna James[6] | Anouk Ridgeway[6] | Leon Cohen[1] | Thomas Roberts[1] | Victoria Field[1] | Rachel E. Collis[1] | Peter W. Collins[2,3]

Journal of Thrombosis and Haemostasis 21:862-879, 2023

Funding

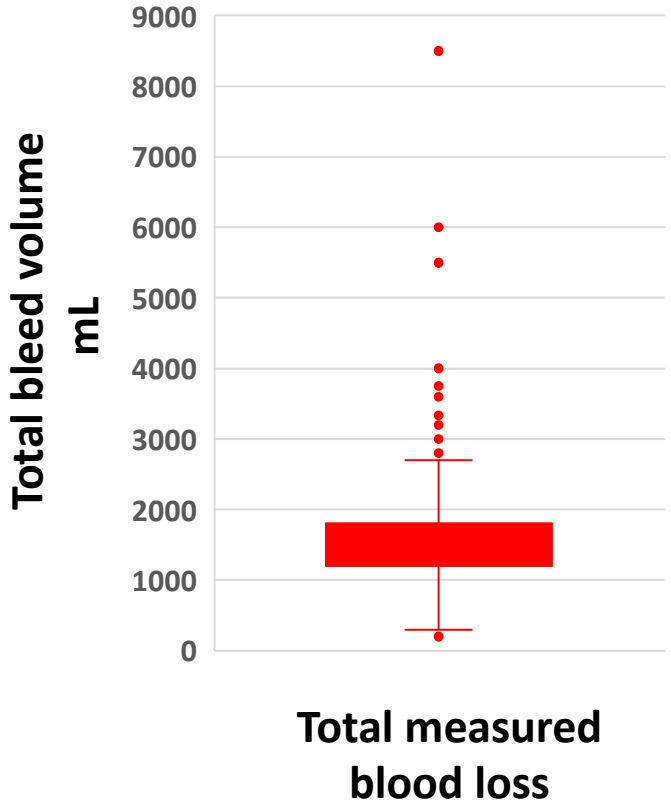
Haemonectics Corp®

Study aim:

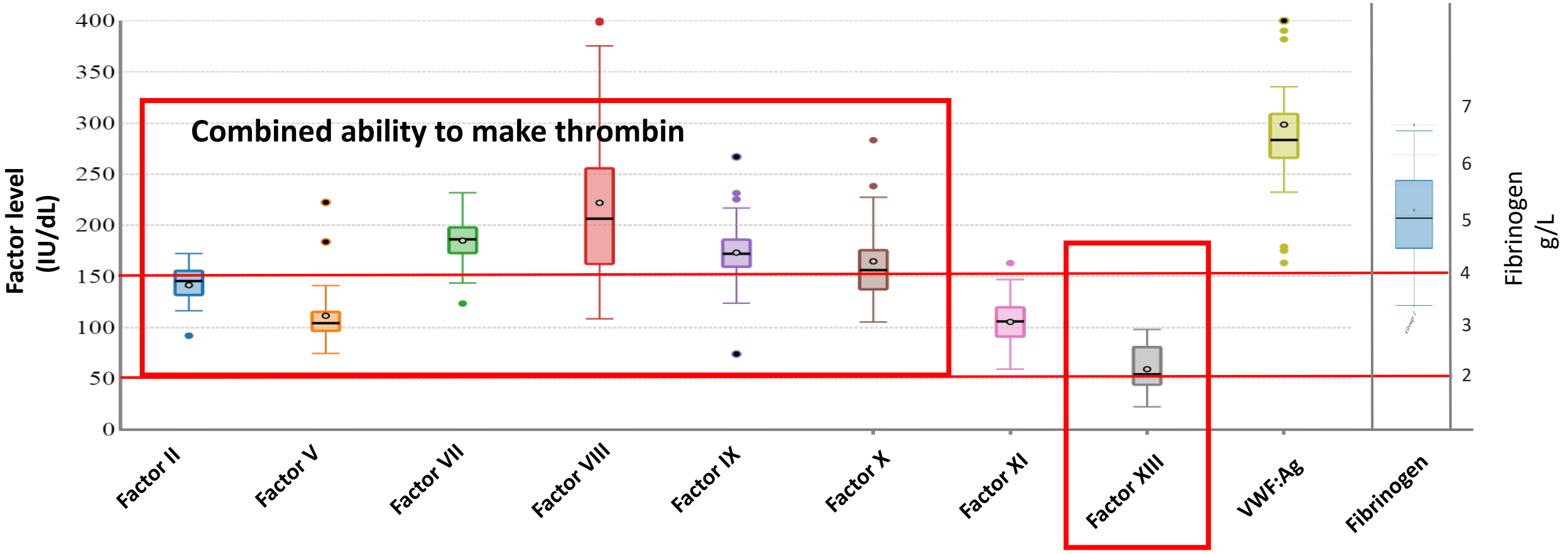
Characterise the coagulopathy of postpartum haemorrhage

Study cohort

- Recruitment criteria
  - Bleed ≥1000 mL or earlier for clinical concern (Abruption/AFE/concealed bleeding)
- Enrolled
  - Postpartum haemorrhage N=518/10790 (4.8%)
  - Non-bleeding term pregnant controls N=37
    - (before elective c section)
- Blood taken for coagulation phenotyping
- Total blood loss: Median 1500 mL
- Transfusion
  - Red cells: N=133 (26%)
  - Fibrinogen: N=19 (3.5%)
  - Platelets: N=7 (1.4%)
  - FFP: N=3 (0.6%)



Haemostasis at term: coagulation factors

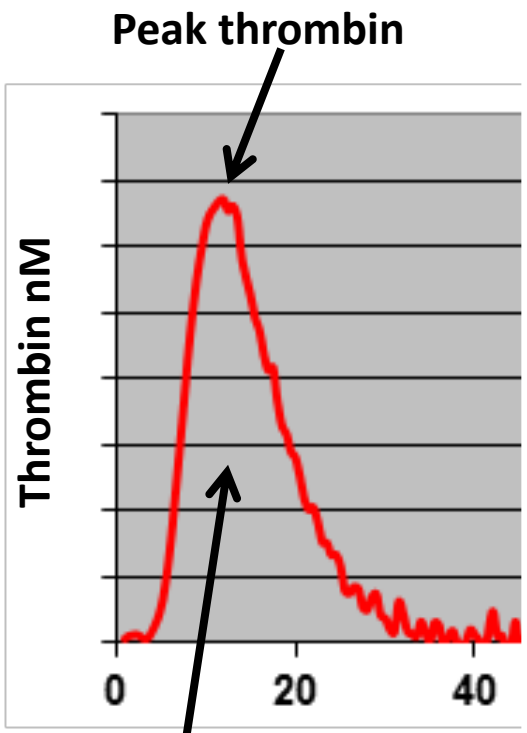


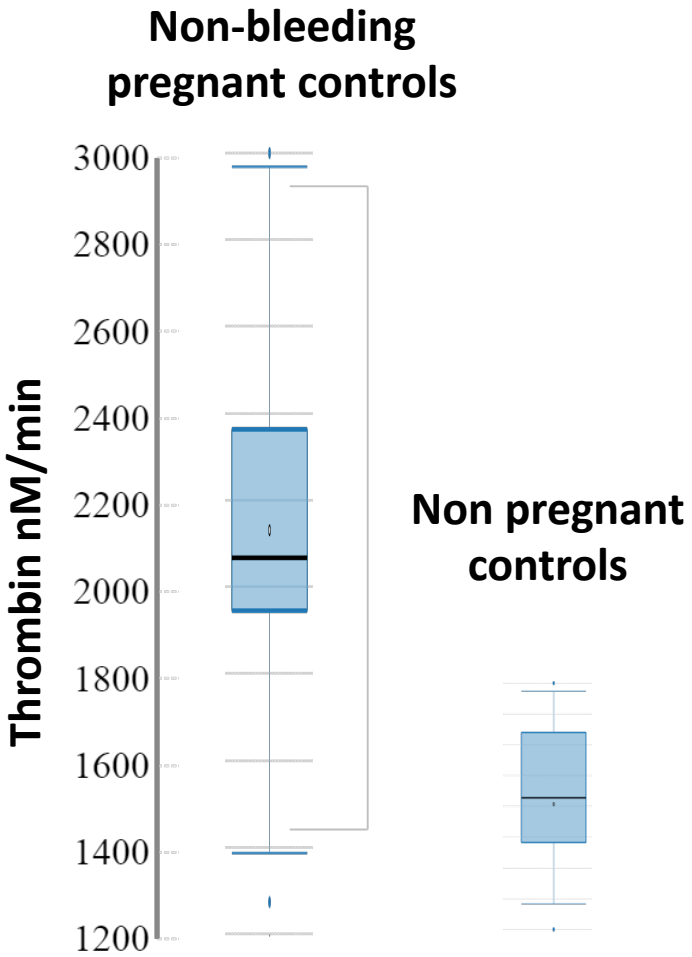
Samples taken at time of elective c section

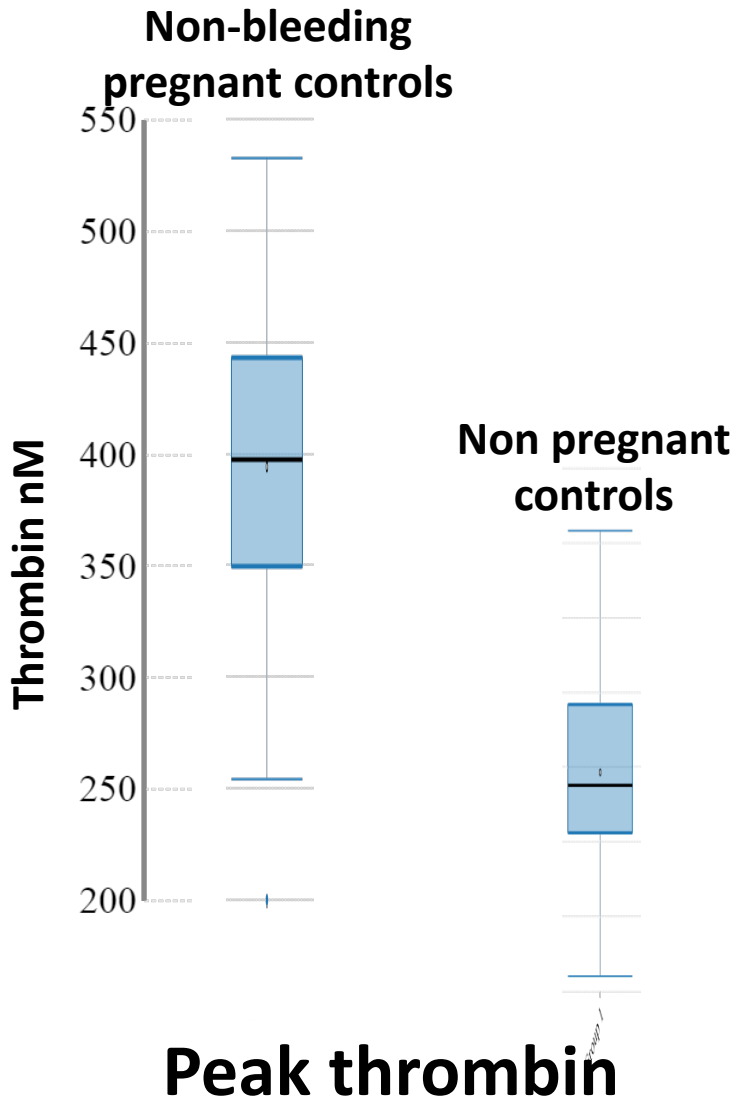
Coagulation factor (IU/dL)

Non-pregnant normal range

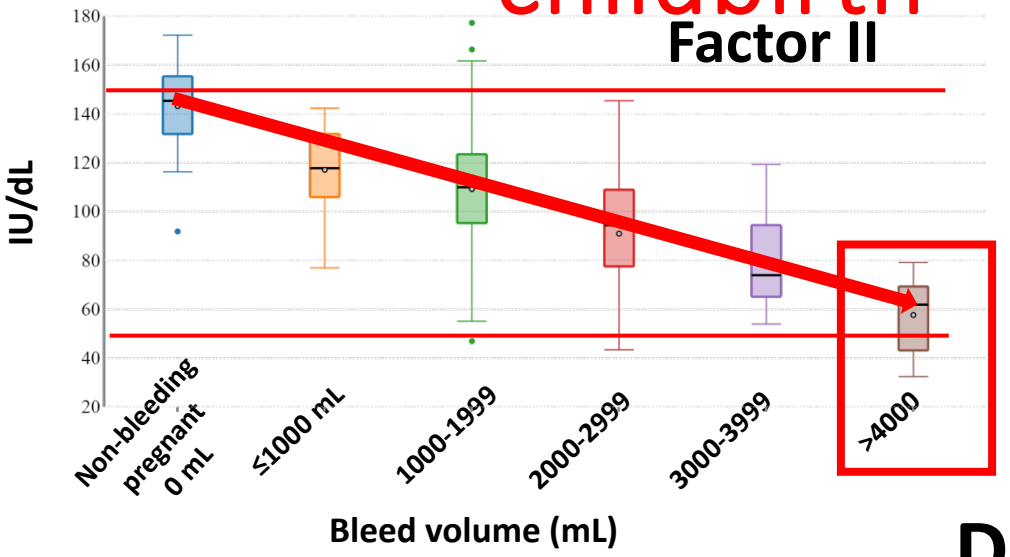
Haemostasis at term: increased ability to make thrombin

