TRANSFUSION INTERVENTION FOR MASSIVE OBSTETRIC HAEMORRHAGE

Update on transfusion for Major Obstetric Haemorrhage – Products, Strategies and Techniques

National Perinatal Epidemiology Centre Study Day, 20th January 2017
Introduction
From a transfusion requirement perspective, among women who fit the basic diagnostic criteria for PPH there are generally 3 groups:

- **Mild PPH**: May require fluid resuscitation but generally respond to first line pharmacological treatment. Do not require blood products.

- **Moderate PPH**: Require blood and/or plasma transfusion for volume resuscitation and Hb correction. Do not develop coagulopathy and do not require specific measures to correct coagulopathy.

- **Severe PPH ('Major' or ' Massive' PPH)**: Present with or develop coagulopathy. Requires multiple blood product components. May require invasive surgical procedure.
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    - Do not develop coagulopathy and do not require specific measures to correct coagulopathy
  - Severe PPH (‘Major’ or ‘Massive’ PPH)
    - Present with or develop coagulopathy (usually rapidly)
    - Requires multiple blood product components
    - May require invasive surgical procedure
So why do some women with PPH progress to develop a Major Obstetric Haemorrhage (MOH)?

Can we pre-emptively identify these women at the onset of PPH?

Can we prevent the development of Major Obstetric Haemorrhage (MOH)?
Normal postpartum haemostasis
Normal postpartum haemostasis

- Primarily dependant on uterine tone
  - Maternal spiral arterioles devoid of muscle layer
  - Rely on uterine muscle fibres to constrict lumen

- Coagulation provides permanent haemostasis
  - But remain relatively ineffective in the absence of adequate uterine tone

- Pro-coagulable state
  - Factors I (Fibrinogen), II (Thrombin), IV, V, VI, VII, VIII, IX, X, XII increase
  - Increase in fibrin production/activation
    - Concomitant increase in local fibrinolysis
    - FPA/D-dimer ratio unchanged
  - Particular increase in thrombin activity after placental separation (placental thromboplastin)
Coagulation cascade

Xa : TFPI
... TF : VIIa

AT : Xa

Xa : Vα

VII : TF

VIIa : TF

X : TF

IX : TF

X : TF

X X : TF

VIII : vWF

VIIIa : IXa

PS : APC

VI : APC

V : APC

VIII : vWF

VIIIa : IXa

AT : Xa

X : Xa

AT : VIIa

AT : Xa

AT : thrombin

FDPs

Fibrinogen

Fibrin

Fibrinogen

t-PA

PAI-1 : t-PA

α2AP : plasmin

Plasminogen

Plasmin
Coagulation cascade

- Xa : TFPI
  - TF : VIIa

- AT : Xa
My simplified coagulation cascade!

Coagulation factors

Fibrinogen

Thrombin

Fibrin

Tissue plasminogen activator (tPA)

Plasmin

Plasminogen

Tranexamic acid

FDPs

The 'KISS' principle to managing coagulation in MOH
My simplified coagulation cascade!

Coagulation factors

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The 'KISS' principle to managing coagulation in MOH
‘Blood’ products
Blood products

- Whole blood
- Packed red cells
- Plasma
- Platelets
- Coagulation factors
- Synthetic products
Figure 2: Production of blood components and plasma derivatives

- Education
- Recruitment
- Selection
- Donation

Test for:
- HIV
- Hepatitis B
- Hepatitis C
- HTLV
- Syphilis
- ABO + RhD
- Other phenotypes
- Red cell antibodies (CMV, HbS, malaria)

Process into blood components

Filter to remove leucocytes

- Red cells
- Pooled platelets
- Fresh frozen plasma

Plasma (from non-UK source)

4°C 35 days

Confirm compatibility

22°C 5 days
(Pool)

-30°C 24 months
(Thaw)

Fractionation

Plasma derivatives, e.g. albumin, immunoglobulin

Patient
Whole blood

- The ideal replacement in haemorrhage
- Limited by storage life (35 days)
- Contains red cells, ± white cells, platelets, plasma proteins and most coagulation factors
- All or nothing replacement
  - No selectivity
- Relatively expensive
- Improved 30 and 90 day survival in military ‘field’ trauma – relatively readily available
Packed red cells

