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 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
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

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

Low Fibrinogen Predicts Severe PPH

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

**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

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
  \((p < 0.001)\)
PITHAGORE6 subanalysis

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)

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

Viscoelastic Clot-based Testing

Two platforms in the U.S.:

1. **TEG**: thromboelastography
2. **ROTEM**: rotational thromboelastometry
Maximum Clot Firmness (MCF): Measures clot “toughness”; Reflects platelets and fibrinogen activity

A5 and A10
Clot firmness at 5 or 10 minutes; Predicts MCF

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

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

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

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 normofibrinogenenemic women with PPH

# Fibrinogen in PPH: Guideline Recommendations

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

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

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

• 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

# TXA in PPH: Guideline Recommendations

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<tr>
<td>European Society of Anaesthesia (2013)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Administer TXA to reduce blood loss, bleeding duration, and transfusion requirements (Grade 1B)</td>
</tr>
<tr>
<td>Royal College of Obstetricians and Gynaecologists (2016)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Consideration should be given to the use of TXA in the management of PPH (Grade B).</td>
</tr>
<tr>
<td>WHO (2012)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>For refractory atonic and trauma-related bleeding (weak recommendation, moderate evidence)</td>
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<tr>
<td>ISTH (2015)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Suggest that women with ongoing PPH be considered to receive 1 g TXA</td>
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3. WHO recommendations for the prevention and treatment of postpartum hemorrhage, 2012
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