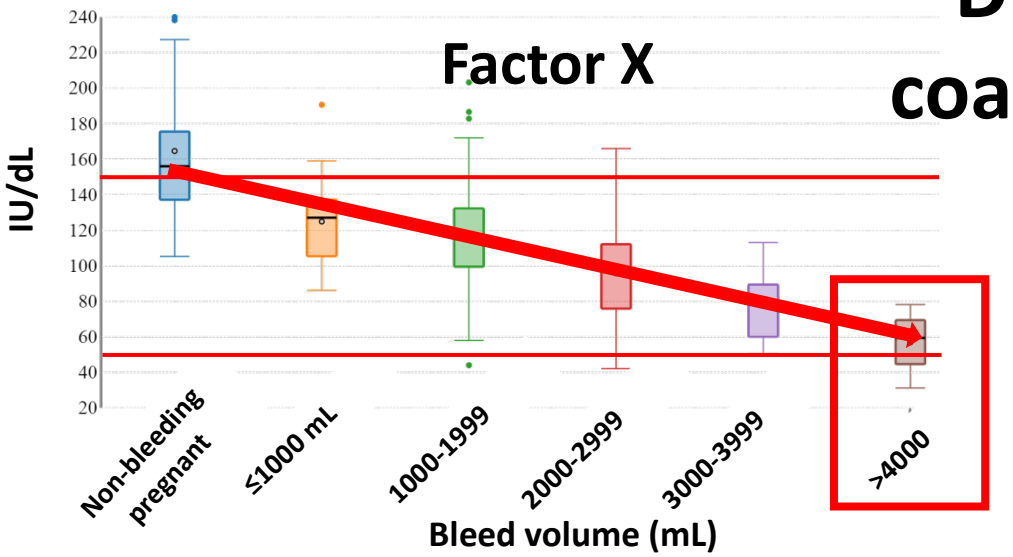




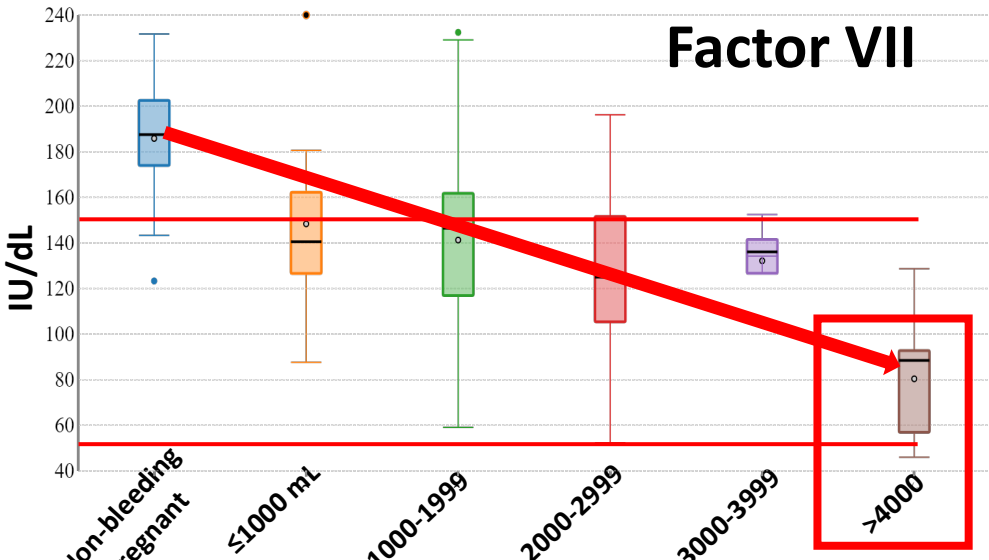


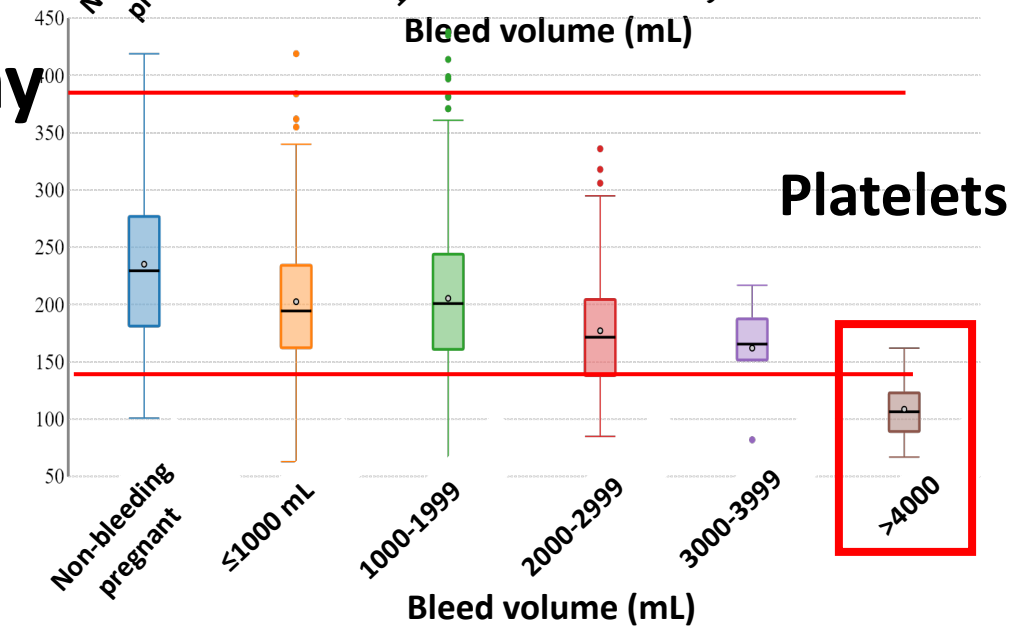
Clotting factors during bleeding after childbirth





Dilutional coagulopathy

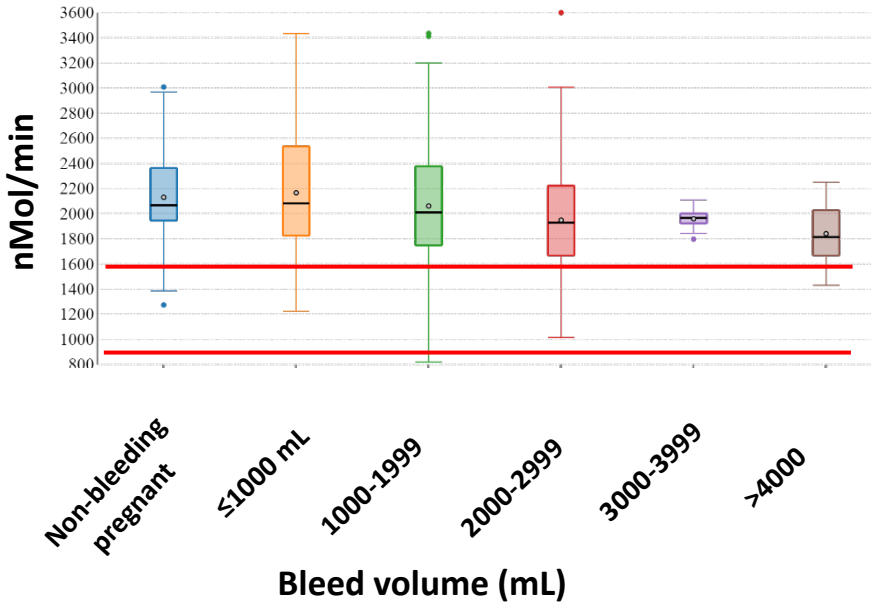




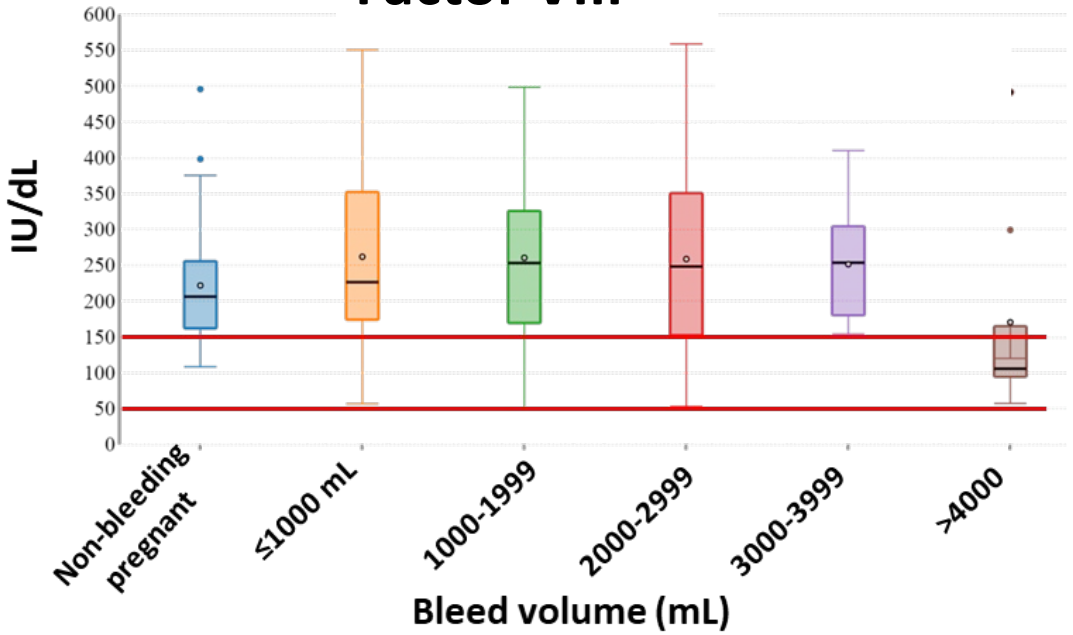
Non-pregnant normal range

Thrombin generation during bleeding after childbirth

Thrombin generation: ETP



Factor VIII



Non-pregnant normal range

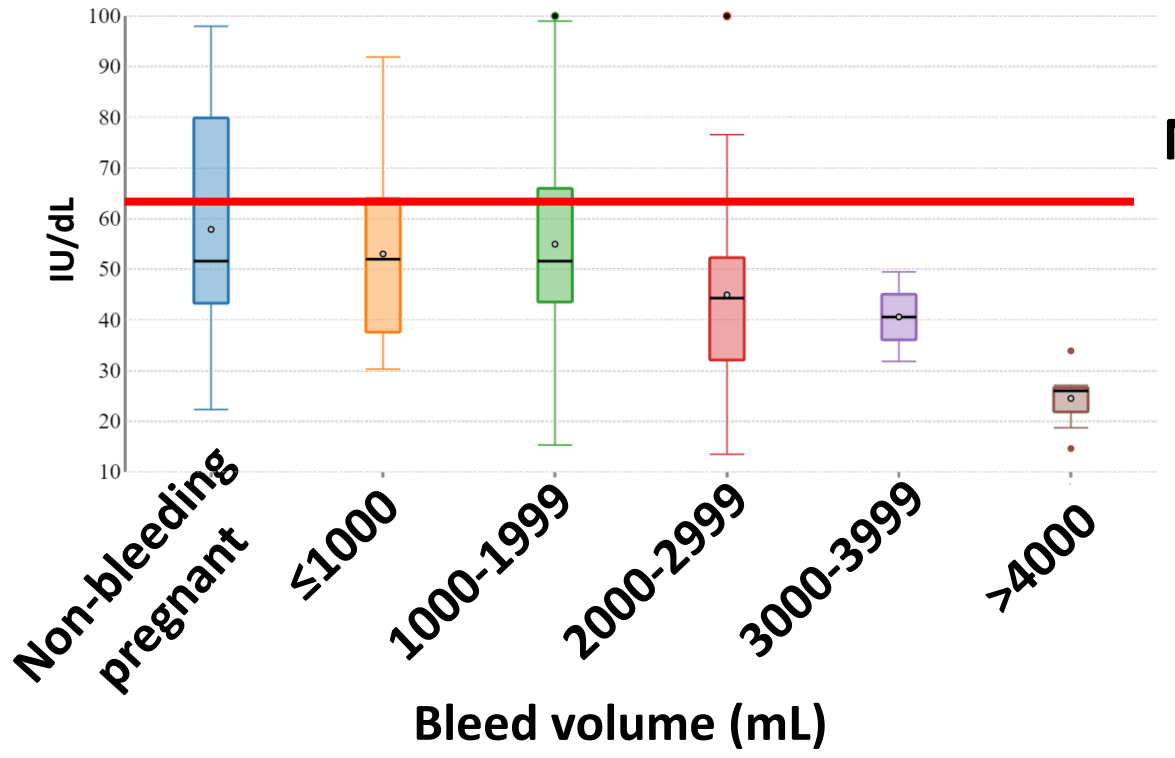
Limited role for fresh frozen plasma or rVIIa

Coagulopathy during PPH: Factor XIII

FXIII cross-links fibrin strands

Stabilises and strengthens clots

Factor XIII



Non-pregnant lower limit

de Lloyd et al JTH 2023

Coagulopathy during PPH: Factor XIII

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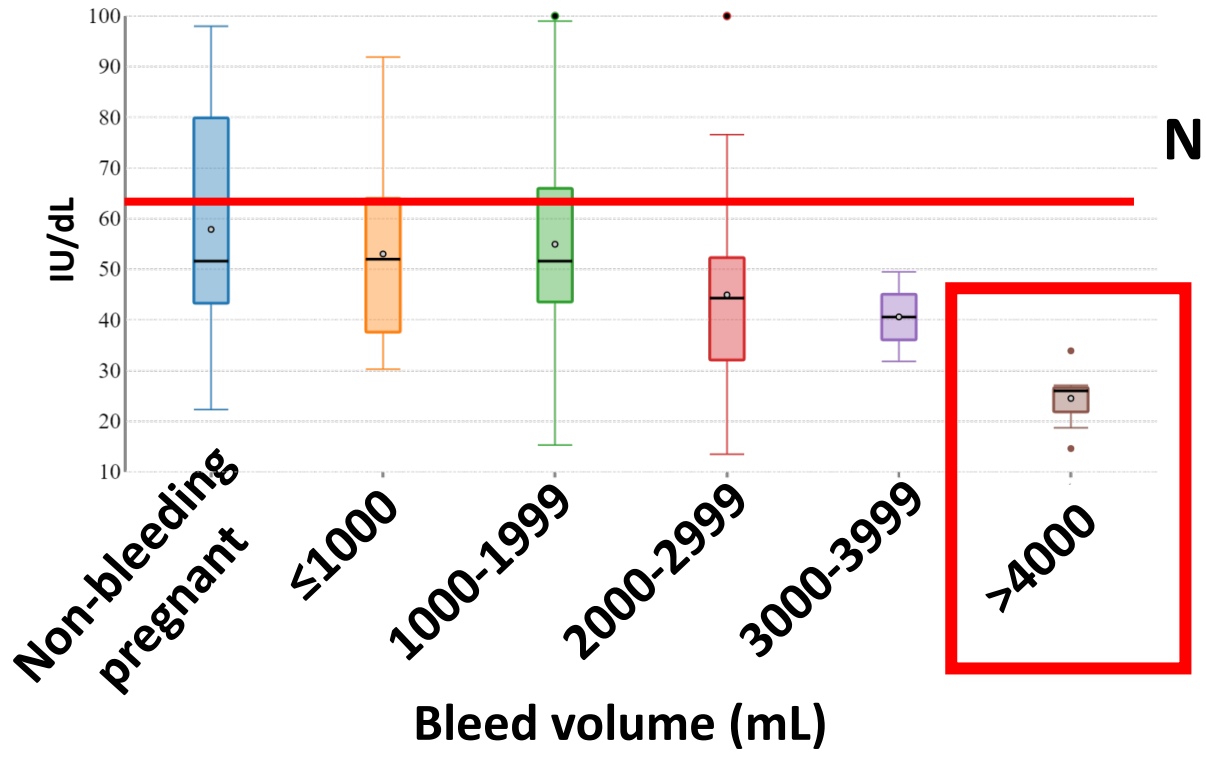
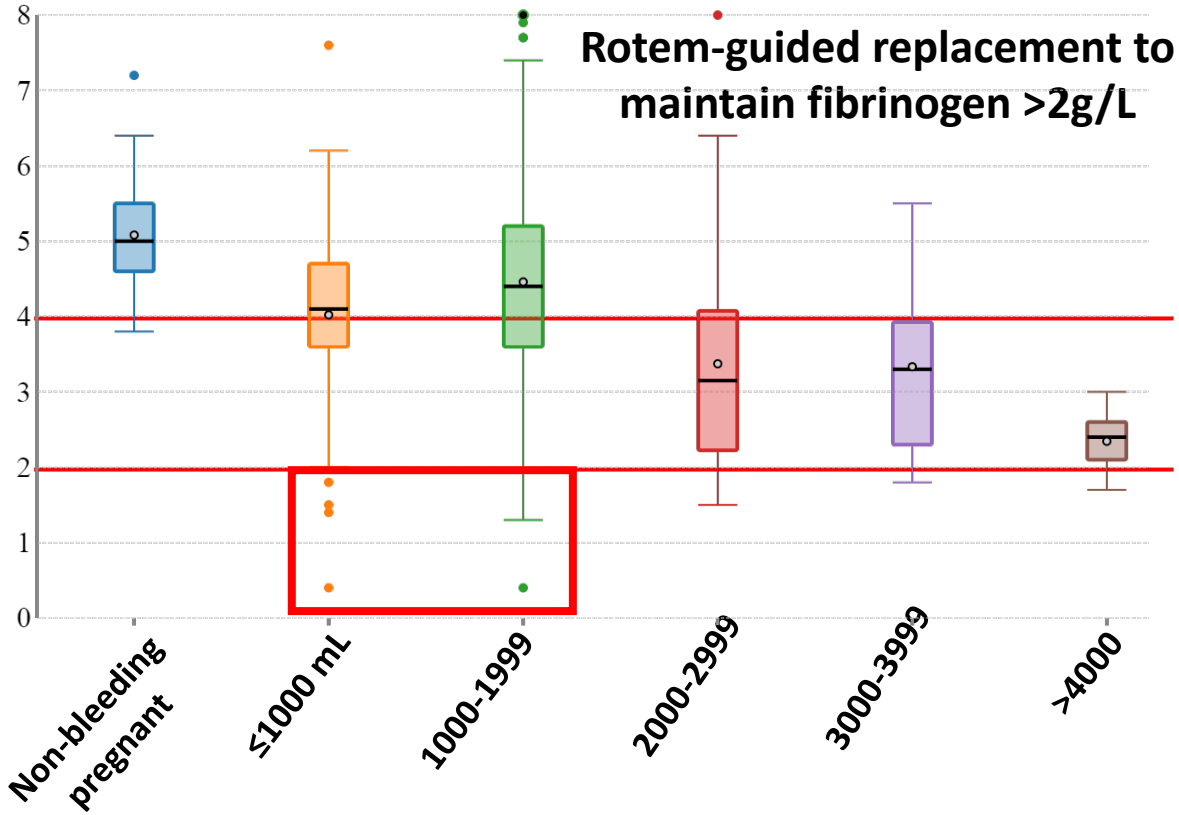