- *Primary effect is to restore O₂ carrying capacity of patient, secondary effect is volume restoration*
- Concentrated red cells (Hct ≈ 70 – 80%)
- Effectively contains *no coagulation factors*
- Must be used within 30 minutes out of cold storage
- Subject to rigorous testing but cannot guarantee infection risk free
Plasma

- **Dual benefit of volume restoration and replacement of coagulation factors**

- 2 products
  - Fresh frozen plasma (FFP) and Octaplas (processed cell free plasma – low infection risk)
    - Both stored frozen and need thawing
      - 20-30 mins for Heated Air Technology, 5-7 minutes for Radiowave Thawing
  - Contain plasma proteins and some coagulation factors
    - 10-15 ml/Kg will increase coagulation factors by ≈20%
      - FFP – approx. 0.5 g fibrinogen per unit (2g/L)
      - **Octaplas - poor source of fibrinogen**
  - Octaplas may promote fibrinolysis
  - Cannot be refrozen
    - stored at 2-4°C, Octaplas can be used for 12 hours [3 hours at room temperature]
    - stored at 1-6°C, FFP can be used for 24 hours
Coagulation factors

• *Effect is to restore ‘normal’ coagulation*

• ‘Batch’ e.g. FFP or Octaplas

• Complexes
  • Cryoprecipitate
    • fibrinogen, von Willebrand factor, factor VIII and factor XIII
    • Variable concentrations – questions reliability/dosing
    • withdrawn in several European countries due to safety concerns
  • Octaplex
    • vitamin K dependent factors (II, VII, IX and X), Protein S and Protein C
    • highly prothrombotic

• Individual factors
  • Fibrinogen concentrate
    • 0.9 – 1.3 g per vial (more reliable than cryoprecipitate)
  • Activated factor VII
‘Synthetic’ products

- Specialised oxygen carrying fluids
  - designed to partially replace red cell transfusion
  - aim to minimise infection risk
- 2 types:
  - Perflourocarbons (e.g. Oxygent)
    - chemical compound which can carry and release oxygen
  - Haemoglobin based (HBOCs)
    - Derived from humans (PolyHeme, USA), animals (Hemopure, SA) and synthesized by recombinant DNA techniques
    - Trials in US – some problems (cardiac ischaemia, renal failure)
- Other
  - US Army investigating dehydrated blood
Definition/Diagnosis of PPH
PPH – definition/diagnosis

- WHO (2012)
  - > 500 mls

- RCOG (Green-top Guideline No. 52, 2009); (IOG, RCPI, 2014)
  - Minor 500 – 1000 mls
  - Major
    - Moderate 1000 – 2000 mls
    - Severe > 2000
  - > 40% blood volume – life-threatening
    - This guideline adopts a pragmatic approach, whereby an estimated blood loss of 500-1000 ml (in the absence of clinical signs of shock) prompts basic measures of monitoring and ‘readiness for resuscitation’, whereas an estimated loss of more than 1000 ml (or a smaller loss associated with clinical signs of shock, tachycardia, hypotension, tachypnoea, oliguria or delayed peripheral capillary filling) prompts a full protocol of measures to resuscitate, monitor and arrest the bleeding.
PPH – definition/diagnosis

- ACOG (2009)
  - “Although >500 ml for vaginal birth and >1000 ml for cesarean birth may be the most common clinical definition in the U.S., it is somewhat arbitrary and may not necessarily take into account a woman’s initial volume status and may be clinically irrelevant to hemodynamic compromise”.
  - “Quantitative measures of 500 ml EBL are appropriate “triggers” for heightened surveillance and/or more aggressive treatment in the face of ongoing bleeding; 1000 ml is an appropriate “trigger” for movement toward more emergent efforts”.
  - Vital Signs as Triggers
    - Heart Rate >110
    - Blood Pressure < 85/45 (>15% drop)
    - Oxygen Saturation <95%
The Cochrane Collaboration (2007)
- Traditionally, primary PPH is defined as bleeding from the genital tract of 500 ml or more in the first 24 hours following the delivery of the baby (Cunningham 1993). Alternative cut-off levels of 600 ml (Beischer 1986), 1000 ml (Burchell 1980), 1500 ml (Mousa 2002), a substantial fall in the haematocrit or the need for blood transfusion (ACOG 1998;Combs 1991) have also been suggested.

