



# Fibrinogen Concentrate and Major Obstetric Haemorrhage

Dr. Matt Simpson

Anaesthetic Consultant and

Lead for Obs Anaesthesia, SJUH, Leeds



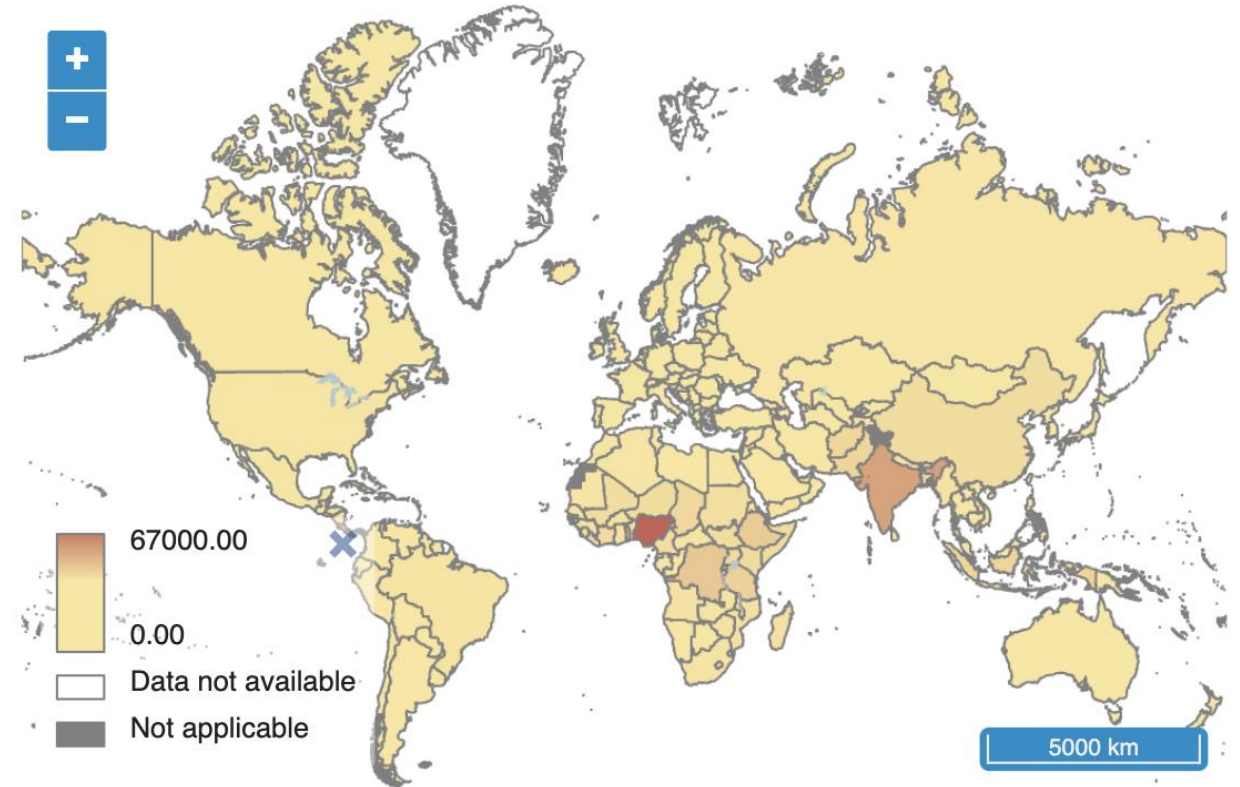
# World Health Organization

## Maternal mortality ~ 300 000/yr

- 94% in developing/low income countries
- ½ in sub-Saharan Africa, ⅓ in South Asia
- unstable regions / humanitarian crises

## Maternal Mortality Ratio (MMR)/100 000 live births

- **239** in developing countries
- Vs
- **12** in developed countries



## Haemorrhage:

Leading cause of maternal mortality and morbidity world-wide

# Key messages

from the surveillance report 2023



In 2019-21, **241 women died** during or up to six weeks after pregnancy among 2,066,997 women giving birth in the UK.