Non-pregnant lower limit

de Lloyd et al JTH 2023

Fibrinogen during postpartum haemorrhage



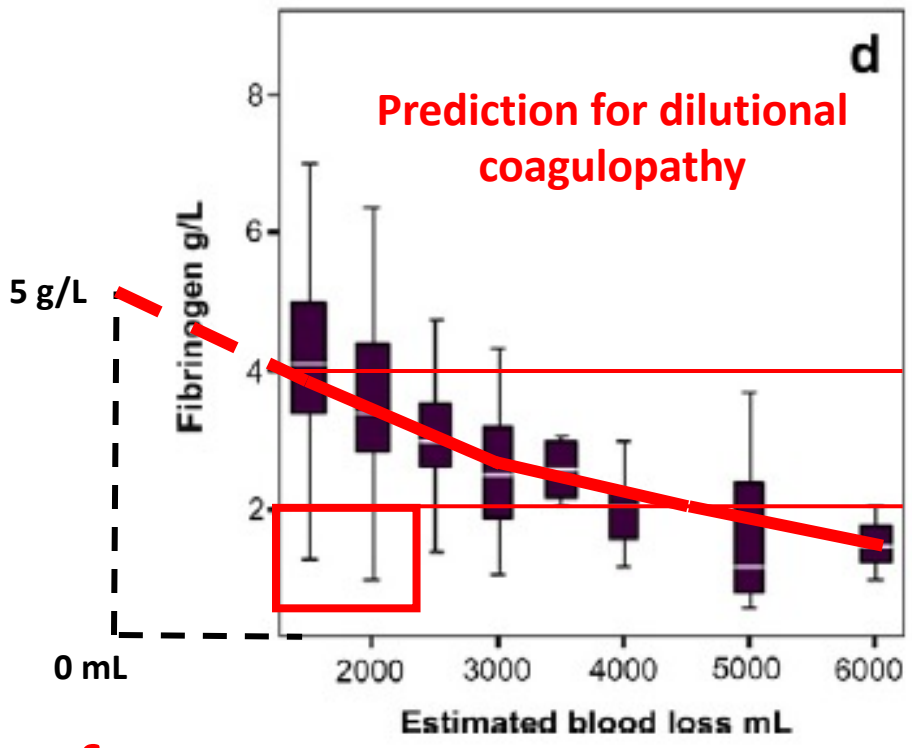
Bleed volume (mL)

Non-pregnant normal range

Standard haemostatic tests following major obstetric haemorrhage

L. de Lloyd,[a] R. Bovington,[b] A. Kaye,[c] R.E. Collis,[a] R. Rayment,[b] J. Sanders,[c] A. Rees, P.W. Collins[b]

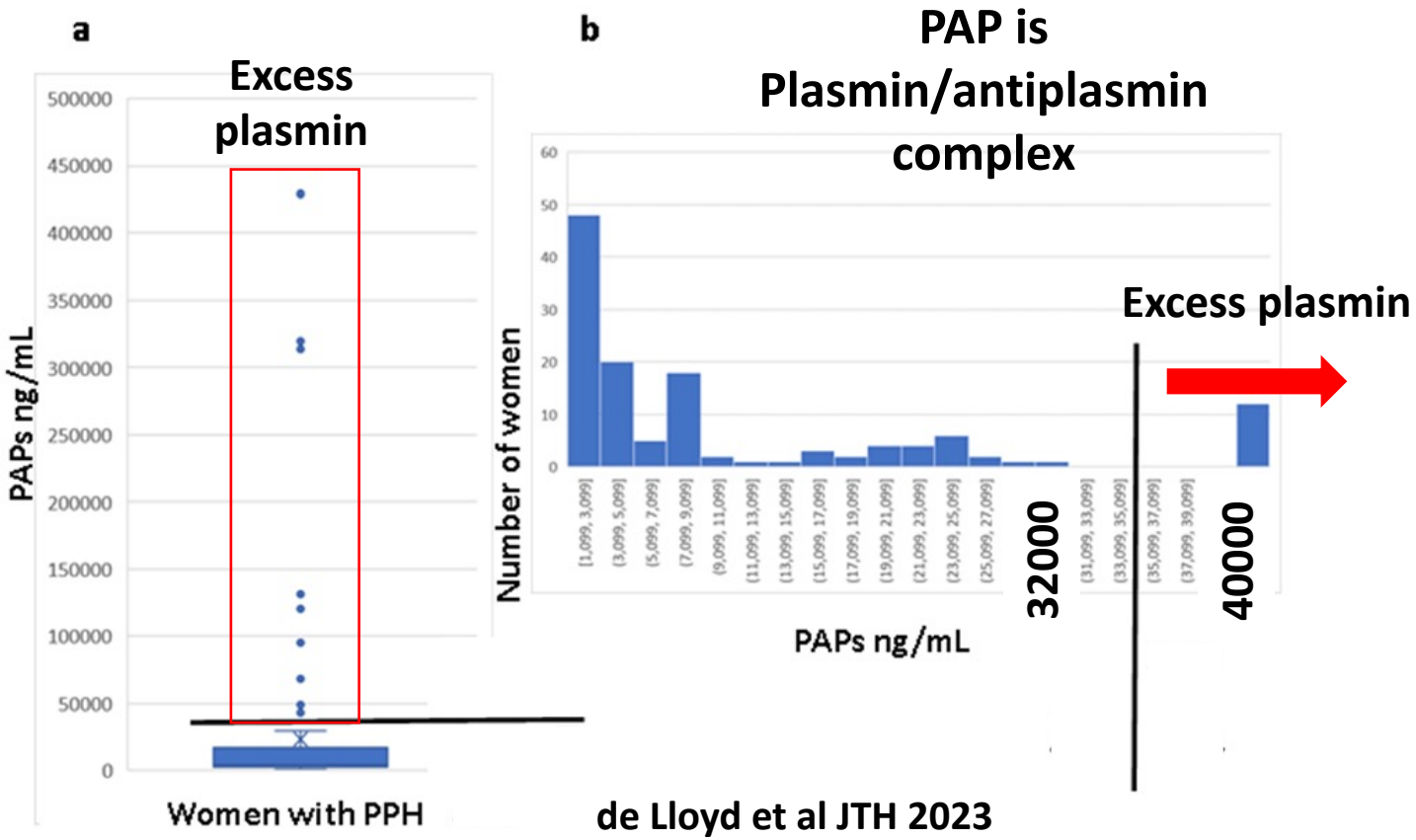
International Journal of Obstetric Anesthesia (2011) 20, 135–141



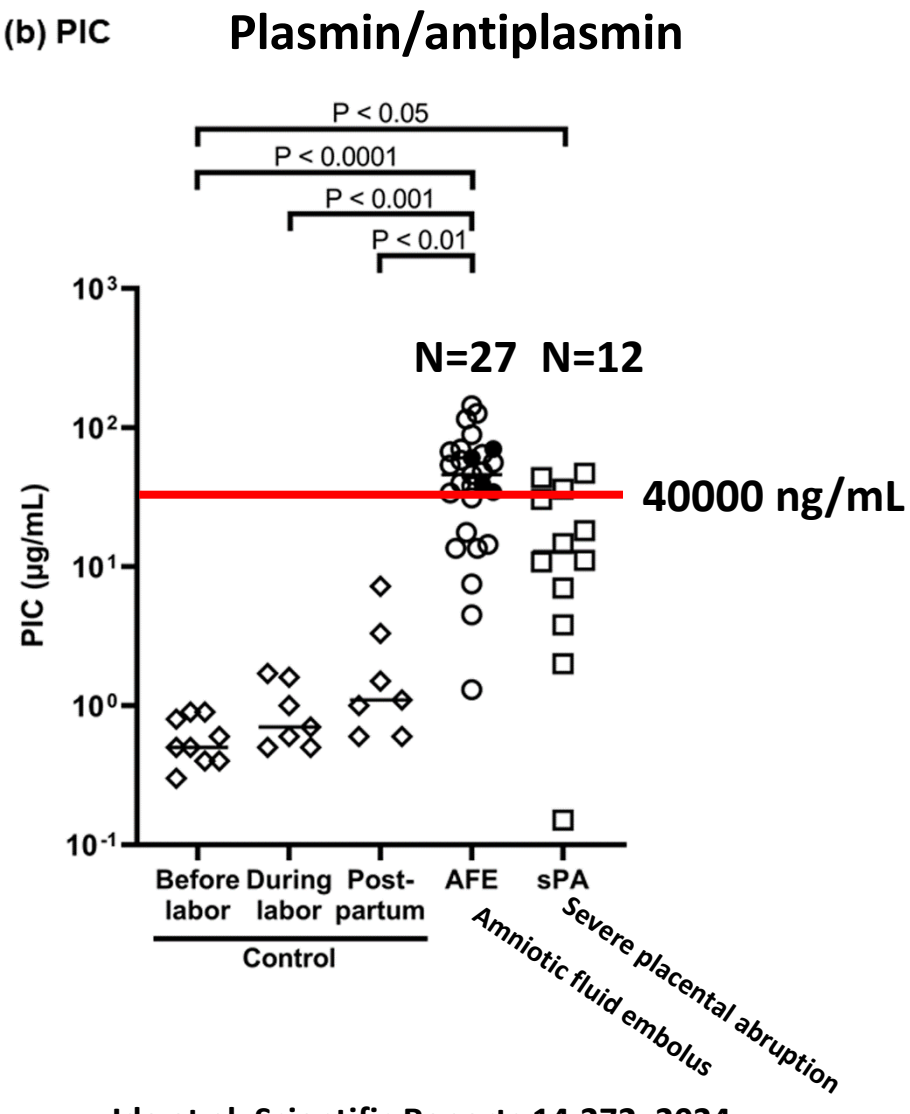
Consumption/loss of functional fibrinogen

Lab guided replacement to maintain fibrinogen >1g/L

Cases of massive fibrinolysis in PPH



de Lloyd et al JTH 2023



Acute obstetric coagulopathy (AOC) N=12

Plasmin/antiplasmin complex >40000 ng/ml

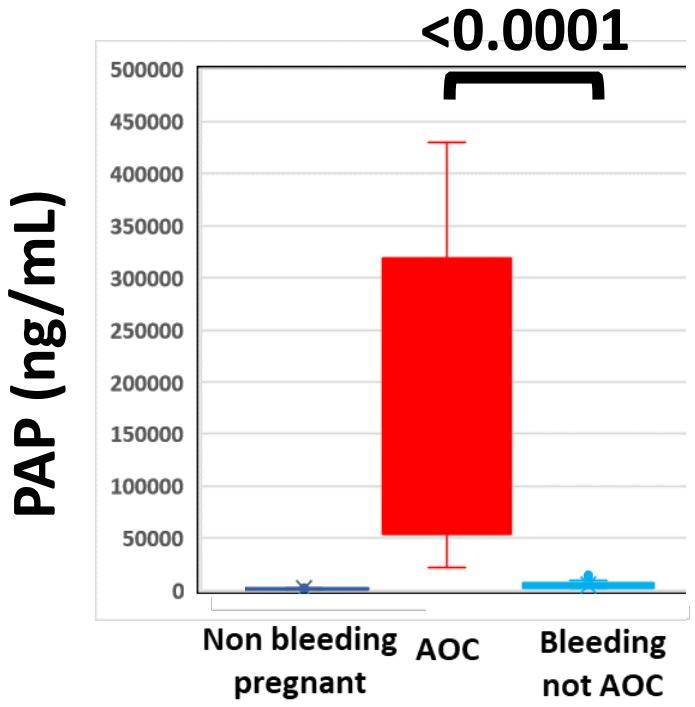
Ide et al. Scientific Reports 14:272, 2024

Clinical features of acute obstetric coagulopathy

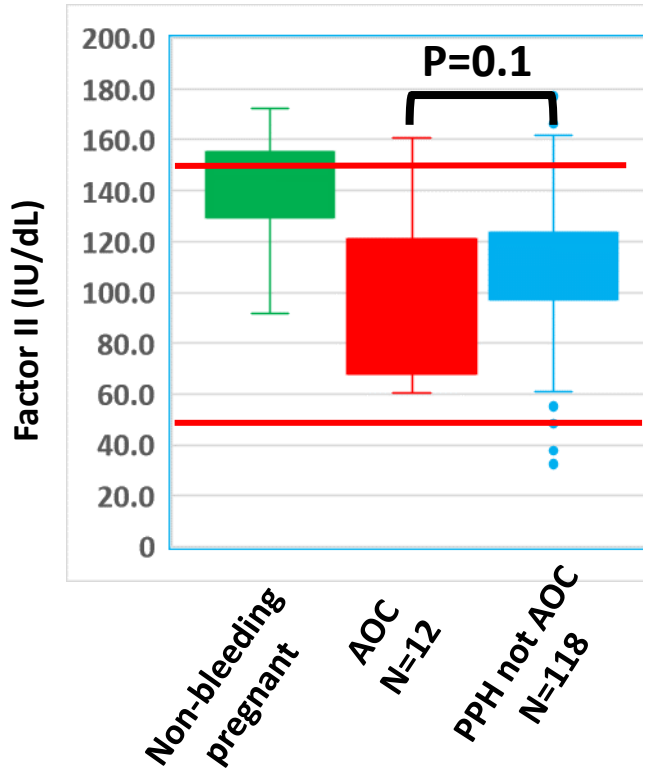
- N=12
  - 2.5% of postpartum haemorrhage
  - 1.5/1000 of all maternities
    - About 1300 case per year in the UK
    - About 150 cases per year in Sweden
- Delivery
  - C section N=6
  - Vaginal N=6
- Cause
  - Abruption: N=5 (42%)
  - AFE/coagulopathy of unknown cause: N=2 (17%)
  - Atony, surgical, retained placenta, praevia: N=5 (42%)
  - Sepsis: N=0/12
- Fetal or neonatal death: 6/12 (50%)
  - Postpartum haemorrhage without AOC 2/506 (0.4%)