Others
- 900 ml of EBL which typically corresponds to a 15% volume deficit
- 10% change in hematocrit or need for blood transfusion
- Measured blood loss from the genital tract >500 ml
PPH – definition/diagnosis

- IOG (RCPI, 2014)
  - Adopted from RCOG
  - If a woman with primary PPH is continuing to bleed after an estimated blood loss of 1000 ml (or has clinical signs of shock or tachycardia associated with a smaller estimated loss), this should be described as major PPH and prompt a full protocol of measures to achieve resuscitation and haemostasis.
Symptoms and signs of PPH
# PPH – symptoms/signs

## Table 3

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<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Blood Loss (mL)</td>
<td>≤1000</td>
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<td>&gt;2000</td>
</tr>
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<td>Heart rate (bpm)</td>
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- ACOG (2009)
  - Vital Signs as Triggers
    - Heart Rate >110 bpm
    - Blood Pressure < 85/45 mmHg (>15% drop)
    - Oxygen Saturation <95%

- Patient symptoms
  - Anxiety, tachypnoea, air hunger, confusion
  - Fatigue/yawning* or onset of thirst*

*personal observation
‘Causes’ of PPH
Causes of PPH

- The 4 T’s
  - Tone, trauma, tissue and thrombin
Examples of the 4 T’s

- The 4 T’s
  - Tone, trauma, tissue and thrombin

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Examples of the 4 T’s – rarely isolated

- The 4 T’s
  - Tone, trauma, tissue and thrombin

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‘Causes’ of postpartum haemorrhage

- Obstetric haemorrhage
- ‘Surgical’
- Mixed
- Coagulopathy
Aims of management – dependent on presentation

Obstetric haemorrhage

- ‘Surgical’
  - e.g. uterine atony, retained placenta
- Mixed
  - e.g. abruption, AFE
Obstetric haemorrhage

Presentation

‘Surgical’
e.g. uterine atony, retained placenta

Mixed
e.g. abruption

Management

Surgical, Pharmacological ± early transfusion interventions

Surgical, pharmacological & early transfusion interventions

Aims of management – dependent on presentation
Obstetric haemorrhage

‘Surgical’
e.g. uterine atony, retained placenta

Surgical, pharmacological ± transfusion interventions

Mixed

Surgical, Pharmacological & Transfusion Interventions

Presentation

Progression

Management

Aims of intervention – dependent on presentation

Transfusion management aims to prevention progression

Aims of intervention – dependent on presentation

Mixed
e.g. abruption

Surgical, pharmacological & early transfusion interventions
Management of PPH
Bonnar describes a five-step management plan for massive obstetric haemorrhage:

- (i) Organisation of the multidisciplinary team
- (ii) Restoration of circulating volume
- (iii) Correction of defective coagulation
- (iv) Evaluation of response to treatment
- (v) Remedying of the underlying cause of the bleeding
Principles of management of PPH

- Bonnar describes a five-step management plan for massive obstetric haemorrhage:
  - (i) Organisation of the multidisciplinary team
    - Obstetrics, anaesthetics, midwifery, haematology, blood bank, portering staff
      - Particularly relevant for remote laboratories
    - Communication protocol
      - Simple wording, precise meaning
      - Contacting senior staff
    - Regular drills/courses based on teamwork
      - MOET, PROMPT
    - Record keeping
  - (ii) Restoration of circulating volume
  - (iii) Correction of defective
  - (iv) Evaluation of response to treatment
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Principles of management of PPH