**11.7 women** per 100,000 died during pregnancy or up to six weeks after childbirth or the end of pregnancy.

## Causes of women's deaths



When maternal deaths due to COVID-19 are excluded, **10.1 women** per 100,000 died during pregnancy or up to six weeks after childbirth or the end of pregnancy

33 women  
**COVID-19** 14%

33 women  
Cardiac disease 14%

33 women  
Blood clots 14%

25 women  
Mental health conditions 10%

23 women  
Sepsis 10%

22 women  
Epilepsy and stroke 9%

19 women  
Other physical conditions 8%

17 women  
Bleeding 7%

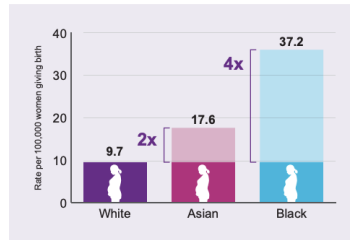
9 women  
Pre-eclampsia 4%

4 women  
Cancer 2%

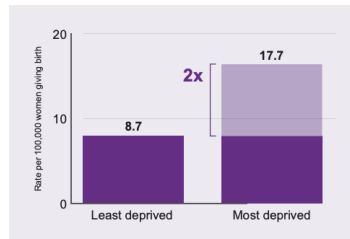
23 women  
Other 10%

## Inequalities in maternal mortality

### Ethnic group



### Living in more deprived areas



## 8<sup>th</sup> cause of mortality

- 17 deaths during the triennium 2019-2021 (7%)
- 20 deaths during the triennium 2016-2018 (9%)

## Preventable

- **Delay or lack of diagnosis** (hidden haemorrhages: concealed)
- **Lack of surveillance** (post-caesarean section)
- **Delayed or inadequate treatment** (surgery or coagulopathy)
- **Inadequate place of care** (comorbidity)

*Multiple causes often intertwined*





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## Definition of PPH

**Minor PPH**: blood loss 500 – 1000ml,  
without clinical shock

**Moderate PPH**: blood loss 1000 - 2000ml  
and continuing to bleed or clinical shock

**Severe PPH**: blood loss > 2000ml

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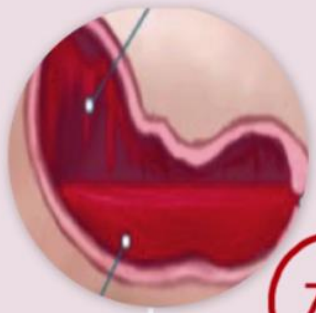
## Incidence

**8.6 %** of deliveries

**3.3 %** of deliveries

**1.3 %** of deliveries

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70%

## TONE

### Abnormal uterine contraction

- Overdistension of uterus
- Anatomic distortion of uterus
- Uterine relaxants administration
- Bladder Distention



20%

## TRAUMA

### Uterine, cervical or vaginal injury

- Laceration of the cervix, vagina or perineum
- Extension, lacerations at caesarean section
- Uterine rupture
- Uterine inversion