Acute obstetric coagulopathy: thrombin

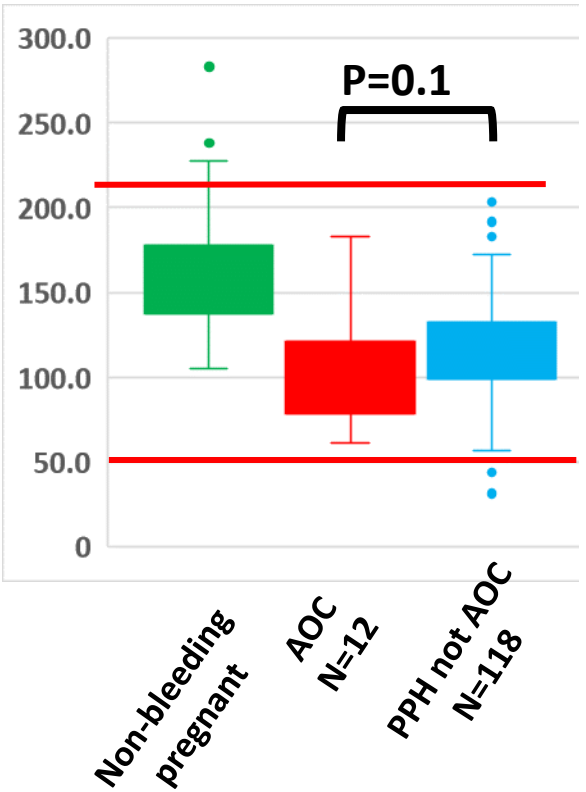
Excess plasmin



Factor II no change



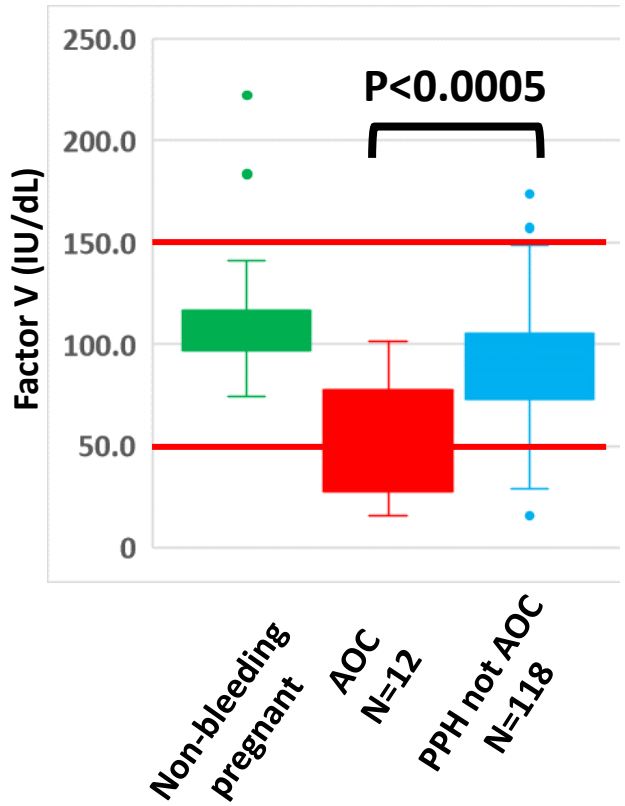
Factor X no change



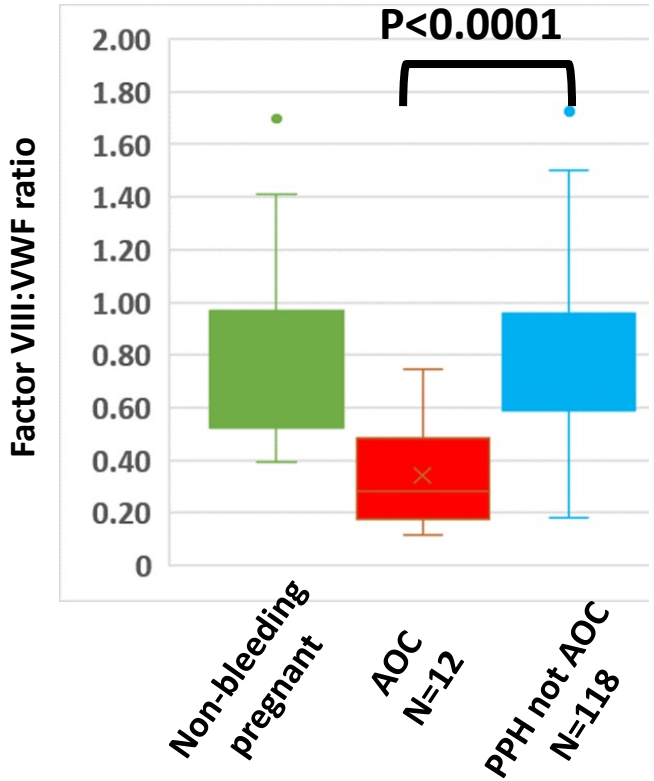
Non-pregnant normal range

Acute obstetric coagulopathy: FV and FVIII

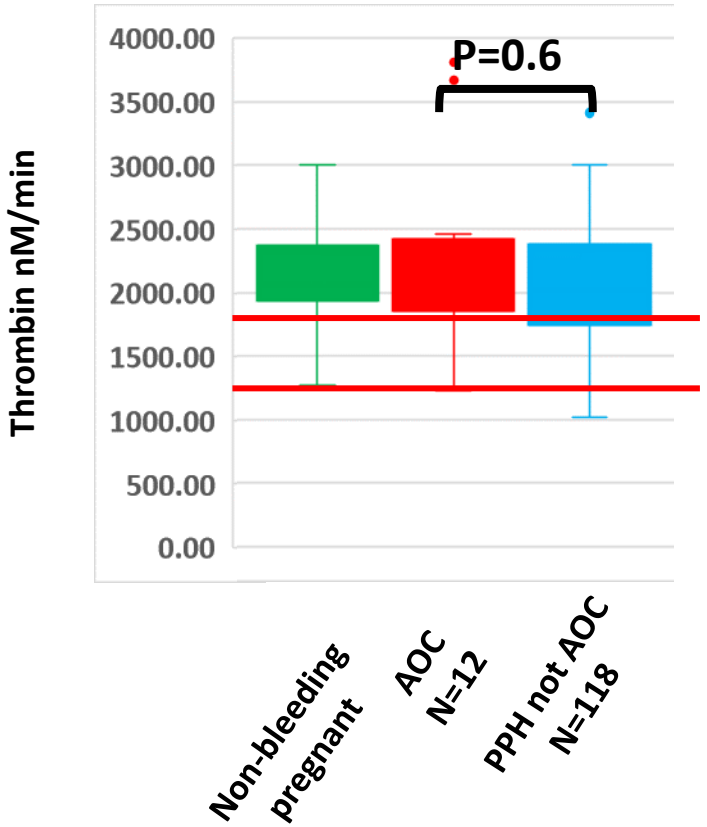
Factor V depleted



Factor VIII depletion FVIII:VWF ratio



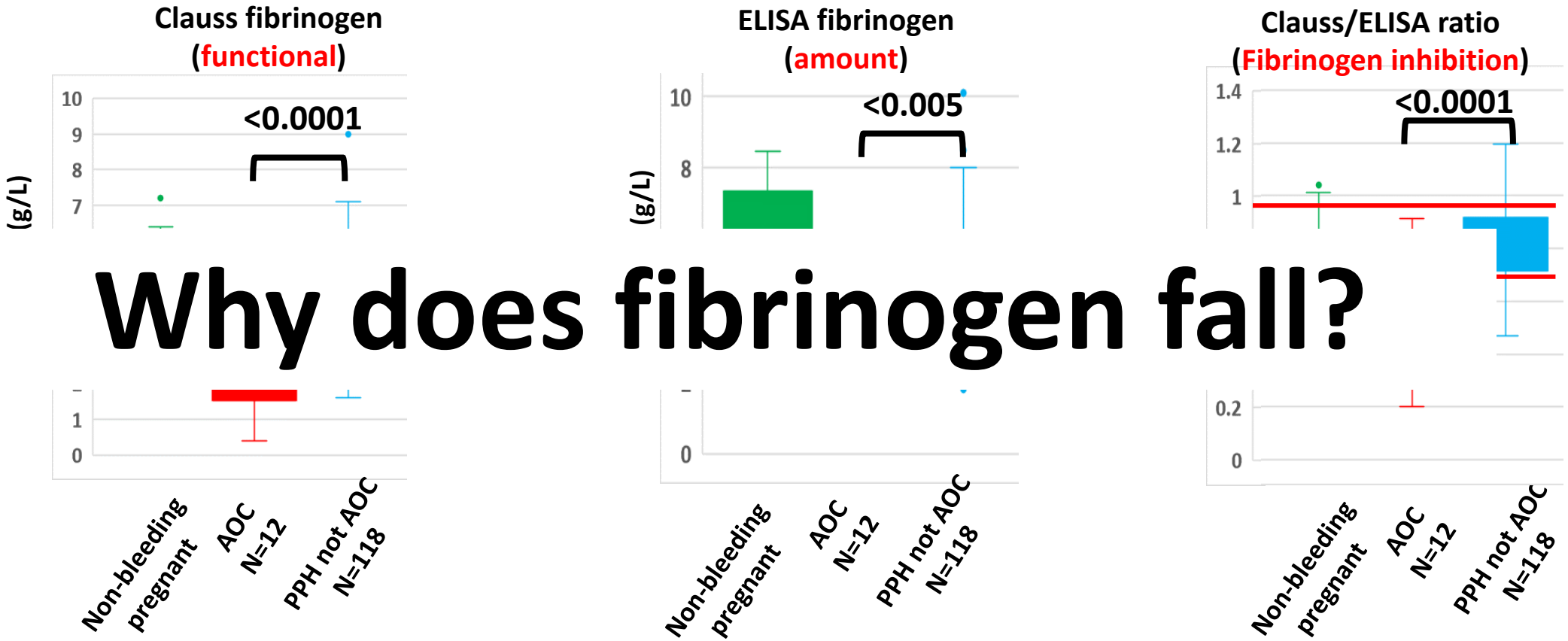
Thrombin generation (ETP) No change



Non-pregnant normal range

Limited role for FFP or rFVIIa in acute obstetric coagulopathy

Acute obstetric coagulopathy: fibrinogen



Why does fibrinogen fall?

Functional fibrinogen critically low

Amount of fibrinogen reduced but not low

Dysfibrinogenaemia
Fibrinogen function inhibited

Non-pregnant normal range

blood advances

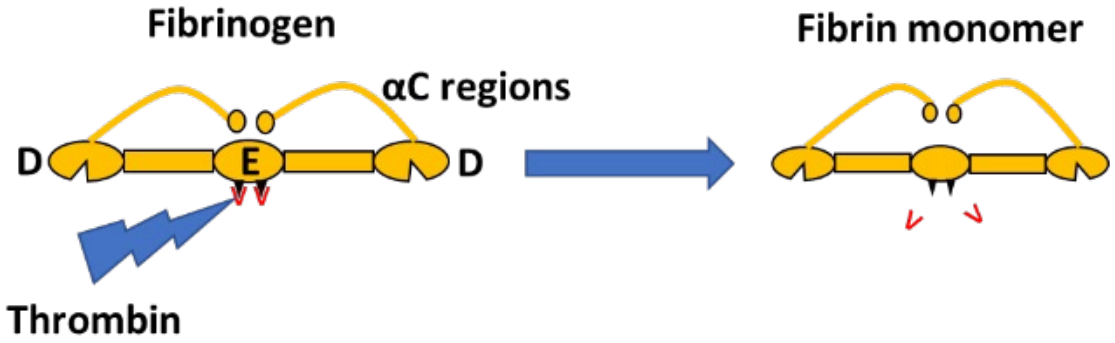
RESEARCH ARTICLE | FEBRUARY 6, 2025

Acute obstetric coagulopathy is associated with excess plasmin generation and proteolysis of fibrinogen and factor V

Peter W Collins ✉, Claire S Whyte, Lucy de Lloyd, Anuj Narwal, Sarah F Bell, Nicholas Gill, Rachel E Collis, Peter V Jenkins, Nicola J Mutch

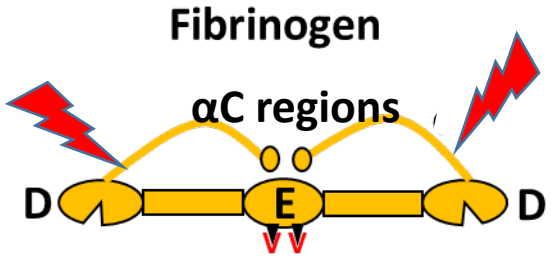
https://ashpublications.org/bloodadvances/article/doi/10.1182/bloodadvances.2024015514/535486

Fibrin clot formation and fibrinolysis



Adapted from Weisel and Dempfle, Fibrinogen Structure and Function in Hemostasis and Thrombosis ed 6 2013.