- Bonnar describes a five-step management plan for massive obstetric haemorrhage:
  - (i) Organisation of the multidisciplinary team
  - (ii) Restoration of circulating volume
    - Large bore iv access
      - May necessitate central venous access
    - Haemodynamic monitoring
      - Often requires invasive arterial monitoring
    - Crystalloids/colloids
      - Avoiding over-infusion leading to dilutional coagulopathy
    - Blood (PRBC) as soon as possible
  - (iii) Correction of defective coagulation
  - (iv) Evaluation of response to treatment
  - (v) Remedying of the underlying cause of the bleeding
Principles of management of PPH

- Bonnar describes a five-step management plan for massive obstetric haemorrhage:
  - (i) Organisation of the multidisciplinary team
  - (ii) Restoration of circulating volume
  - (iii) Correction of defective coagulation
    - Timely plasma transfusion
    - Coagulation factor complexes or individual components
    - Avoiding over-infusion of ‘clear’ fluids
    - Maintaining patient temperature/acid-base balance
  - (iv) Evaluation of response to treatment
  - (v) Remedying of the underlying cause of the bleeding
Principles of management of PPH

- Bonnar describes a five-step management plan for massive obstetric haemorrhage:
  - (i) Organisation of the multidisciplinary team
  - (ii) Restoration of circulating volume
  - (iii) Correction of defective coagulation
  - (iv) Evaluation of response to treatment
    - Appropriate laboratory tests
    - Vigilant haemodynamic monitoring
    - Setting realistic targets or end points
    - Direct observation
  - (v) Remedying of the underlying cause of the bleeding
Bonnar describes a five-step management plan for massive obstetric haemorrhage:

- (i) Organisation of the multidisciplinary team
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- Pharmacological agents
  - Local/regional/national guidelines and protocols
- Surgical intervention
  - Agreed techniques
  - Appropriate equipment
- Second opinion as appropriate
Principles of management of PPH

- “Care for the patient with maternal bleeding should follow an algorithm that goes through a rapid and successive sequence of medical and surgical approaches to stem bleeding and decrease morbidity and mortality”

- Major difficulty is reaching a consensus on what the most appropriate algorithm(s) is(are)
Strategies for transfusion therapy in MOH
Strategies for transfusion therapy in MOH

- ‘Reactive’ and ‘Proactive’
Strategies for transfusion therapy in MOH

- ‘Reactive’
‘Reactive’ approach to massive haemorrhage

‘Traditional sequential transfusion approach’

- Crystalloid/colloid as per BP/HR then…….
  - PRBC as per volume needs or laboratory Hb then…….

- Octaplas/FFP
  - as per volume needs
  - As per PRBC transfused units/volume
  - laboratory coagulation results (INR/APTT) then …….

- Platelets as per laboratory platelet levels then…….

- Fibrinogen as per laboratory fibrinogen levels
Dependence on laboratory results with potential disadvantages
  - ‘Delays’
    - getting sample to laboratory
    - processing of sample
    - thawing FFP/Octaplas
    - potential outcome is interpretation ‘errors’

  - “Laboratory-guided component therapy is limited as a decision-guiding tool during cases of rapid, massive exsanguination” (Young et al, Transfus Med Rev 2001)
How much crystalloid/colloid and when?

- Traditionally infused as much as needed to maintain blood pressure while awaiting blood product availability
  - dilutional issues
- Recent guidelines suggest limiting crystalloid to 2 L and colloid to 1 – 1.5 L
  - Aim is to minimise dilutional coagulopathy and extravascular fluid overload
  - One suggestion is a ratio of 2:1 crystalloid:colloid
  - Maximum recommended therefore is 2L crystalloid and 1L colloid (3L total)
  - Further volume resuscitation achieved by PRBC and FFP transfusion
    - Use O Neg PRBC if X-match or type-specific unavailable
There was no uniform consensus on the optimal ratio of blood products to transfuse into severely bleeding patients

- Recommendations:
  - pRBCs:fresh-frozen plasma range from 10:1 to 3:2
  - pRBCs:platelets transfusion ratios range from 10:6 (1 pool) to 10:12 (2 pools).

How much platelets and when?

