FOUNDATION FOR
Women & Girls
with Blood Disorders

Hematologic Management of Obstetric Hemorrhage

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FWGBD Uterine Hemostasis Colloquium
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Disclosures

No disclosures in prior 12 months.

Previous Disclosures:

Consultant:
CSL Behring, Octapharma, Bayer, Cerus

Speaker:
Octapharma, TEM Systems, Inc.

Honoraria:
CSL Behring, Octapharma, TEM Systems, Inc., Bayer

Research Support:
TEM Systems, Inc.

Obstetric Hemorrhage Protocols

Obstetric hemorrhage protocols recommended:

- **ACOG**: Postpartum Hemorrhage. Practice Bulletin #76, 2006
- **Joint Commission**: Preventing Maternal Death. Sentinel Event Alert 2010 44:1-4
- **RCOG:** Green-top Guidelines #52, revised 2016
- **Nat'l Partnership for Maternal Safety:** Main, et al. *Obstet Gynecol.* 2015; 126(1):155-62

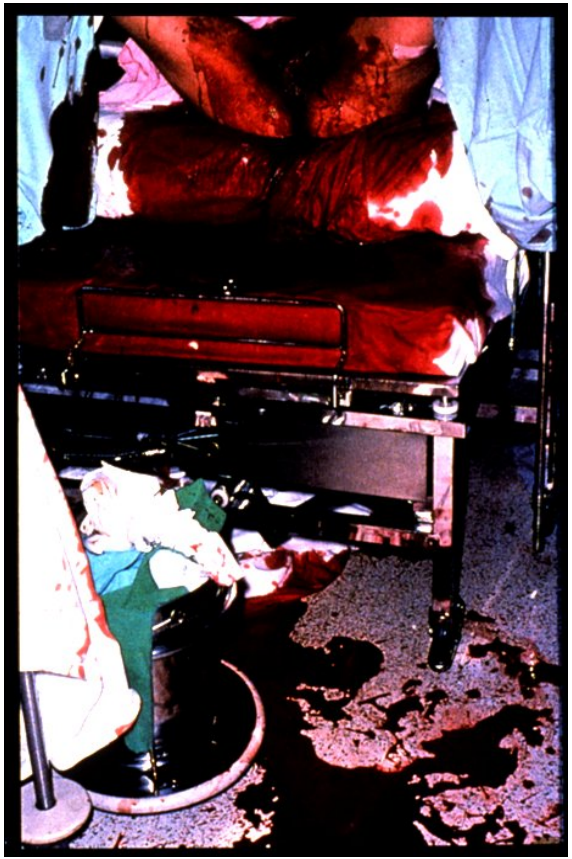


Image courtesy of Dr. Andra James, Duke University Medical Center

Coagulation in Pregnancy

Hypercoagulable state:

- Lowered Protein S
- Reduced fibrinolysis, increased PAI-1
- Increased procoagulant factors (Fgn, FVII, FVIII, FIX)
  - **Fibrinogen (non-pregnant): 197-400 mg/dL**
  - **Fibrinogen (term pregnancy): 350-650 mg/dL**

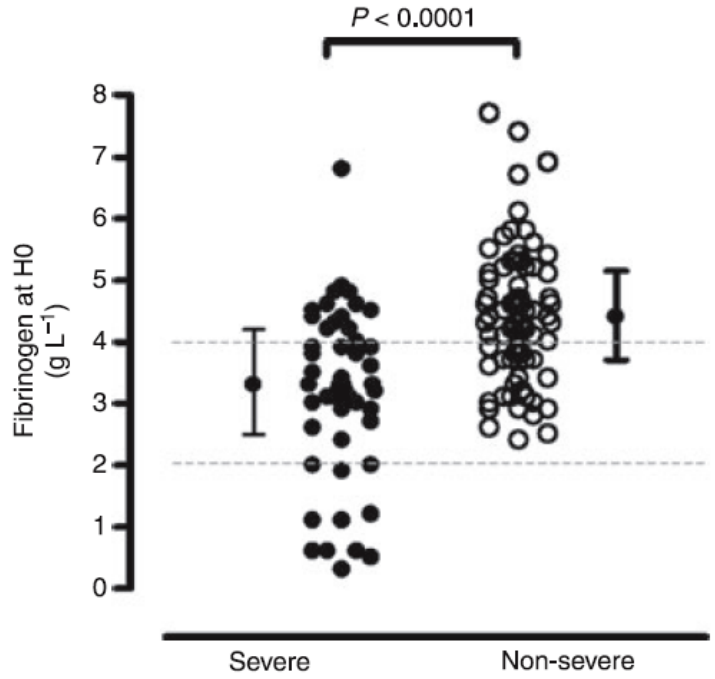
Szecsi, et al. *Thromb Haemost.* 2010; 103(4):718-727