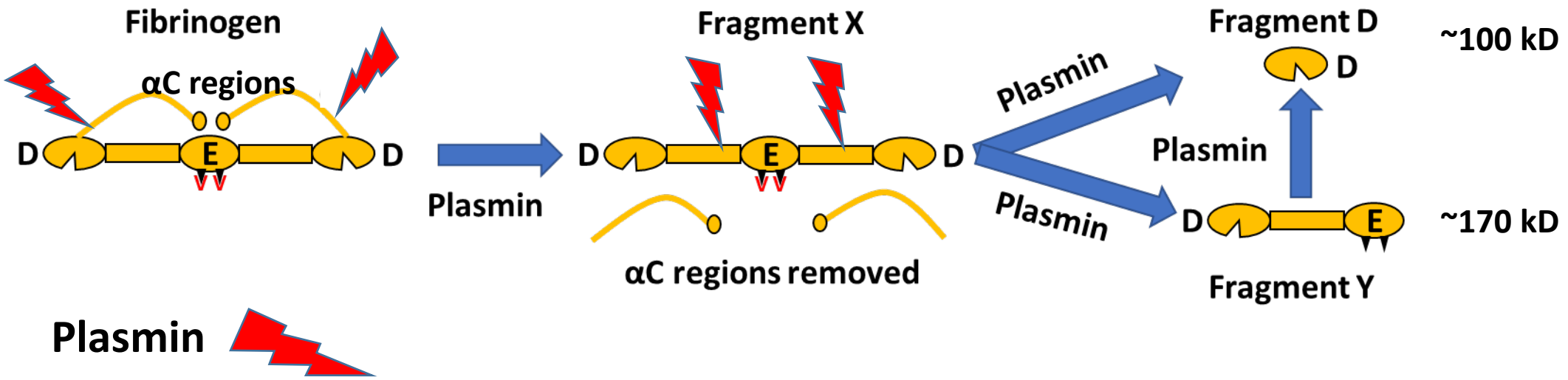
Acute obstetric coagulopathy: Excess dysregulated plasmin



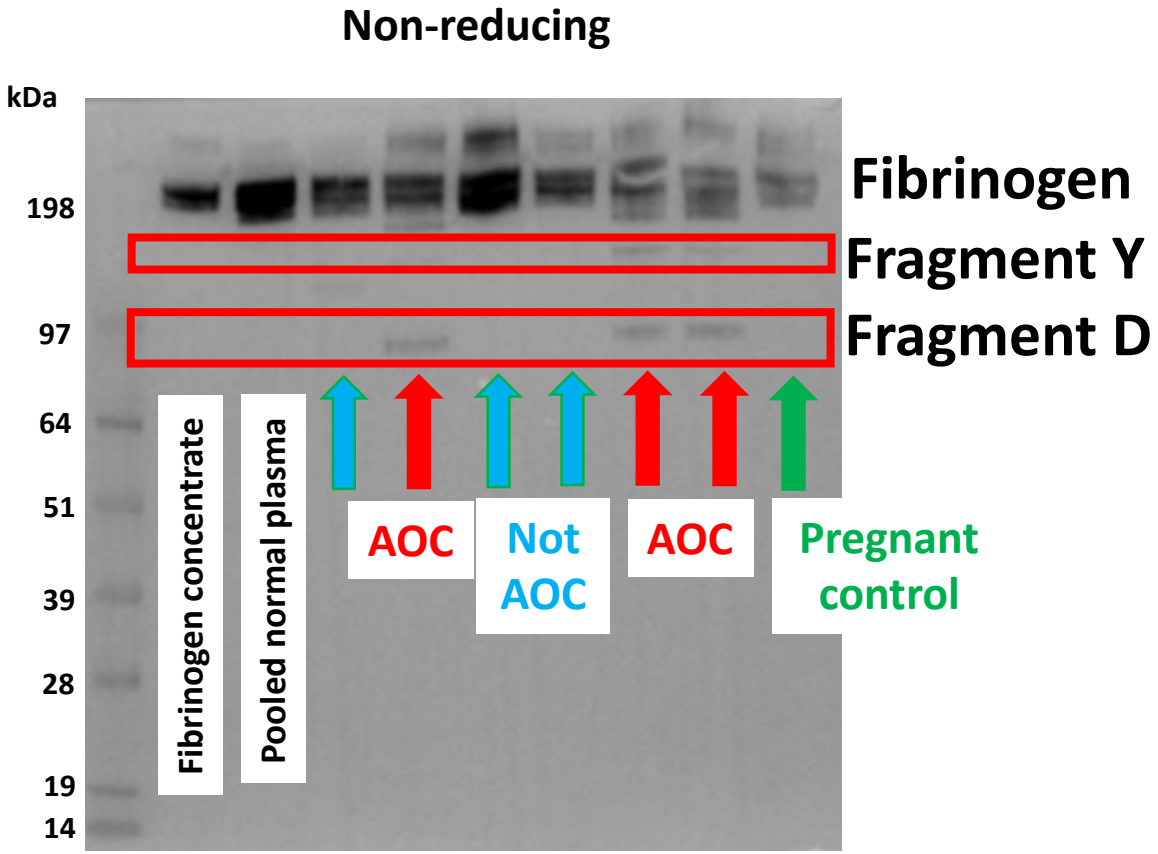
Plasmin

Acute obstetric coagulopathy: Excess dysregulated plasmin

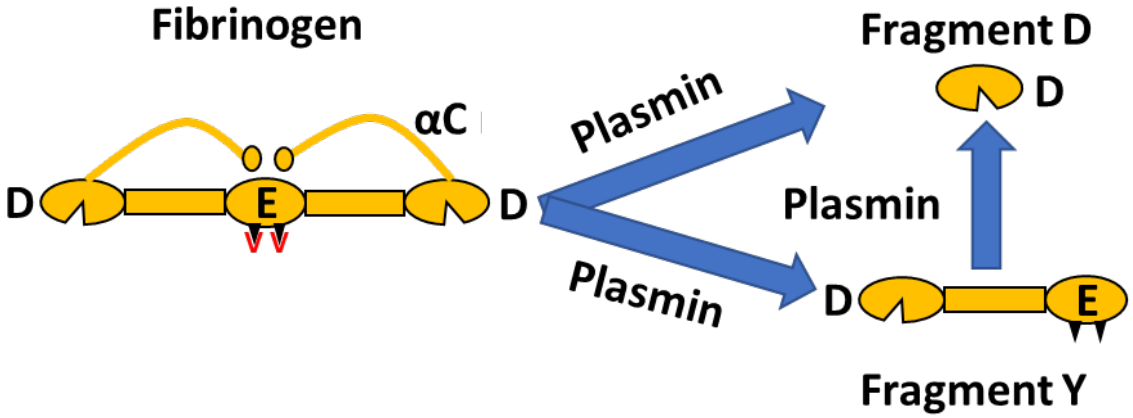
Fibrinogenolysis



Fibrinogen breakdown products in AOC



AOC: acute obstetric coagulopathy
Not AOC: severe PPH without AOC
Pregnant control before elective c section
Representative gel

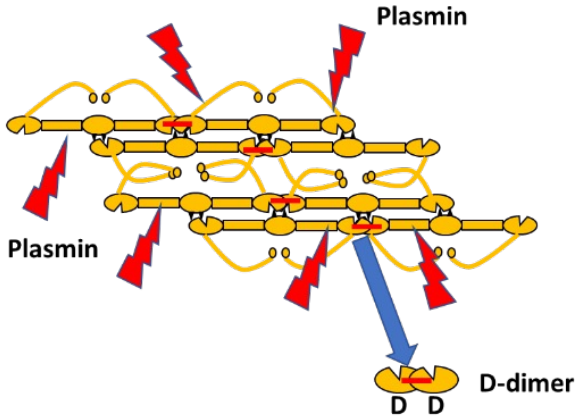


Confirms plasmin-mediated breakdown of fibrinogen in the circulation

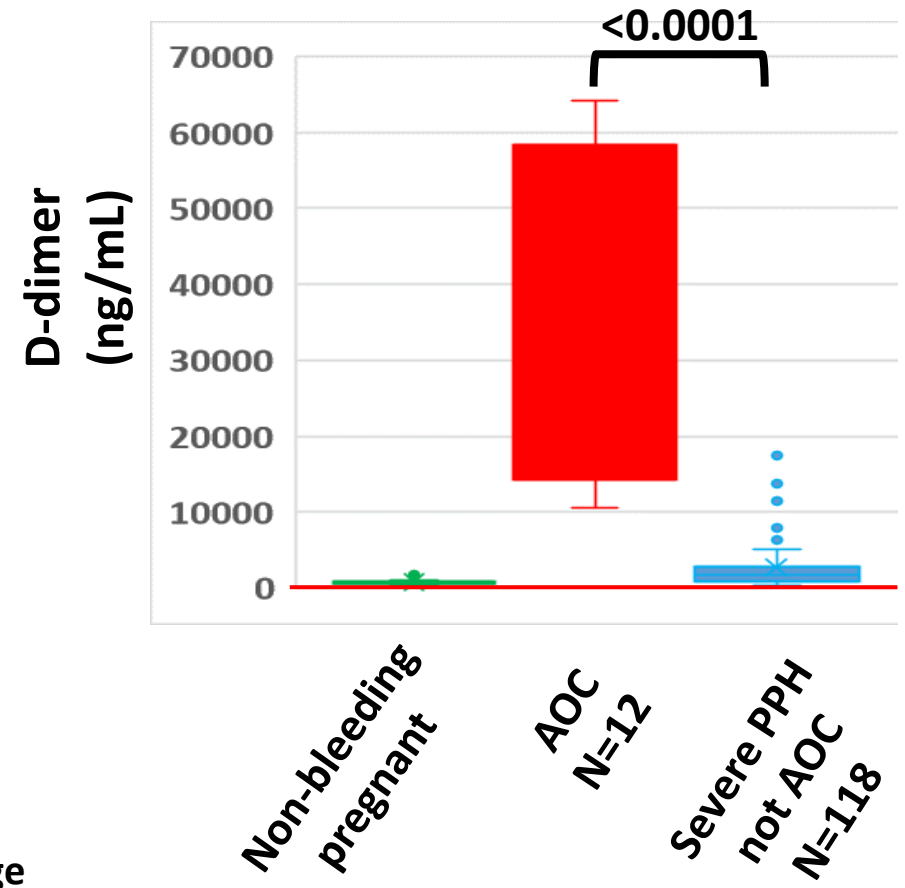
Mechanism for early reduction in fibrinogen

Acute obstetric coagulopathy: fibrinolysis

Confirms hyperfibrinolysis



D-dimer



Non-pregnant normal range

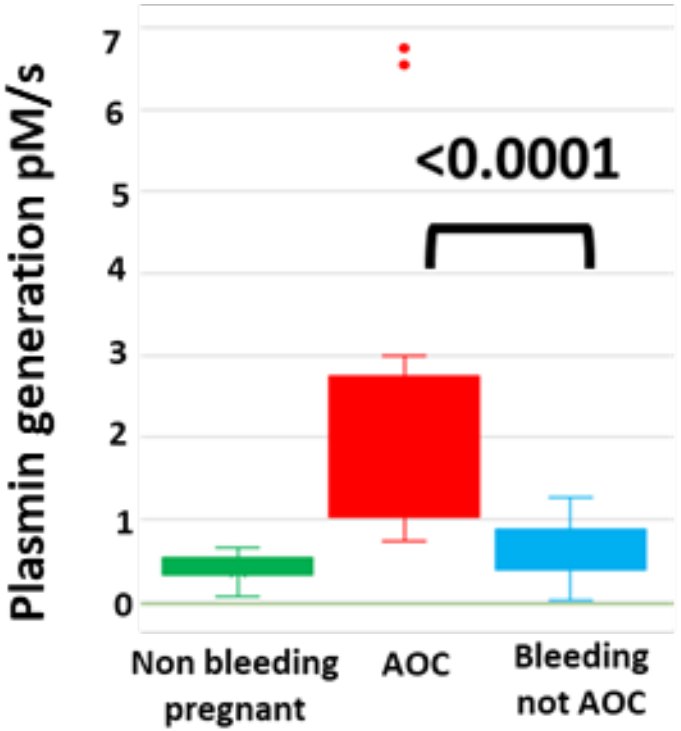
Ide et al. Scientific Reports 14:272, 2024

	D-dimer ng/mL Median (range)
Non-bleeding pregnant controls	1,900 (1400-3100)
Amniotic fluid embolus	300,000 (4000-1,484,000)
Placental abruption with DIC	107,900 (9,700-490,000)

Why does fibrin/fibrinogenolysis become dysregulated?