- Count of $< 50 \times 10^9$/litre is associated with an increase in microvascular bleeding

- When to give
  - laboratory results
    - platelet count $< 50 \times 10^9$/litre at any time
  - empirical
    - *anticipate platelet count $< 50 \times 10^9$/litre if the patient has received $\geq 1$ blood volume replacement (6 litres ???!!!!)
    - *cases of uncontrollable bleeding
      - Dose: 1 or 2 pools (6-12 units)

- Monitor
  - repeat the FBC 30-60 minutes post transfusion to ensure the platelet count is $\geq 75 \times 10^9$/litre
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**INDICATIONS FOR BLOOD COMPONENT THERAPY**

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….”after the event” laboratory results based / reactive therapies!
‘Proactive’

- an attempt to stratify/unify the initial response to obstetric haemorrhage in order to pre-empt progression of the condition
- development of the concept of the Massive Transfusion Pack (MTP)
Proactive approach to massive haemorrhage – the ‘MTP’

- Background – military and non-obstetric civilian studies
  - Presence of coagulopathy is associated with poorer outcomes
    - x 3-fold ↑ in mortality
  - INR > 1.5 – 30% mortality; < 1.5 – 5% mortality
  - Factors affecting coagulation include:
    - Degree of trauma
    - Hypoperfusion
    - Consumption
    - ↑ Fibrinolysis
    - Reperfusion
    - Haemodilution – crystalloid & pRBCs without concomitant plasma infusion
  - Early correction or prevention of coagulopathy may improve outcomes
Proactive approach to massive haemorrhage - the ‘MTP’

- Primary goals - damage control resuscitation
  - Permissive hypotension
  - Limiting large volume crystalloid/colloid infusions
  - Transfusion of blood products pre-emptively using a balanced ratio of pRBCs, plasma and platelets
“Considering the similarities between maternal haemorrhage and major haemorrhage due to trauma with regard to the accompanying hypothermia, acidosis, and coagulopathy, it might be appropriate to extend these recommendations to massive PPH, although definitive data are not available.”

Proactive approach to massive haemorrhage – the ‘MTP’

- Limit initial clear fluid volume to 2L

- Immediate laboratory response to notification of ‘Massive Obstetric Haemorrhage’
  - one phone call
  - bloods for FBC, coagulation, fibrinogen, FDPs may be sent early but results not awaited

- ‘Pack’ consists of pRBCs, Plasma and Platelets
  - O Neg or type specific (if known)
    - immediately released to theatre
      - as each product is available
    - no consensus on ideal ratios
      - however suggested ratio of 6:4:1 (Burtleow et al. Transfusion, 2007: 47)
Proactive approach to massive haemorrhage – the ‘MTP’

- Repeat the MTP ‘pack’ if continued bleeding
  - Ideally with cross-matched blood

- Instigation of MTP does not
  - imply mandatory use of all products supplied
  - preclude transfusion of other blood products as laboratory results direct

- If bleeding is becoming controlled – may revert to laboratory guidance
Potential downside to the MTP:
  ◦ inappropriate over transfusion of some/all components
    ◦ primarily due to delayed laboratory results in determining if targets have been met
    ◦ unreliable laboratory results – results available some time after sample time
The British Committee for Standards in Haematology’s guidelines suggest the following transfusion thresholds:

- Hb <8 g/dl (?10g/dl)
- Platelets <75x10⁶/ml if still bleeding; <50 at any time
- PT time and APTT time ratio of < 1.5
- Fibrinogen <2.0g/l***

*** 1.0 g/dl in 2009 guidelines
Fibrinogen in MOH
Is this the goose that lays the golden eggs?
Fibrinogen in MOH

2 reasons fibrinogen so important 😅
2 reasons fibrinogen so important:

1. Also known as….Factor 1 – top of the list!
Fibrinogen in MOH

2 reasons fibrinogen so important:

1. Factor 1 – top of the list!
2. Familiar shape?
Fibrinogen in MOH

- Plasma glycoprotein
- 2 essential functions
  - Primary haemostasis
    - Promotes platelet activation and aggregation
    - Glycoprotein IIb/IIIa receptors on platelets
  - Secondary haemostasis
    - Substrate for fibrin
    - Undergoes cleavage by thrombin
- Levels increase in pregnancy
  - Non-pregnant 1.5–4 g/dl, at term 3.5 – 6 g/dl.
  - Mainly during 3rd trimester
    - Probably oestrogen related
    - Levels decrease postpartum
- Laboratory assay can take 30–60 minutes
The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. Charbit B et al, Thromb Haemost. 2007

OBJECTIVES:
This study's objective was to determine whether changes in haemostasis markers during the course of PPH are predictive of its severity.

PATIENTS AND METHODS:
128 women with PPH requiring uterotonic prostaglandin E2 (sulprostone) infusion
- Severe PPH (39% of patients) was defined by occurrence of one of the following events: peripartum haemoglobin decrease ≥ 4 g/dl, transfusion of > 4 units PRBC, arterial embolization or emergency surgery, admission to intensive care, or death.
- Serial coagulation tests were performed at enrolment (H0), and 1, 2, 4 and 24 hours thereafter.

RESULTS:
At H0, and through H4, women with severe PPH had significantly lower fibrinogen, factor V, antithrombin activity, protein C antigen, prolonged prothrombin time, and higher D–dimer and TAT complexes than women with non–severe PPH.
In multivariate analysis, from H0 to H4, fibrinogen was the only marker associated with the occurrence of severe PPH.
At H0, the risk for severe PPH was 2.63–fold higher for each 1 g/L decrease of fibrinogen.
The negative predictive value of a fibrinogen concentration >4 g/L was 79% and the positive predictive value of a concentration ≤2 g/L was 100%.

CONCLUSION:
These findings indicate that a simple fibrinogen measurement can anticipate the risk of severe bleeding in PPH.
Fibrinogen in MOH

- Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial.
  - Cortet M et al, BJA 2012

- METHODS:
  - Secondary analysis of a population-based study in 106 French maternity units
  - PPH was defined by a blood loss > 500 ml or a peripartum Hb drop of more than 2 g/dl
    - 738 women with PPH after vaginal delivery
  - Fibrinogen levels were compared in patients whose PPH worsened and those whose PPH remained non-severe.
  - Severe PPH was defined as haemorrhage by occurrence of one of the following events: peripartum haemoglobin decrease ≥ 4 g/dl, transfusion of concentrated red cells, arterial embolization or emergency surgery, admission to intensive care, or death.

- RESULTS:
  - Fibrinogen concentration at diagnosis was 4.2 ± 2.4 g/L among the patients without worsening and 3.4 ± 1.8 g/L (P<0.001) in the group whose PPH became severe.
  - The fibrinogen level was associated with PPH severity independently of other factors
    - adjusted odds ratio=1.90 (1.16–3.09) for fibrinogen between 2 and 3 g/L and 11.99 (2.56–56.06) for fibrinogen <2 g/l.

- CONCLUSIONS:
  - The fibrinogen level at PPH diagnosis is a marker of the risk of aggravation and should serve as an alert to clinicians.
“However, current PPH management guidelines do not account for the altered baseline coagulation status observed in pregnant patients, and the appropriate transfusion triggers to use in PPH are unknown, due to a lack of high-quality studies specific to this area.”

“Recent guidelines for the management of massive haemorrhage acknowledge that target fibrinogen levels of 1 g litre$^{-1}$ are usually insufficient and that plasma fibrinogen >1.5 g litre$^{-1}$ is more likely to improve haemostasis. Notably, the European Guideline for the management of bleeding after major trauma has updated its recommended trigger level for fibrinogen replacement from <1 to <1.5–2.0 g litre$^{-1}$. The evidence supporting this change included prospective data in an obstetric setting. In the light of these changing guidelines, the current recommended trigger of only 1 g litre$^{-1}$ for PPH warrants reconsideration.”
How much fibrinogen and when?