Fibrinogen Levels and Severe Postpartum Hemorrhage (PPH)

- Prospective multicenter study in atonic PPH (n=128)
- Enrolled at time of second-line uterotonic administration (sulprostone)
- Two groups:
  1. **Severe PPH:** 4+ pRBC transfusion, Hgb drop > 4 g/dL, procedure intervention, or death
  2. **Non-severe PPH**
- Compared laboratory values between groups:
  - PT/INR, PTT, platelet count, fibrinogen, FII, FV, D-dimer, antithrombin, Protein C, euglobulin clot lysis time, thrombin-antithrombin complex, plasmin-antiplasmin complex, thrombomodulin

Charbit *J. Thromb Haemost.* 2007; 5:266-273

Low Fibrinogen Predicts Severe PPH



Fibrinogen <200 mg/dL at time of PPH recognition: predictive of severe PPH

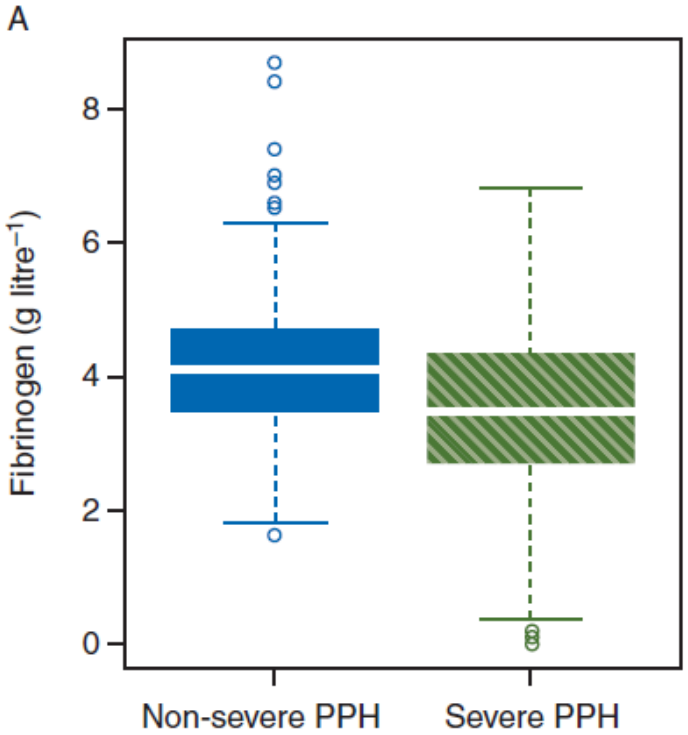
Charbit, et al. *J. Thromb Haemost.* 2007; 5(2):266-273

PITHAGORE6 Trial

- Cluster-randomized controlled trial of 106 French maternity units over 2 year period (2004-2006)
- Intervention: protocol education for early PPH management
- Primary outcome: rate of severe PPH in each unit
- Results: No significant difference between groups (1.64% intervention, 1.65% control)
- Secondary analysis performed correlating fibrinogen levels with PPH following vaginal delivery

Deneux-Thareux, et al. *BJOG*. 2010; 117:1278-1287

PITHAGORE6 subanalysis



Subjects: 738 of 6,324 patients with fibrinogen drawn within 2 hours of PPH diagnosis.

Severe PPH: n = 323

Non-severe PPH:

Mean fibrinogen = 420 +/- 120 mg/dL

Severe PPH:

Mean fibrinogen = 340 +/- 90 mg/dL

($p < 0.001$)