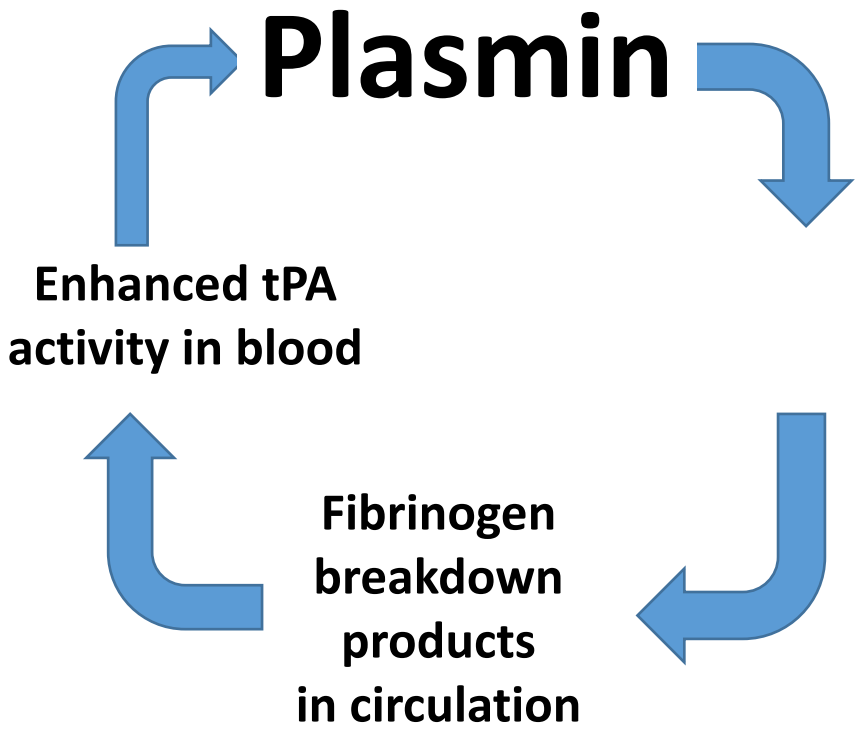
Enhanced plasmin generation in AOC

Ability of blood to make plasmin

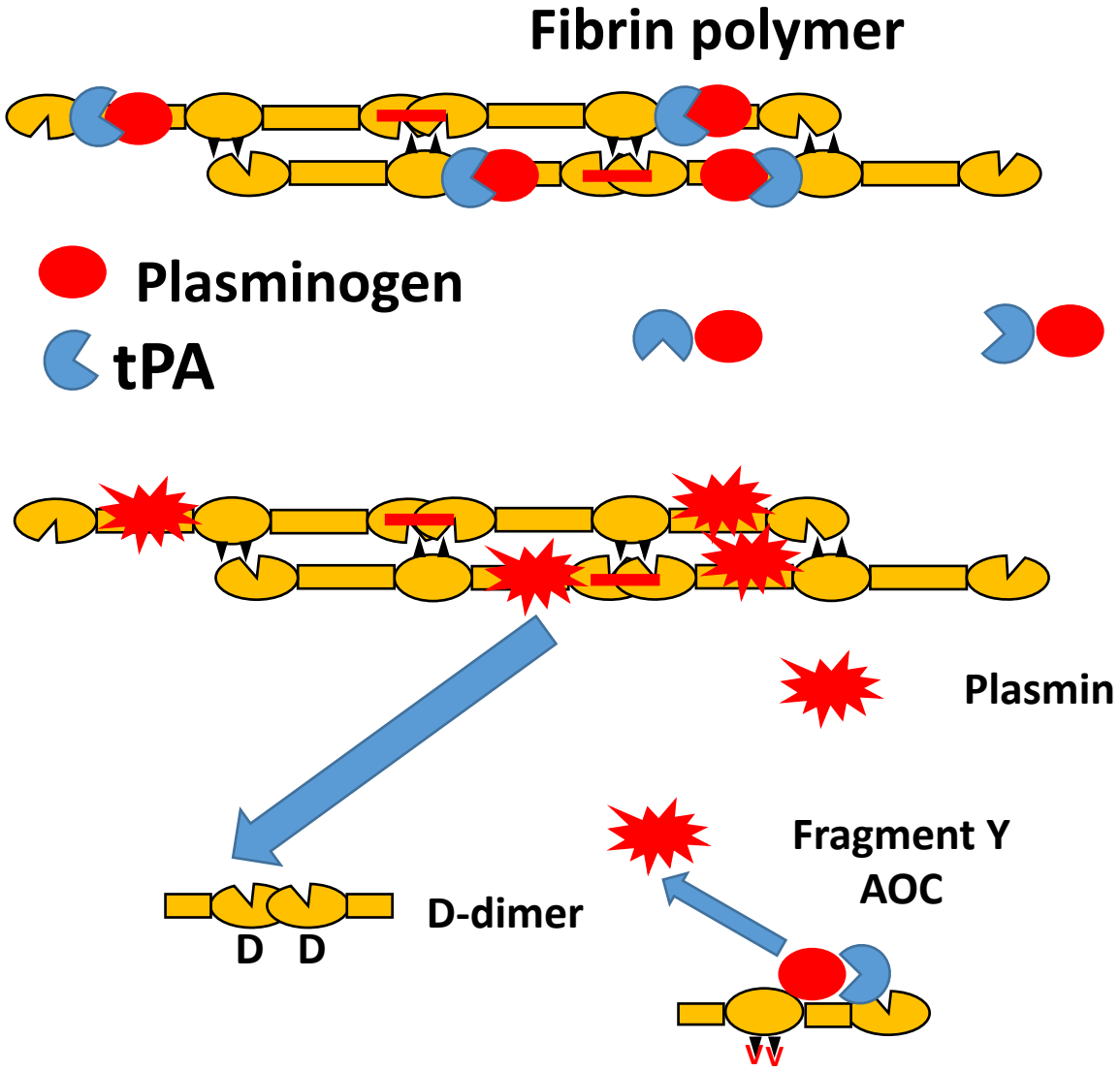


tPA added to patient samples and plasmin generation measured

Possible positive feedback loop

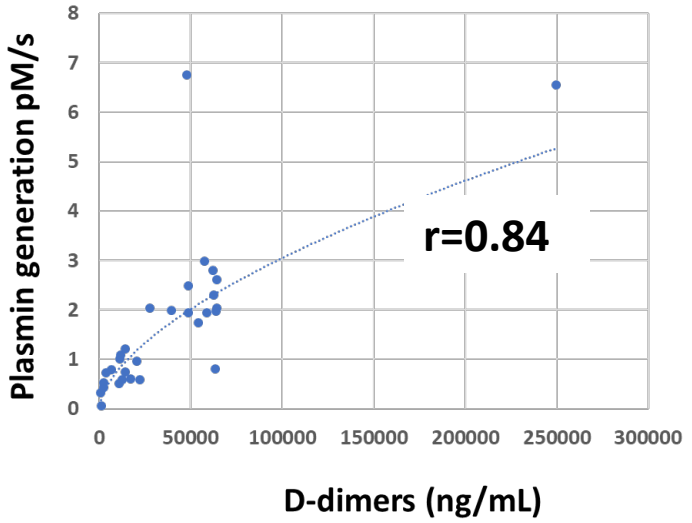


Enhanced plasmin generation in AOC

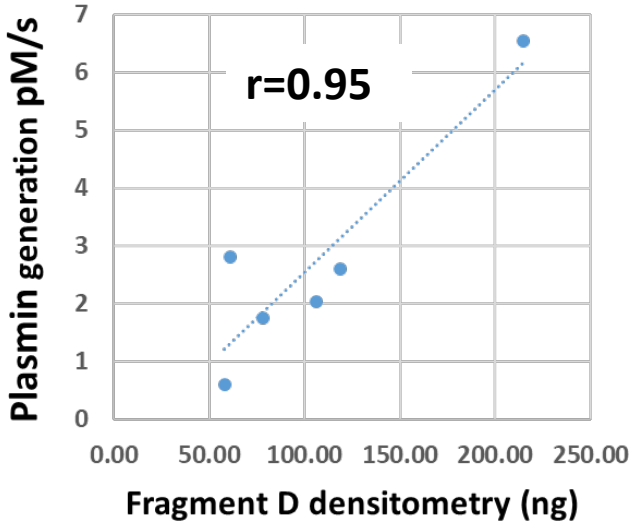


Potential mechanism

Fibrin and fibrinogen degradation products in the blood enhance tPA through cofactor activity

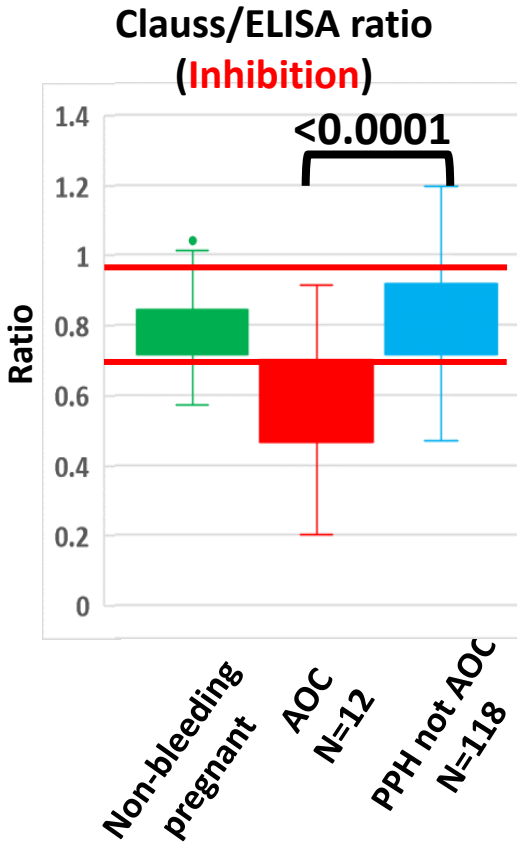


Measure of <u>fibrin</u> breakdown products

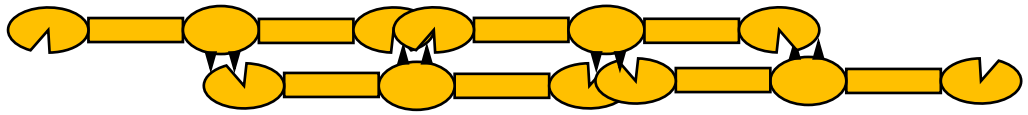


Measure of <u>fibrinogen</u> breakdown products

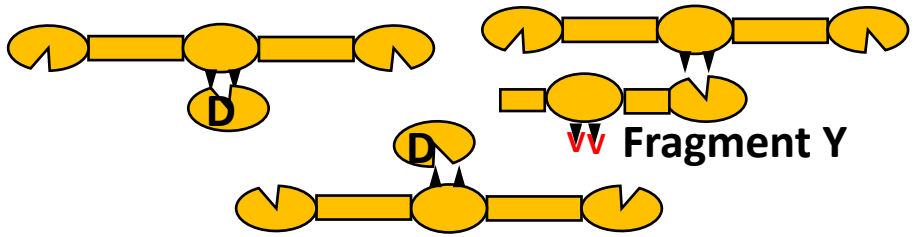
Potential mechanism for fibrinogen inhibition in AOC



Fibrinogen function inhibited



Normal fibrin polymerisation



Inhibition of fibrin polymerisation

Latallo ZS, et al. Inhibition of thrombin and of fibrin polymerization, two activities derived from plasmin-digested fibrinogen. *Nature* 1964;203(4950):1184-85.

Williams JE, Hantgan RR, Hermans J, et al. Characterization of the inhibition of fibrin assembly by fibrinogen fragment D. *Biochemical Journal* 1981;197(3):661-68.

Fibrinogen replacement: mathematical modeling

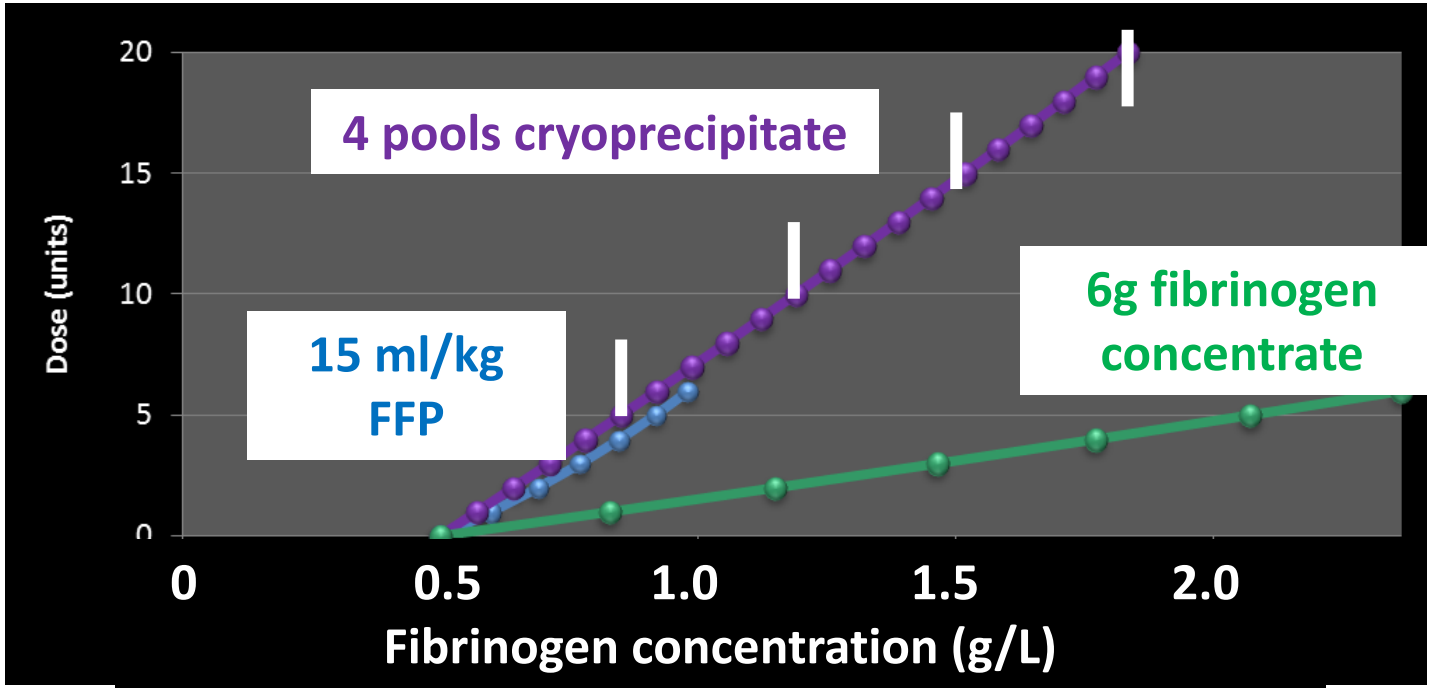
Target in severe PPH is >2 g/L

Severe acute obstetric coagulopathy

60 kg woman

Placental abruption

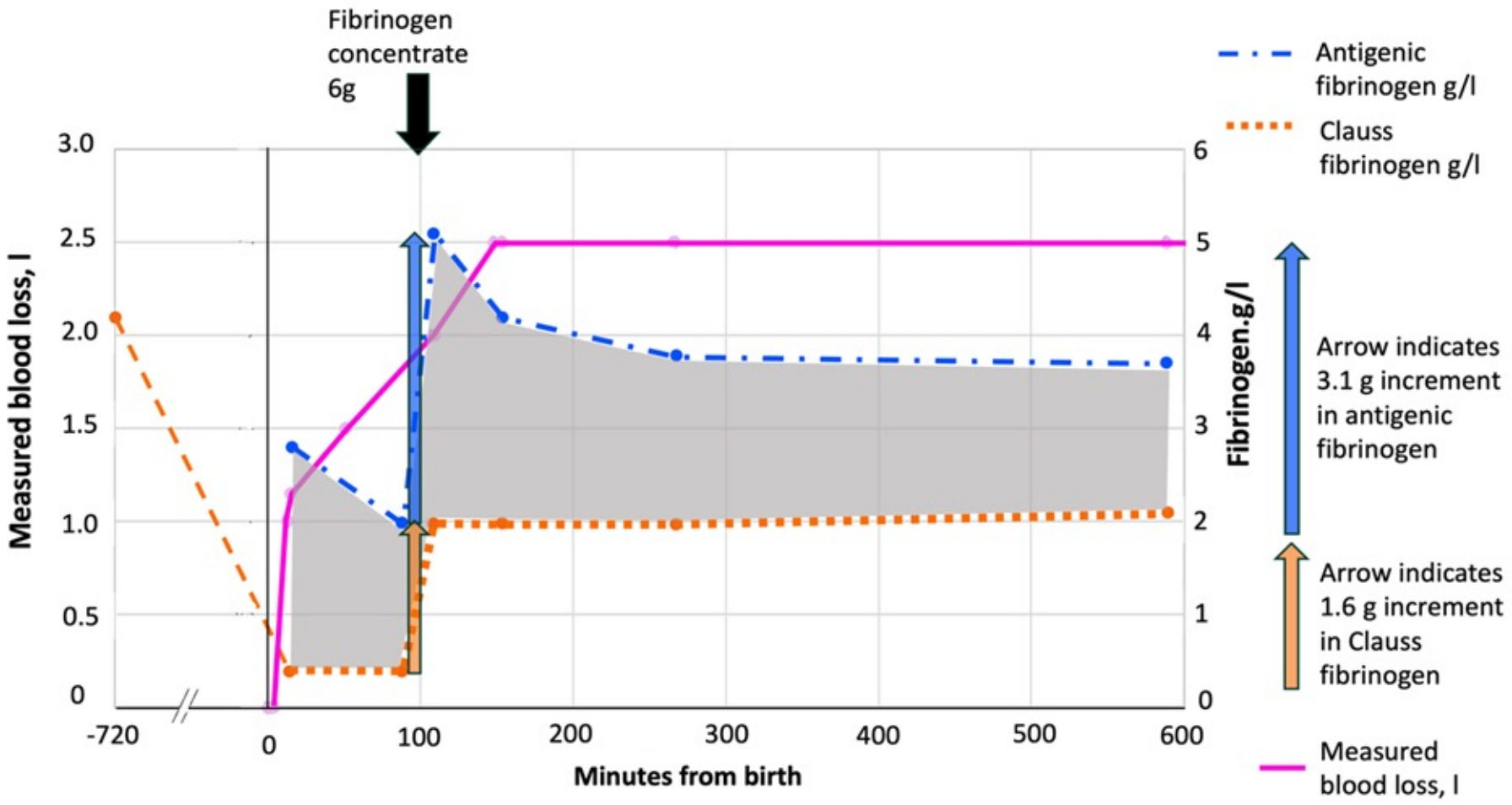
Fibrinogen 0.5 g/L



Does fibrinogen inhibition affect infused fibrinogen?