- Fibrinogen concentrate replaced cryoprecipitate in 2009 (IBTS)

- No thawing time, easily reconstituted powder
  - Vial: 0.9 – 1.3 g/vial

- When to give – lab results (traditional approach)
  - A fibrinogen level of < 0.5g/l is strongly associated with microvascular bleeding.
  - Give if the fibrinogen is <2 g/l despite initial appropriate treatment with FFP***
  - Dose: ([Target-Measured]/17) g/kg

***However must also give other coagulation factors (Plasma)
How much fibrinogen and when?

- When to give - empirical
  - In the presence of *placental abruption*, fibrinogen should always be considered empirically due to the associated low fibrinogen levels
  - ‘Non-surgical’ bleeding despite FFP (e.g. oozing from venepuncture sites)
  - On-going, uncontrollable surgical bleeding i.e. MOH
  - Dose: 70 mg/kg (4g recommended)

- Assess the response to fibrinogen by repeating a coagulation screen (fibrinogen level) a minimum of 30 minutes after fibrinogen has been given

- Aim is to maintain fibrinogen level > 2 g/l
Several case reports of favourable outcome (reduced transfusion requirements) with early use of fibrinogen (before laboratory results)

- The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomised controlled trial
  - Results:
    - **Conclusions** We found no evidence for the use of 2 g fibrinogen concentrate as pre-emptive treatment for severe PPH in patients with normofibrinogenaemia

- “Current literature on the use of fibrinogen concentrate in non-obstetric haemorrhage only moderately suggests an efficacy on transfusion requirement and morbidity.” Bonnet, F1000Research, 2016
  - even if it appears to be a promising therapeutic, there is still no strong evidence that the use of fibrinogen concentrate would improve maternal outcomes in severe PPH
  - the risk of thromboembolic events associated with the use of fibrinogen concentrate has never been explored in this context
  - therefore, we still need valid data before administration of fibrinogen concentrate as a curative treatment of PPH can be firmly recommended.
Fibrinogen – the future

- Fibrinogen concentrate as a treatment for postpartum haemorrhage–induced coagulopathy: A study protocol for a randomised multicentre controlled trial. The fibrinogen in haemorrhage of delivery (FIDEL) trial. ClinicalTrials.gov Identifier: NCT02155725

- A randomised, multicentre, double-blind, placebo-controlled study on the efficacy and safety of a therapeutic strategy of post partum haemorrhage comparing early administration of human fibrinogen versus placebo in patients treated with intravenous prostaglandins following delivery. EudraCT: 2013-002484-26

- Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: study protocol for a randomised controlled trial. EudraCT: 2012-005511-11
What do we do?

- CUMH MTP
  - 6:4:1:2
    - 6 units PRC
      - O Neg available for immediate collection
      - Cross-match available in 20 to 40 minutes
    - 4 units Octaplas
      - Radiowave thawing
      - Available in 15–20 minutes
    - 1 pool platelets
      - External site – up to 1 hour wait
    - 2 grams fibrinogen
      - Immediately available in anaesthetic room fridge
Tranexamic acid
Tranexamic acid

- Inhibits conversion of plasminogen to plasmin
  - Also binds to plasmin, reducing its activity
- Will only work if patient is both producing and lysing fibrin clot!
- Doubtful if it has a place as frontline *management* of MOH
- Few publications of use in PPH
  - Consistent reduction in blood loss but volume difference small (non-obstetric bleeding)
    - ‘At the time of patients’ inclusion (T1), blood loss did not differ between the two groups.... The blood loss between T1 and T4 was significantly lower in the TA group (median, 170 mL (first to third quartiles, 58 to 323)) than in the control group (median, 221 mL (first to third quartiles, 110 to 543) (P = 0.041).’ *Ducloy-Bouthors Crit Care* 2011
  - Variable dose regimes
  - Almost all publications aimed at use for prevention
Tranexamic acid