10%

## TISSUE

### Retained products of conception, blood clots



1%

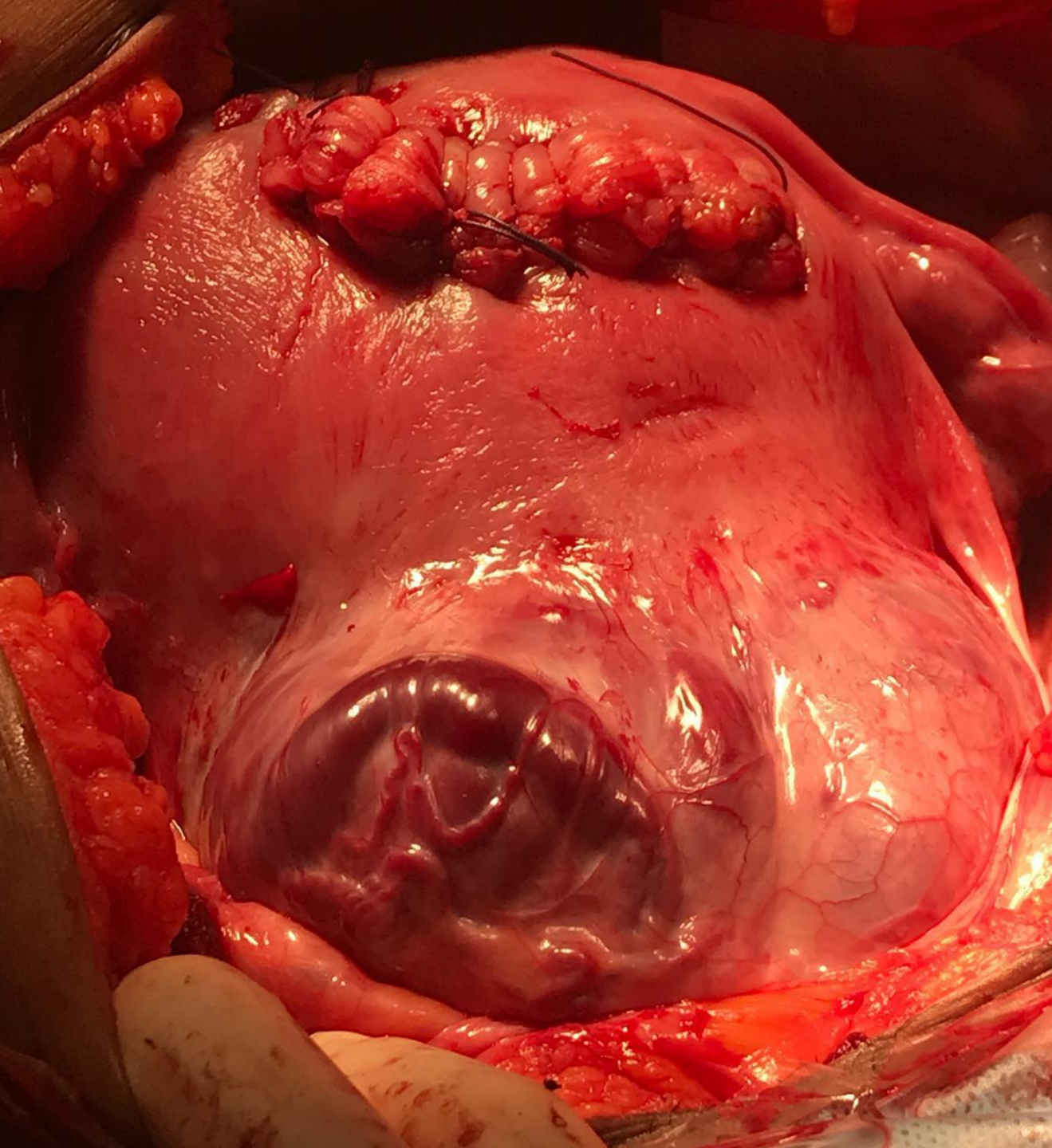
## THROMBIN

### Pre-existing or acquired

- Thrombocytopenic
- Von Willebrand disease
- Gestational
- Anticoagulation
- DIC: Amniotic
- Fluid embolism
- Severe infection, in utero fetal demise abruption