Calculated response based on BJA 113:585-595, 2014

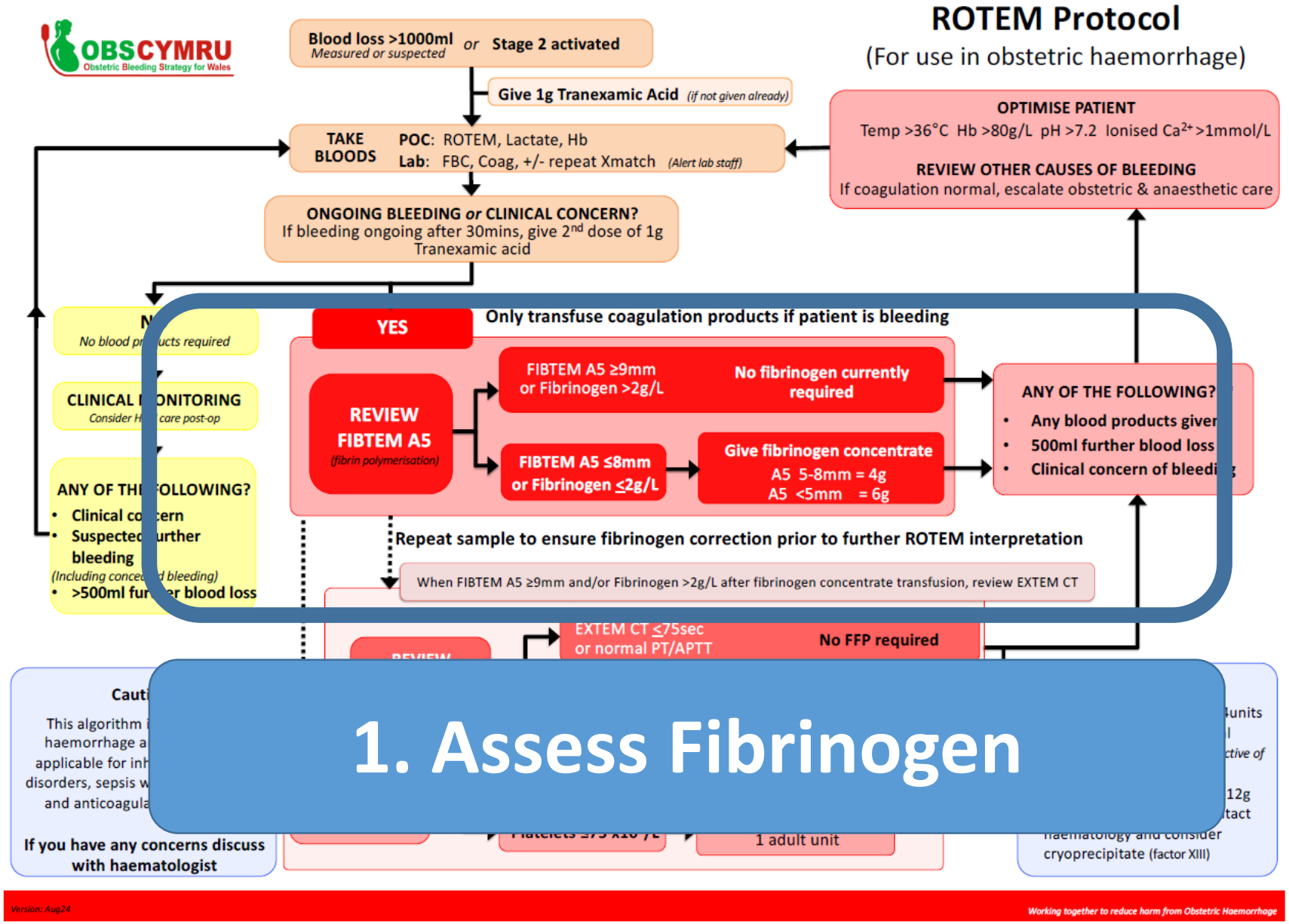
Case of severe acute obstetric coagulopathy



Fibrinogen <u>amount</u> increased by 3.1 g/L

Fibrinogen <u>function</u> increased by 1.6 g/L

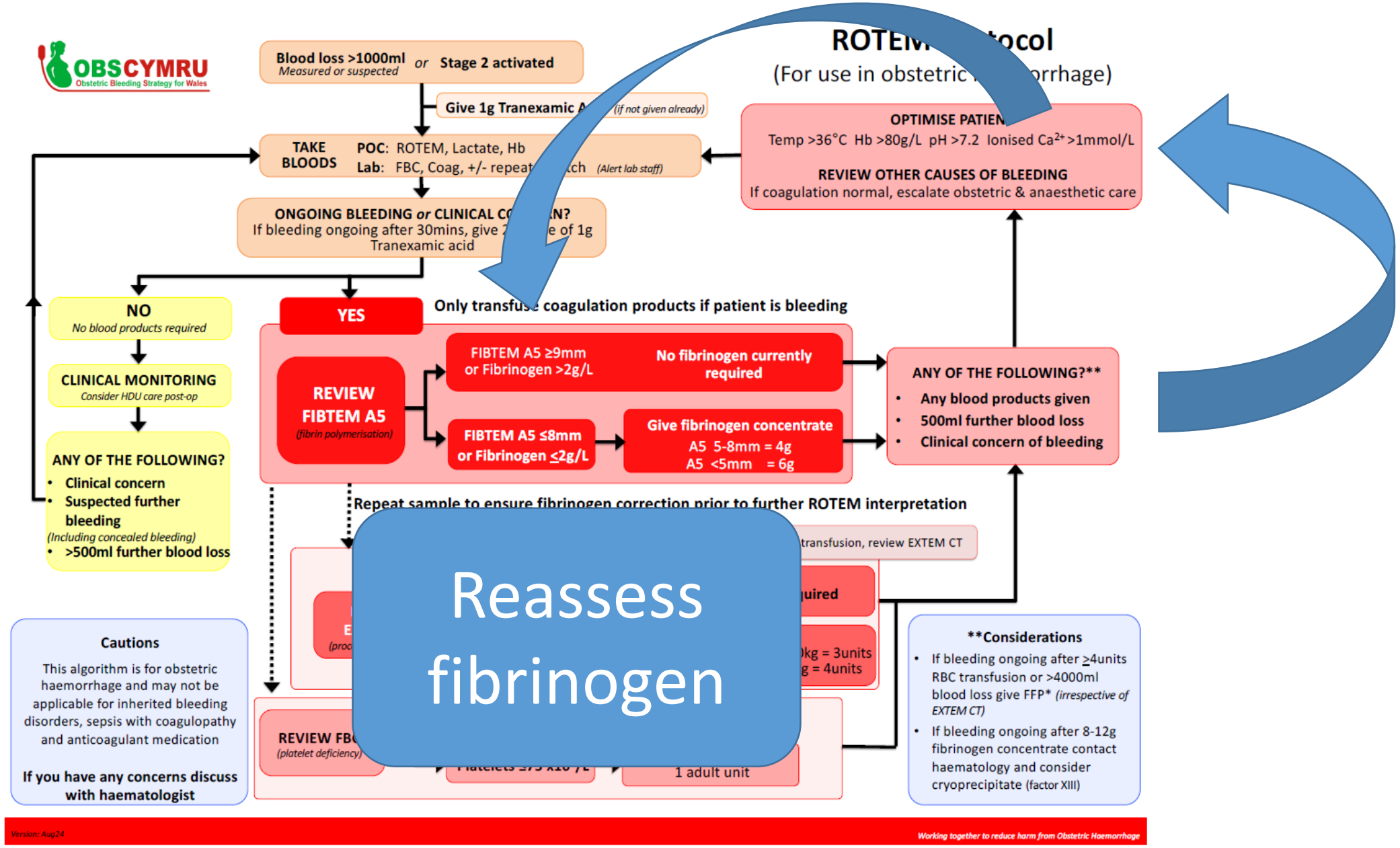
About half the fibrinogen was inhibited

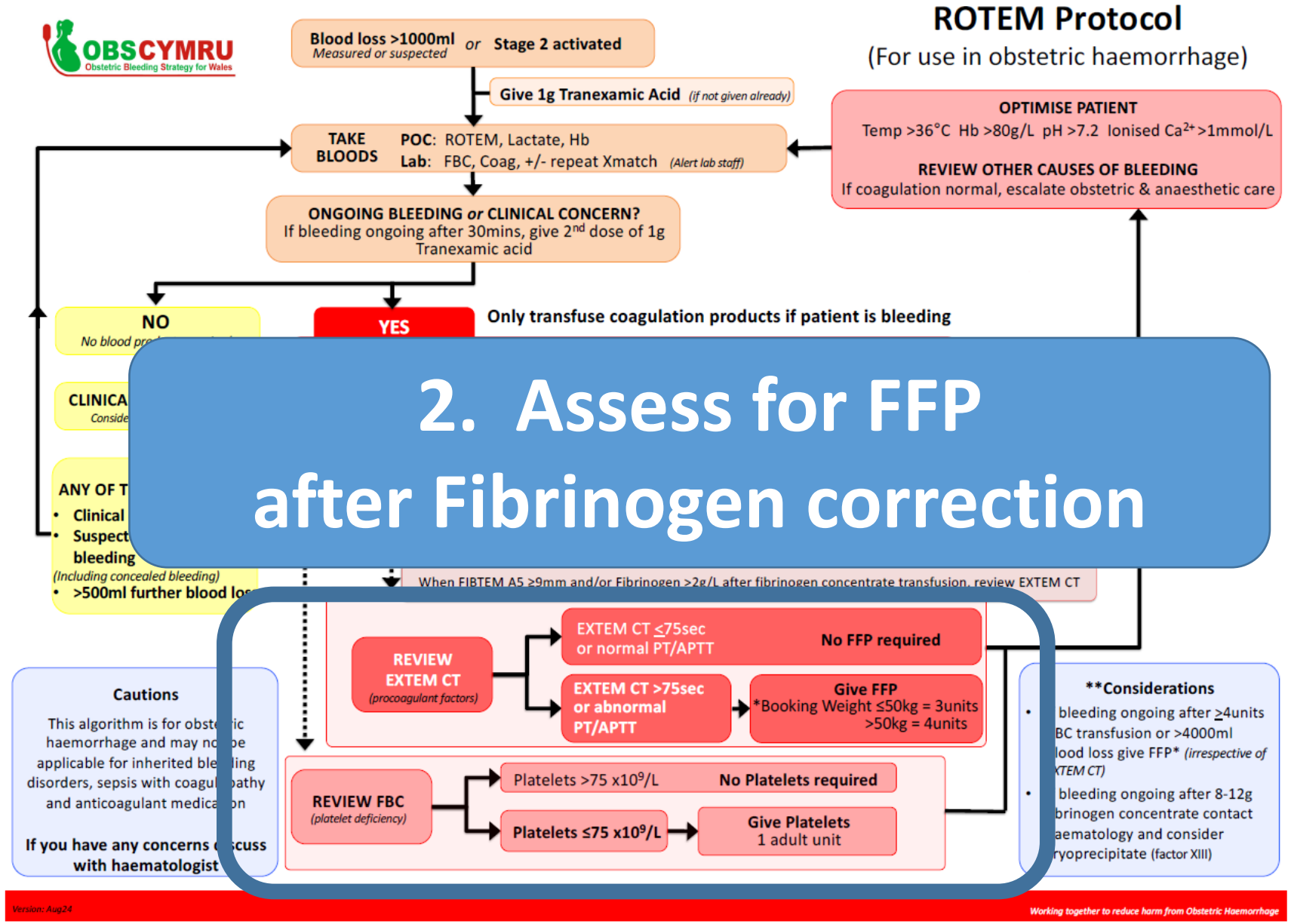


1. Assess Fibrinogen

Fibrinogen concentrate
4-6 g

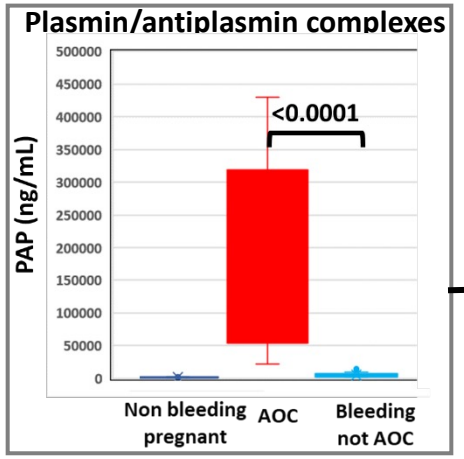
Cryoprecipitate
3 pools
4 pools


OBSCYMRU
Obstetric Bleeding Strategy for Wales
ROTEM protocol
(For use in obstetric haemorrhage)
Blood loss >1000ml
Measured or suspected
or
Stage 2 activated
Give 1g Tranexamic A
(if not given already)
TAKE BLOODS
POC: ROTEM, Lactate, Hb
Lab: FBC, Coag, +/- repeat
(Alert lab staff)
ONGOING BLEEDING or CLINICAL C
If bleeding ongoing after 30mins, give
of 1g Tranexamic acid
OPTIMISE PATIEN
Temp >36°C Hb >80g/L pH >7.2 Ionised Ca2+ >1mmol/L
REVIEW OTHER CAUSES OF BLEEDING
If coagulation normal, escalate obstetric & anaesthetic care
NO
No blood products required
CLINICAL MONITORING
Consider HDU care post-op
ANY OF THE FOLLOWING?
Clinical concern
Suspected further bleeding
(Including concealed bleeding)
>500ml further blood loss
YES
Only transfuse coagulation products if patient is bleeding
REVIEW FIBTEM A5
(fibrin polymerisation)
FIBTEM A5 ≥9mm
or Fibrinogen >2g/L
No fibrinogen currently required
FIBTEM A5 ≤8mm
or Fibrinogen ≤2g/L
Give fibrinogen concentrate
A5 5-8mm = 4g
A5 <5mm = 6g
ANY OF THE FOLLOWING?**
Any blood products given
500ml further blood loss
Clinical concern of bleeding
Repeat sample to ensure fibrinogen correction prior to further ROTEM interpretation
transfusion, review EXTEM CT
uired
kg = 3units
g = 4units
REVIEW FB
(platelet deficiency)
1 adult unit
Reassess fibrinogen
Cautions
This algorithm is for obstetric haemorrhage and may not be applicable for inherited bleeding disorders, sepsis with coagulopathy and anticoagulant medication
If you have any concerns discuss with haematologist
**Considerations
If bleeding ongoing after ≥4units RBC transfusion or >4000ml blood loss give FFP* (irrespective of EXTEM CT)
If bleeding ongoing after 8-12g fibrinogen concentrate contact haematology and consider cryoprecipitate (factor XIII)
Version: Aug24
Working together to reduce harm from Obstetric Haemorrhage



2. Assess for FFP after Fibrinogen correction

Proposed mechanisms underpinning acute obstetric coagulopathy (AOC)



? Trigger

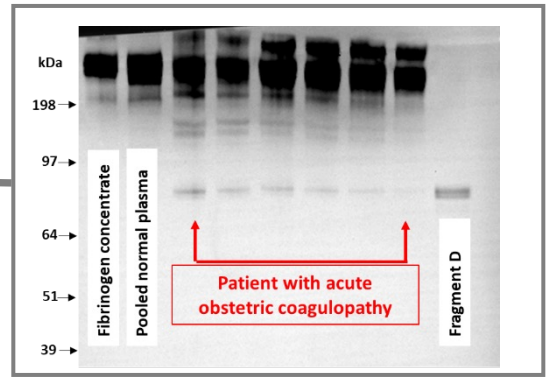
Associated with Abruption and Amniotic fluid embolus