Cortet, et al. *BJA*. 2012; 108:984-989

PITHAGORE6 subanalysis

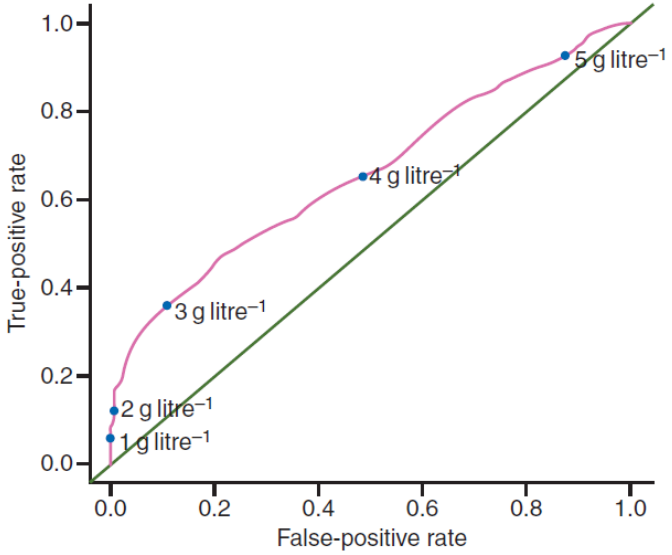


Fig 3 ROC curve of fibrinogen concentration at diagnosis for the prediction of severe PPH. Area under the curve=0.66, 95% CI=(0.64–0.68).

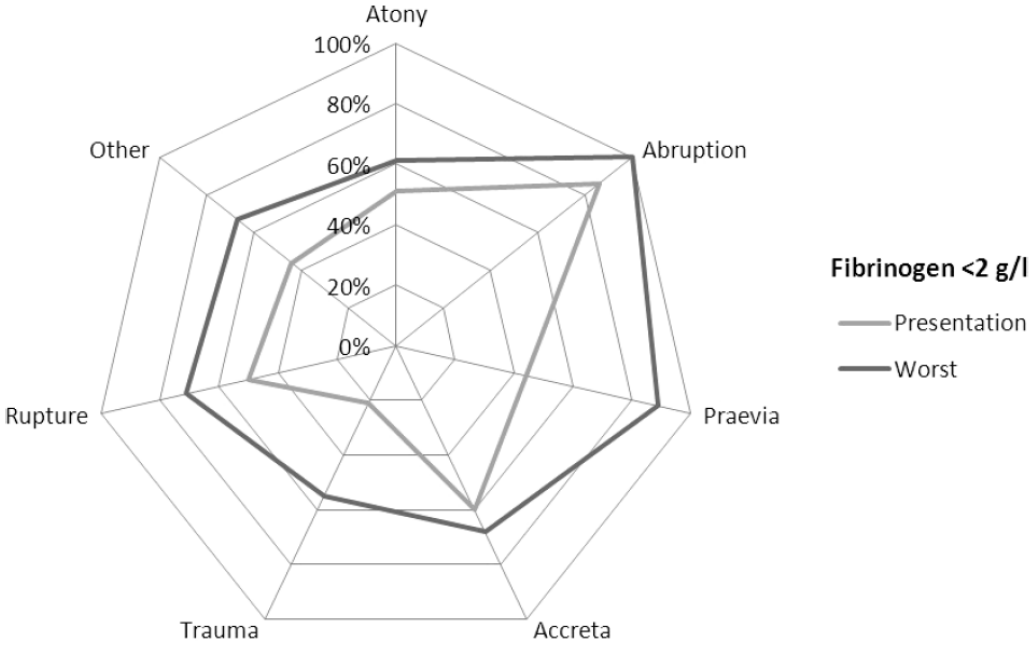
Laboratory variables at time of diagnosis: Hgb, platelets, PT, ACT ratio

After multivariate analysis, only fibrinogen was predictive of severe PPH.

O.R. for fgn < 200 mg/dL: 11.99 (2.56-56.06)