# Risk factors and associated levels of risk for PPH

| Risk factor                         | The four Ts | OR (95% CI)                     |
|-------------------------------------|-------------|---------------------------------|
| Multiple pregnancy                  | Tone        | 3.30 (1.00–10.60) <sup>16</sup> |
|                                     |             | 4.70 (2.40–9.10) <sup>24</sup>  |
| Previous PPH                        | Tone        | 3.60 (1.20–10.20) <sup>16</sup> |
| Pre-eclampsia                       | Thrombin    | 5.00 (3.00–8.50) <sup>16</sup>  |
|                                     |             | 2.20 (1.30–3.70) <sup>31</sup>  |
| Fetal macrosomia                    | Tone        | 2.11 (1.62–2.76) <sup>20</sup>  |
|                                     |             | 2.40 (1.90–2.90) <sup>24</sup>  |
| Failure to progress in second stage | Tone        | 3.40 (2.40–4.70) <sup>23</sup>  |
|                                     |             | 1.90 (1.20–2.90) <sup>31</sup>  |
| Prolonged third stage of labour     | Tone        | 7.60 (4.20–13.50) <sup>16</sup> |
|                                     |             | 2.61 (1.83–3.72) <sup>20</sup>  |
| Retained placenta                   | Tissue      | 7.83 (3.78–16.22) <sup>20</sup> |
|                                     |             | 3.50 (2.10–5.80) <sup>23</sup>  |
|                                     |             | 6.00 (3.50–10.40) <sup>24</sup> |
| Placenta accreta                    | Tissue      | 3.30 (1.70–6.40) <sup>23</sup>  |
| Episiotomy                          | Trauma      | 4.70 (2.60–8.40) <sup>16</sup>  |
|                                     |             | 2.18 (1.68–2.76) <sup>20</sup>  |
|                                     |             | 1.70 (1.20–2.50) <sup>24</sup>  |
| Perineal laceration                 | Trauma      | 1.40 (1.04–1.87) <sup>20</sup>  |
|                                     |             | 2.40 (2.00–2.80) <sup>23</sup>  |
|                                     |             | 1.70 (1.10–2.50) <sup>24</sup>  |
| General anaesthesia                 | Tone        | 2.90 (1.90–4.50) <sup>31</sup>  |



The bleeding will get worse

- Increasing LSCS rate (36%)
- Increase in PAS
- Increasing BMI
- Increase in inductions
- Increase multiple pregnancies (IVF)

# Maternal Morbidity

## *Immediate*

- **Admission to intensive care**
  - 2 % of PPH
  - Leading cause of admission to ITU postpartum
- **Labile blood products transfusion:**
  - 10 % of PPH
- **Haemostasis hysterectomy:**
  - 1 % of PPH (1/2000 deliveries)
- **VTE postpartum complications**
  - (risk  $\times$  2-5 in cases of severe PPH)

## *Delayed*

- Post-traumatic stress
- Bond with the newborn
- Mutilation
- Chronic renal failure
- Recurrent PPH in subsequent deliveries
- Reduction in libido/ Relationship breakdown



## Guide to estimating blood loss



Small swab:  
50ml



Medium swab:  
100ml



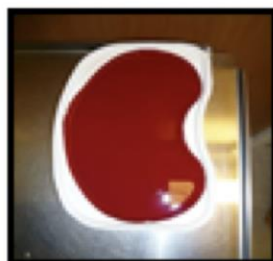
Large swab:  
350ml



Sanitary towel:  
100ml



Inco sheet:  
250ml



Kidney dish:  
600ml



Bedpan:  
500ml



Vomit bowl:  
300ml



Floor spills:  
50x50cm (500ml)  
75x75cm (1000ml)  
100x100cm (1500ml)



PPH:  
On bed only(1000ml)  
Spilling to floor(2000ml)