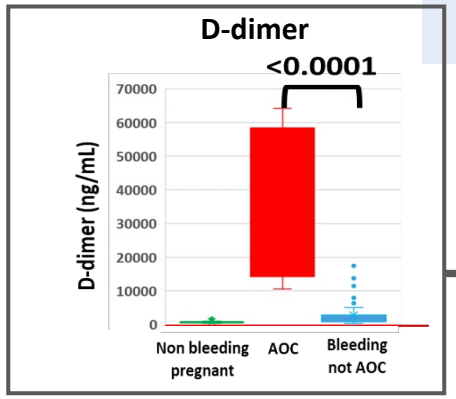
Plasmin

Positive feedback loop for plasmin generation

Excess fibrinolysis

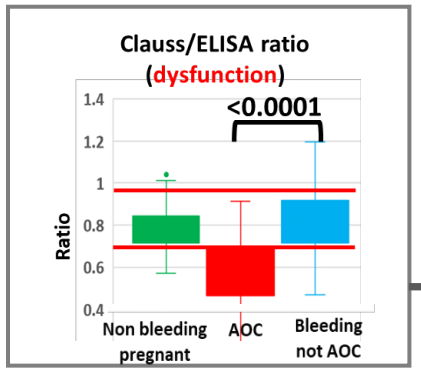
Fibrinogen proteolysis in the circulation releases fragment D





Fibrinogen and fibrin degradation products in the circulation

Clinical consequence
Rapid fall in Clauss fibrinogen exacerbates bleeding

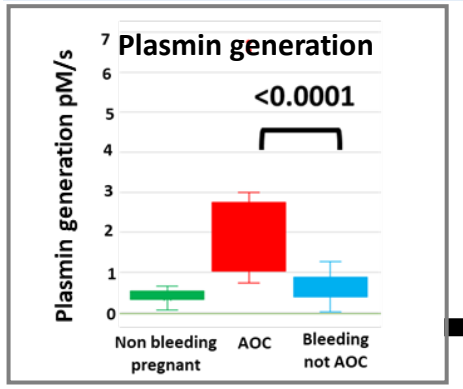


Inhibition of fibrinogen polymerisation

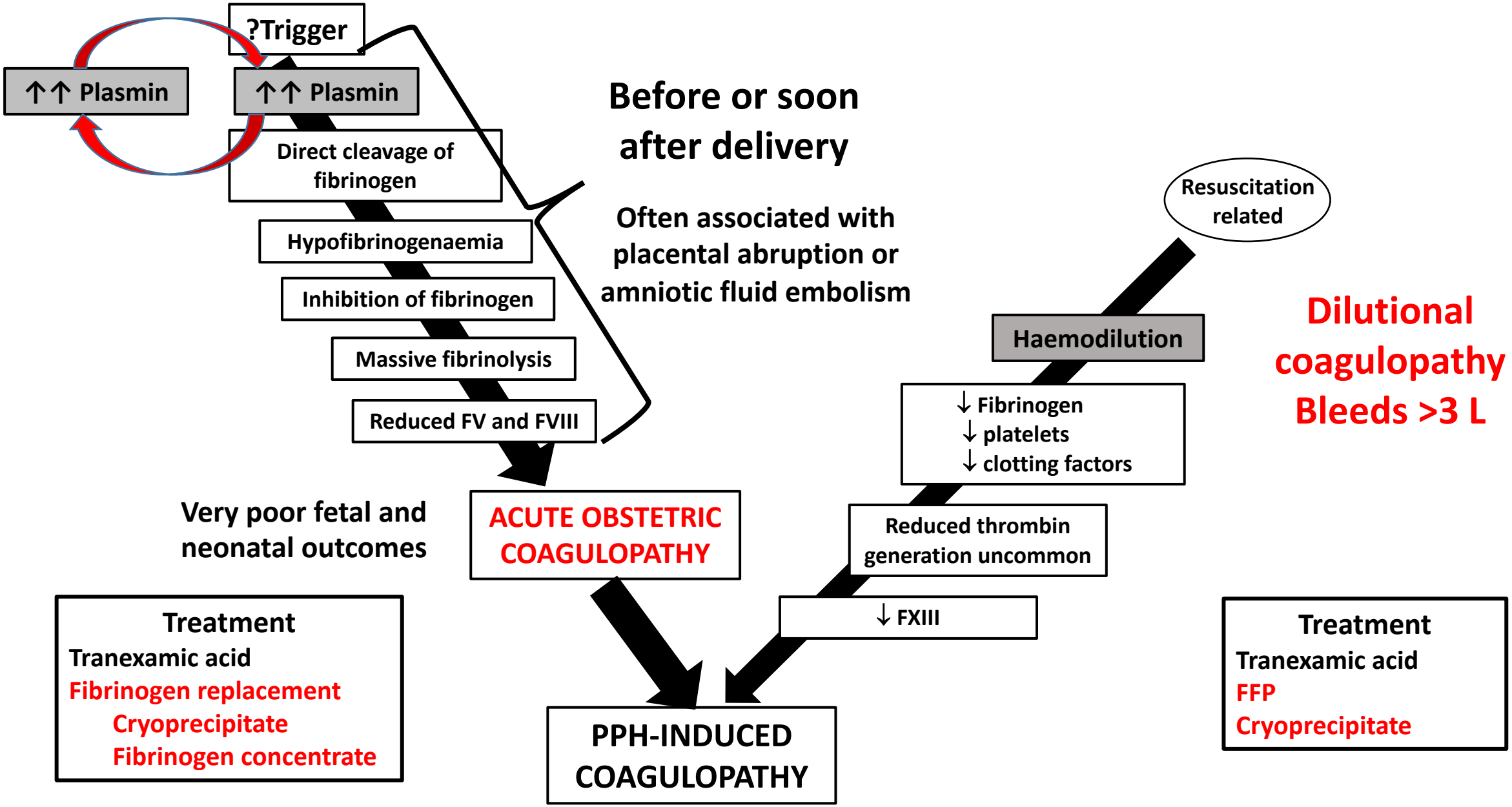
Tissue plasminogen activator cofactor activity

Inhibition of fibrinogen function

Enhanced plasmin generation



Overview of PPH-induced coagulopathy



Acknowledgments OBS plus study

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- **Cardiff**
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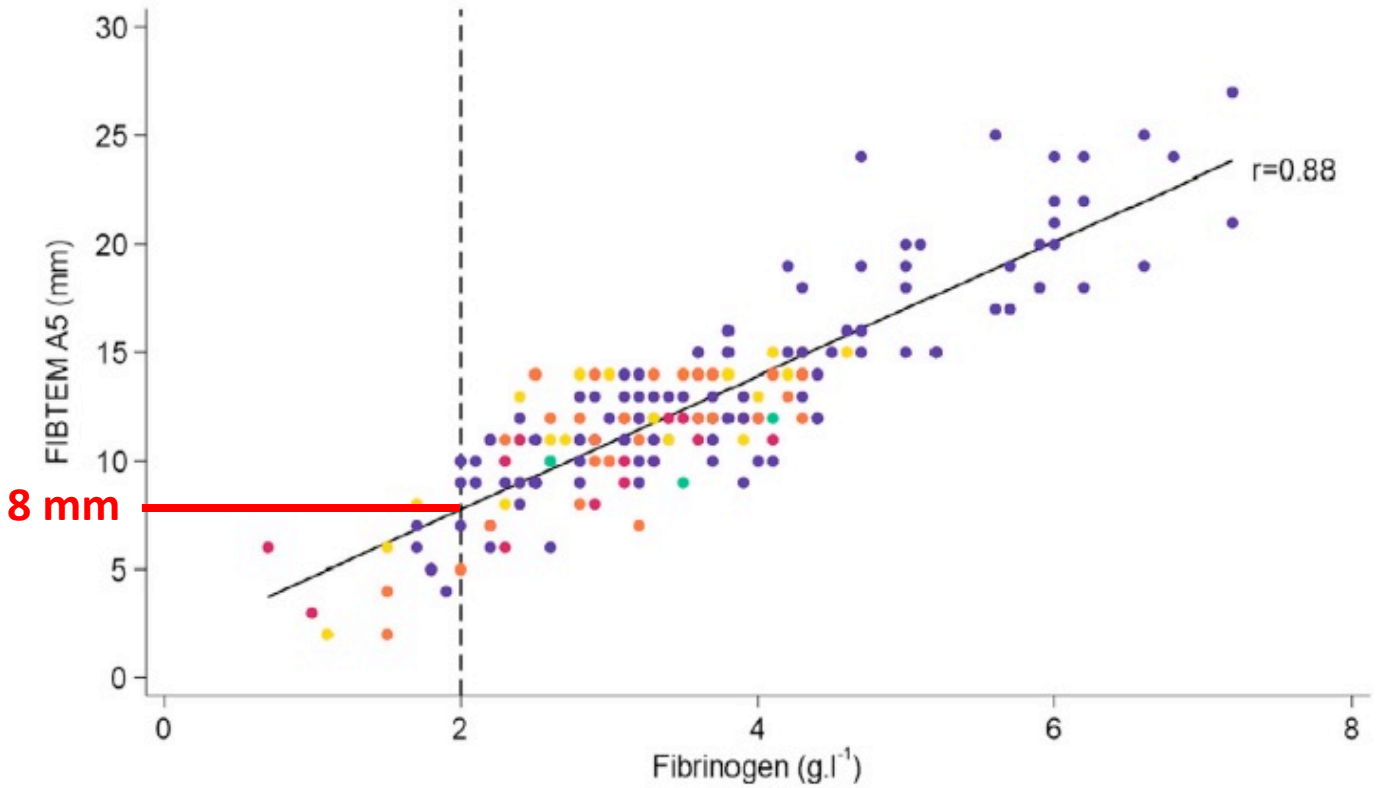
  - **Research nurse and officers: Doria Barboncheilli, Rachel Purser, Rachel Norman, Arwen Hutchings**

Anaesthesia 2025, 80, 104–106 doi:10.1111/anae.16455

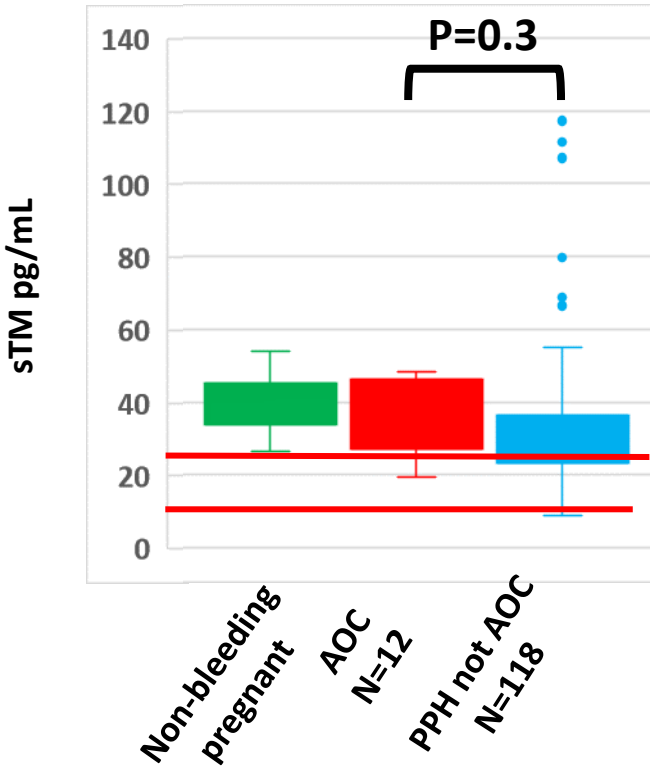
Science Letter

Relationship between the dual platelet-inhibited ROTEM® Sigma FIBTEM assay and Clauss fibrinogen during postpartum haemorrhage

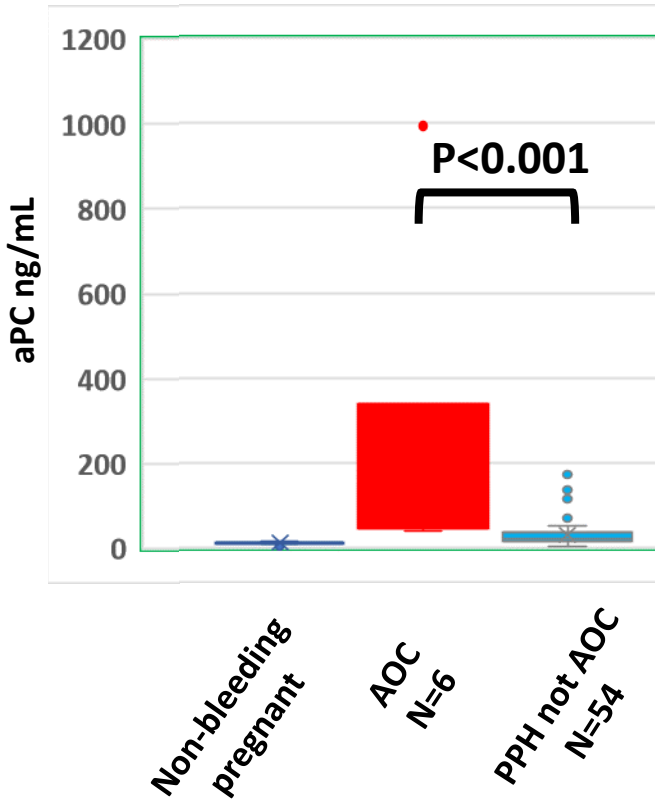


Acute obstetric coagulopathy: protein C

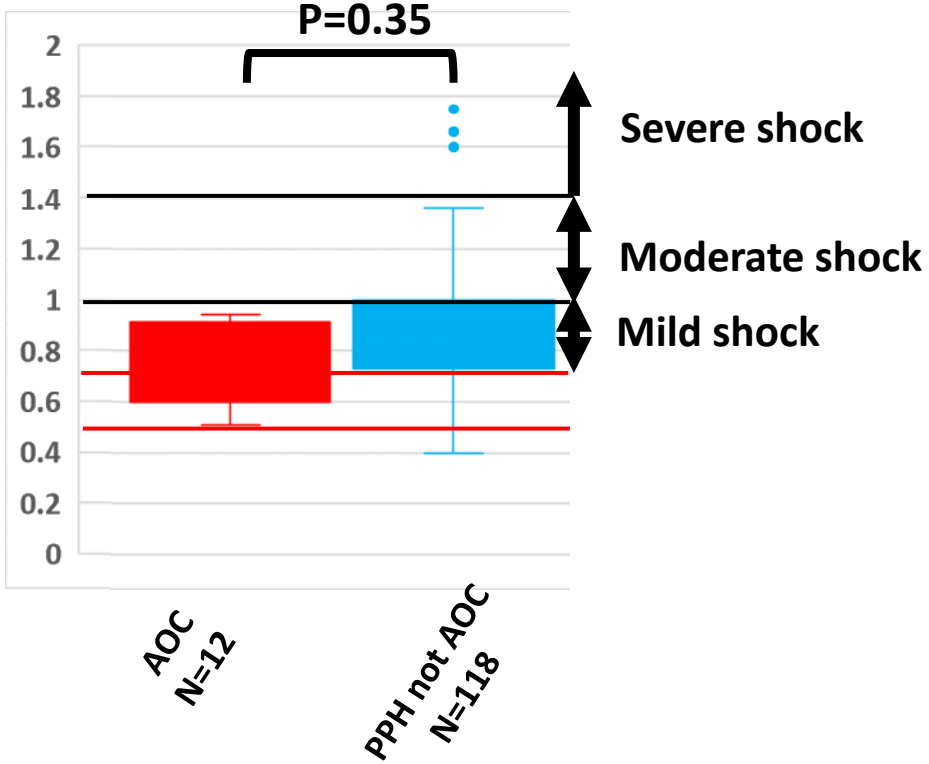
Soluble thrombomodulin



Activated protein C



Shock index*



*Heart rate/systolic BP

Non-pregnant normal range

de Lloyd et al JTH 2022