Cortet, et al. *BJA.* 2012; 108:984-989

Major Obstetric Hemorrhage with Hypofibrinogenemia



UK Obstetric Surveillance System: July 2012 – June 2013

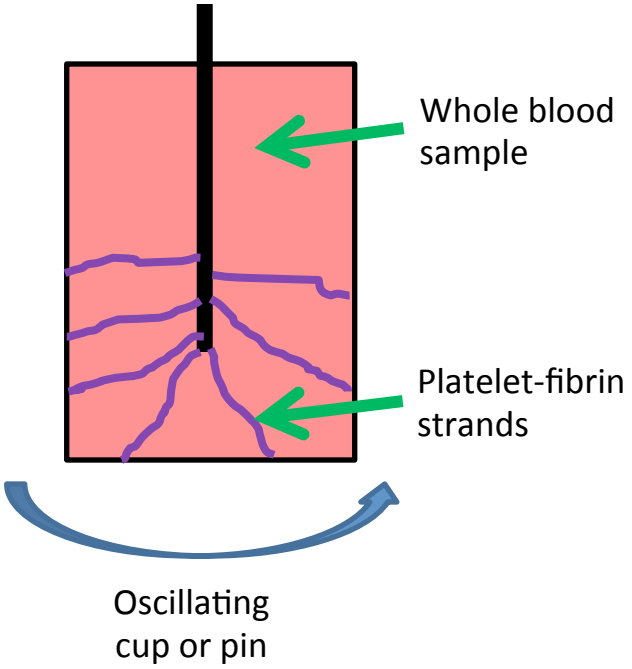
Subjects: 8+ RBC transfusion within 24 hours of delivery

N=181 cases

Median nadir fgn level:
< 200 mg/dL for all causes

Green, et al. *Brit J Haematol.* 2016; 172:616-624

Viscoelastic Clot-based Testing



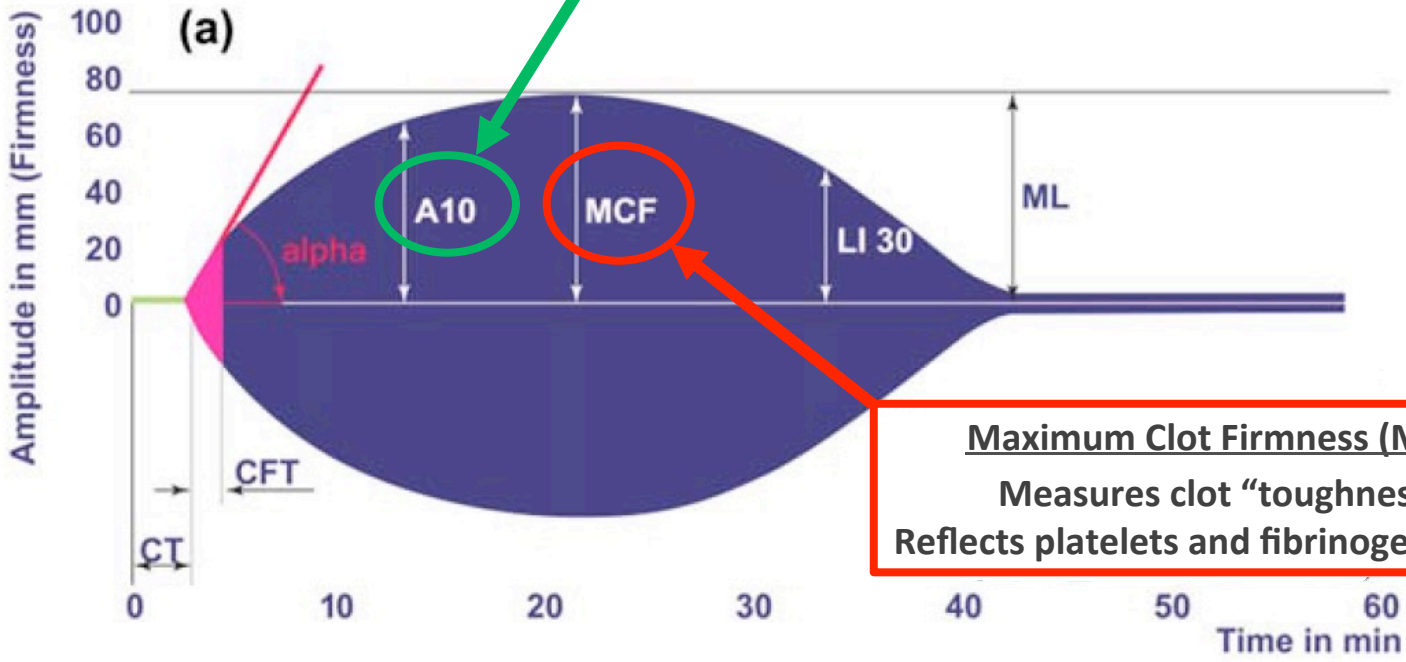
Two platforms in the U.S.:

1. **TEG:** thromboelastography
2. **ROTEM:** rotational thromboelastometry

ROTEM tracing

A5 and A10

Clot firmness at 5 or 10 minutes;
Predicts MCF



Maximum Clot Firmness (MCF):