# Improved 'Haemorrhage Pack' Required



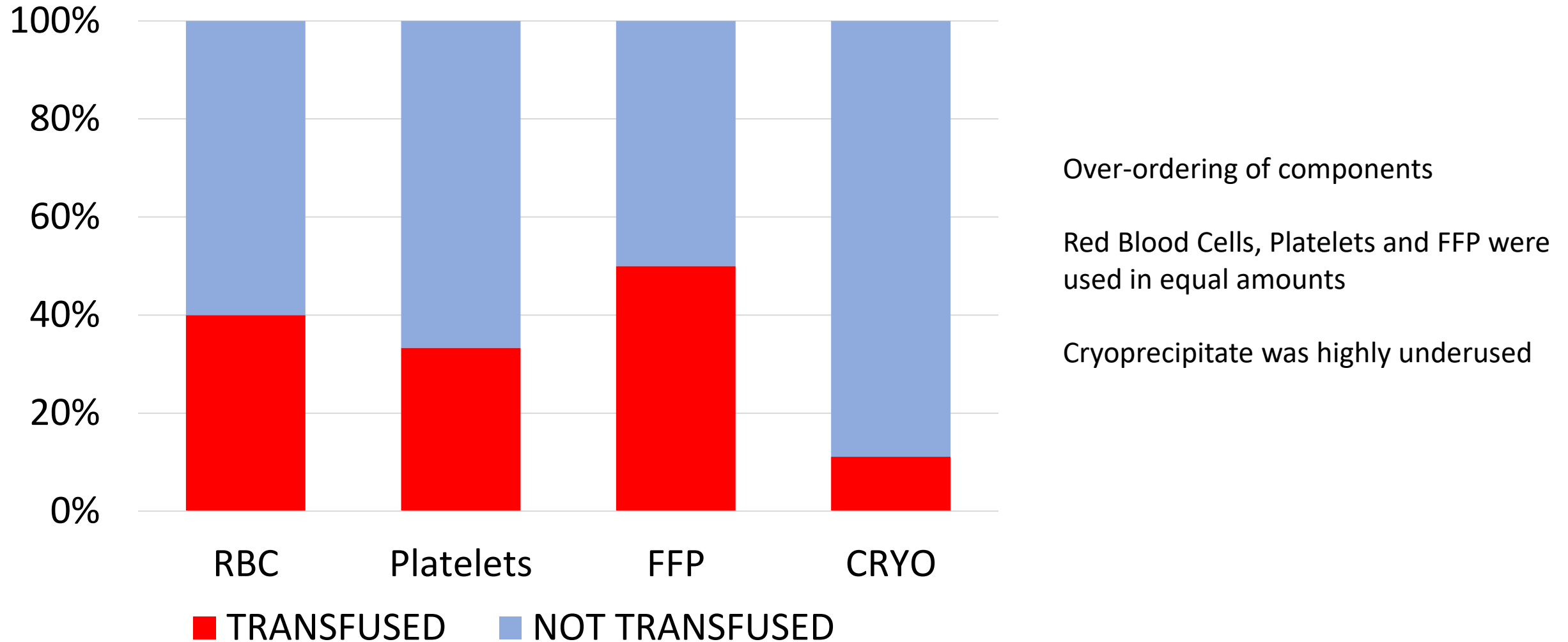
**Prior to July 2015:**

**'PACK 1' (2:1 RBC:FFP) & 'PACK 2' (2:1:1:1 RBC:FFP:PLATELETS:CRYO)**

.....but < 10% of anaesthetists knew what each pack contained!!

.....and neither pack suitable for obstetric population.

## AUDIT RESULTS: July '15 – October '15



## Outcome of Audit

- **Joint Meeting – Anaesthetist, Haematologists, Obstetricians**
- **New Single MoH Pack Developed**
  - 1:1:1 (RBC : FFP : Platelets)
  - Pre-thawed FFP immediately available from lab
- **Fibrinogen concentrate** available on labour ward for ‘upfront use’
  - 5g was proposed and used initially for 12m. Then changed to 3g

# Massive Obstetric Haemorrhage (SJUH)

Massive Obstetric Haemorrhage is defined as blood loss of:

- >1.5L total and Continuing to bleed
- 50% of total blood volume in 3 hours
- 150ml/min

eg \*Delivery Suite at St James's

Blood Bank will give you direct number for you to contact them on for further products

- 1.5g vials are kept in blood fridge
- Give 3g Total (2 vials)
  - If <70kg give 2g

**Call 2222**

Ask switchboard for the:  
**MAJOR HAEMORRHAGE ALERT TEAM**  
give **SITE and LOCATION\***  
also alert obstetric & anaesthetic consultants

Give switch the best number for blood bank to contact you on

When blood bank call, request:  
**"Major Obstetric Haemorrhage Pack"**

Give fibrinogen concentrate  
FibClot upfront while waiting for blood products

This sends emergency bleeps to:

- Blood Bank
- Obstetric anaesthetist
- Anaesthetic senior registrar
- Delivery suite co-ordinator
- Obstetric registrar
- Haematology registrar

Major Obstetric Haemorrhage Pack:

- 4 units packed red cells
- 4 units pre-thawed FFP
- 1 dose platelets

If bleeding continues, request further MOH pack. Please note that unless TEG or laboratory coagulation results support the use of further fibrinogen concentrate, no more will be issued by the lab. In the absence of these tests, you should specifically request an adult dose of cryoprecipitate with the MOH pack.

Please ensure that blood bank is stood down once bleeding is controlled. Return all completed 'brown tags' to blood bank immediately to ensure emergency stock is replenished.