- 2010 Chochrane Review
  - Authors’ conclusions: Tranexamic acid decreases postpartum blood loss after vaginal birth and after caesarean section based on two RCTs of unclear quality which reported on only a few outcomes. Further investigations are needed to confirm efficacy and safety of this regimen for preventing PPH. These results also provide a basis for the investigation of tranexamic acid for the treatment of PPH.
    - Mean reduction: 75 mls
    - 2 studies, 361 patients
      - Vaginal delivery or elective LSCS
  - Ongoing trial for prevention of PPH
    - WOMAN trial: ‘...fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use an antifibrinolytic agent in a particular woman with postpartum haemorrhage’. (using WHO definition of >500 mls)
    - Still waiting for results
Recombinant activated factor VII
Recombinant activated factor VII

- Synthetic vitamin K-dependent FVIIa works via activation of the extrinsic pathway of the coagulation cascade leading to an enhanced generation of thrombin and a stable fibrin plug at the site of injury.

- Originally developed for the treatment of bleeding in patients with haemophilia A or B with inhibitors to factor VIII or IX but also been successfully used to prevent or control bleeding in several other conditions including thrombocytopenia, platelet function disorders, impaired liver function and severe trauma with massive bleeding.

- Consideration for the use of rFVII in PPH must take into account efficacy, side-effects including increased risk of thromboembolism, and costs of rFVII vs other treatment.
Recombinant activated factor VII

- Although no randomized controlled studies have been published on the use of FVIIa in PPH, case reports have suggested great efficacy in helping to control massive obstetric bleeding.

- The American Society of Anesthesiologists recommends consideration of rFVIIa when ‘traditional well tested options for treating microvascular bleeding have been exhausted’.
  
  - After failure of all medical and surgical treatments and after multiple transfusions of RBCs, fresh-frozen plasma, platelets and fibrinogen but before hysterectomy a dose of 90 μg/kg, followed by a second identical dose if no response is seen after 20 min
  
- unlikely to work if the platelet count is $< 50 \times 10^9$/litre, fibrinogen is $< 0.5$g/litre and the pH is $< 7.2$
POC testing in MOH
POC testing

- Increasing doubt being cast upon the validity of ‘routine’ coagulation tests such as PT and APTT in MOH
  - Developed primarily for testing patients with inherited bleeding disorders or to test the effects of pharmacological anticoagulation
  - Results may take 40 – 50 minutes
  - May increase the complexity of transfusion product selection resulting in suboptimal transfusion therapy and subsequent poor outcome (UKOSS)
- Aim – to produce a rapid, meaningful measurement of a specific physiological parameter or process that is both amenable to and responsive to immediate correction, where a delayed laboratory result may compromise treatment
POC testing

- **Haemacue/ABG**
  - Established for rapid Hb monitoring
  - Haemacue accuracy questioned in multiple reports
  - ABG monitoring is already a standard investigative/diagnostic tool in most maternity units
  - ABG monitoring during MOH may also be used to guide other aspects of management e.g. lactate levels
  - Well maintained ABG machines correlate closely with laboratory Hb analysis
POC testing

- **TEG/ROTEM**
  - Measures the ‘physiological’ clotting process: clot formation time, clot firmness and clot lysis
  - Normal values for pregnancy/labour recently published
  - FIB–TEM correlates very well with fibrinogen levels
  - Can distinguish between hypofibrinogenaemia and reduced ‘other factors’ or platelets as cause of continued bleeding
  - Can rapidly rule out ongoing coagulopathy as cause of ongoing bleeding
    - Helps surgeon to decide on more drastic interventions
  - Becoming established as the ‘main’ test of coagulation in MOH in many centres in the UK
    - Despite current unenthusiastic reception from NICE
  - Demonstrable reduction in total amount of products transfused and reduction in cost per patient
    - ‘Before and after’ study from Liverpool Women’s Hospital
Summary

- MTP helps in the logistics of MOH management protocols
- MTP may reduce overall transfusion requirements in MOH
- Remains to be seen if MTP affects morbidity or mortality
- Early use of fibrinogen may affect course of PPH
- Fibrinogen target increased to 2g/L
- Use of tranexamic acid in PPH remains uncertain
- POC testing may reduce total transfusion requirements
- Remains to be seen if POC testing affects morbidity or mortality
Thank you