Measures clot "toughness";
Reflects platelets and fibrinogen activity

Image from Whiting and DiNardo. *Am J Hematol.* 2013; 89:228-232

ROTEM: Biomarker for PPH Progression

- Prospective, observational study
- N=356 woman with PPH > 1,000 mL
- Primary outcome: ROTEM (Fibtem A5) or Clauss fgn level as predictor for PPH progression to > 2,500 mL
- In final multivariate model:
  - Fibtem A5 independent predictor (O.R. 0.85 [0.77-0.95])
  - Lower Fgn (<2 g/L) and Fibtem MCF (<10 mm) associated with longer bleeds, invasive procedures, and earlier transfusion

Collins, et al. *Blood.* 2014; 124(11):1727-1736

Fibrinogen concentrate (FC)

- FDA approved in 2009 for treatment of congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia).
- ***Not approved in US for acquired hypofibrinogenemia.***
- Lyophilized powder made from cryoprecipitated pooled human plasma.
- Pathogen reduced for both enveloped and non-enveloped viruses.
- Pharmacovigilance data: risk of thrombosis 3.48 per 10^5 doses used.[1]

1. Dickneite, et al. *Blood Coag Fibrinolysis.* 2009; 20(7):535-540

FIB-PPH trial

- Multicenter, double blinded RCT in Denmark
- n=249 randomized
- Subjects: primary PPH (regardless of delivery mode)
- Treatment: early preemptive 2 g fibrinogen concentrate (FC) vs. saline placebo
- Primary outcome: RBC transfusion 6 weeks following delivery

Wikkelsø AJ, et al. *Br J Anaesth.* 2015 Apr; 114(4):623-33.

FIB-PPH Trial Results

- All subjects had EBL >1L (mean EBL=1.5 L)
- Baseline fgn level mean: 4.5 g/L for both arms
  - Only 2.2% had fgn levels < 2.0 g/L at baseline

- Primary outcome: no difference
  - FC group RBC transfusion: 20.3%
  - Placebo group RBC transfusion: 21.5% (*P*=0.88)

- Conclusions: empiric early FC not helpful in normofibrinogenemic women with PPH

Wikkelsø AJ, et al., *Br J Anaesth* 2015 Apr; 114(4):623-33.

Fibrinogen in PPH: Guideline Recommendations

Organization/Group	Recommendation
European Society of Anaesthesia (2013)[1]	• Fgn less than 2g/L may indicate increased risk for PPH (Grade 2C) • Fgn <1.5–2.0 g/L deficit should be triggers for Fgn substitution (Grade 1C)
Royal College of Obstetricians and Gynaecologists (2016)[2]	• Fgn level greater than 2 g/L should be maintained during ongoing PPH (Grade C).
California Maternal Quality Care Collaborative (2015)[3]	• Initial order for cryoprecipitate when Fgn < 100 mg/dL or if patient has severe abruption or amniotic fluid embolism • Maintain Fgn > 100-125 mg/dL
ISTH (2015)[4]	• Suggest maintaining Fgn > 2 g/L with cryo or fibrinogen concentrates

1. Kozek-Langnecker, et al., *Eur J Anaesthesiol.* 2013; 30(6):270–382
2. Mavrides E, et al., *BJOG.* 2016; 124:e106-e149
3. Lyndon, et al. CMQCC OB Hemorrhage toolkit. From URL: cmqcc.org/ob_hemorrhage, last accessed 12/2/2015
4. Collins P, et al. *J Thromb Haemost.* 2015; 14:205-210

Tranexamic Acid (TXA) and PPH

- Cochrane review on TXA for prevention of PPH[1]
  - 12 trials, 3285 subjects
  - Blood loss > 400-500 mL and blood transfusion less common in women receiving TXA (moderate quality evidence)
  - Effect on maternal mortality and severe morbidity uncertain

- CRASH-2 [2]: RCT of TXA in trauma
  - >20,000 adult subjects
  - 1 g IV TXA + 1 g IV TXA infusion vs. saline placebo
  - Significant reduction in all-cause mortality and bleeding deaths
  - No increase in thromboembolic complications

1. Novikova and Hofmeyer. *Cochrane Database Syst Rev.* 2015; (6):CD007872
2. CRASH-2 trial collaborators, *Lancet.* 2010; 376:23-32

TXA for Treatment of PPH

- French multicenter RCT at eight obstetric centers
- Subjects: vaginal deliveries with EBL >800 mL
  - N = 72 per group
- Intervention: 4 g TXA, followed by 1 g/hour for 6 hours.
  - Additional procoagulant treatments (plasma, fgn concentrates, platelets) allowed after EBL = 2,500 mL
- Primary outcome: reduction of blood loss in PPH
- Note: not blinded or placebo-controlled

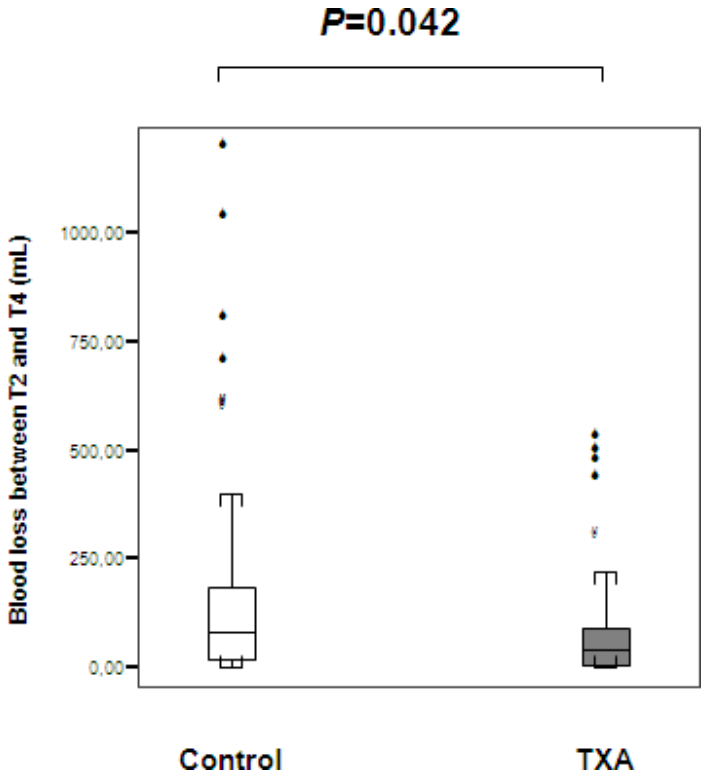
Ducloy-Bouthors, et al. *Crit Care.* 2011; 15:R117

TXA for Treatment of PPH

Use of procoagulant blood products significantly less in TXA group:
7% versus 20% (p = 0.013)

Blood loss from 30 min to 6 hours significantly lower in TXA group:
p = 0.042

Not a clinically significant blood loss difference: 173 mL vs. 221 mL



Ducloy-Bouthors, et al. *Crit Care.* 2011; 15:R117

- Randomized trial enrolling 20,000 women; completed enrollment in 2016
- Subjects: PPH after vaginal or C-section delivery
- Intervention: 1 g I.V. TXA vs. placebo (2 g TXA max dose)
- Primary outcome: maternal death or hysterectomy
- End point: death, discharge, or 42 days post-intervention
- Secondary endpoints include thromboembolic events in both mother and infant

Shakur, et al. *Trials.* 2010; 11:40

TXA in PPH: Guideline Recommendations

Organization/Group	Recommendation
European Society of Anaesthesia (2013)[1]	Administer TXA to reduce blood loss, bleeding duration, and transfusion requirements (Grade 1B)
Royal College of Obstetricians and Gynaecologists (2016)[2]	Consideration should be given to the use of TXA in the management of PPH (Grade B).
WHO (2012)[3]	For refractory atonic and trauma-related bleeding (weak recommendation, moderate evidence)
ISTH (2015)[4]	Suggest that women with ongoing PPH be considered to receive 1 g TXA

1. Kozek-Langnecker, et al. *Eur J Anaesthesio.* 2013; 30(6):270–382
2. Mavrides E, et al. *BJOG.* 2016; 124:e106-e149
3. WHO recommendations for the prevention and treatment of postpartum hemorrhage, 2012
4. Collins P, et al. *J Thromb Haemost.* 2015; 14:205-210

Conclusions

- Fibrinogen levels < 2g/L are associated with severe PPH
- Uncertainty regarding therapeutic fibrinogen targets; many guidelines suggesting maintaining fibrinogen > 2g/L
- Tranexamic acid recommended in many guidelines for PPH management; safety and efficacy to be determined in large RCTs