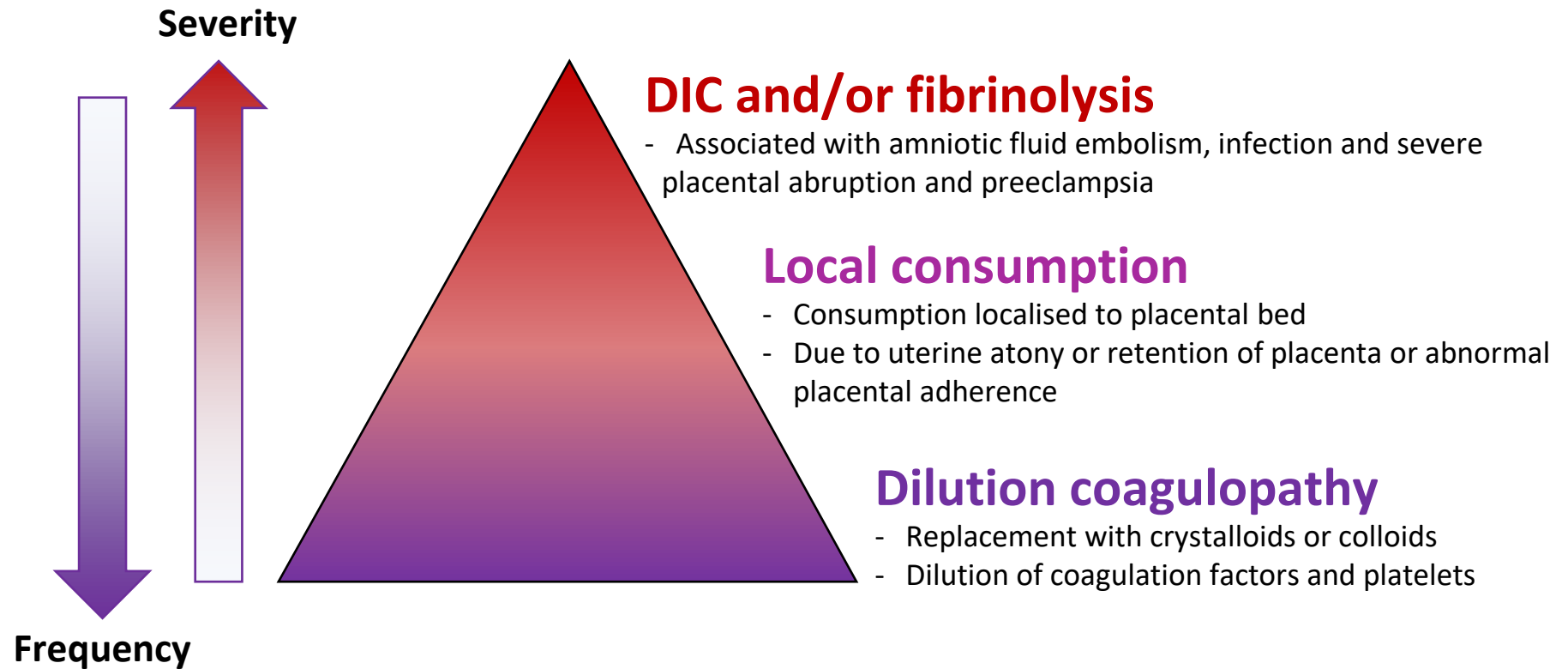
Re-Audited after 1 year

- **Improvement in blood usage/reduction in product wastage**
- **Rapid delivery of MOH pack (usually within 10 minutes)**
  - Dedicated lab technician for MoH
- **Reduced incidence of acidosis**
- **Reduction in ITU admissions**
- **Improved inter-professional relationships**

## RCoG Recommendations to reduce risk of PPH

- Uterine massage is of no benefit in the prophylaxis of PPH.
- Prophylactic uterotonics should be routinely offered in the management of the third stage of labour in all women
- For women without risk factors for PPH delivering vaginally, oxytocin (10 IU IM) is the agent of choice for prophylaxis in the third stage of labour. A higher dose of oxytocin is unlikely to be beneficial.
- For women delivering by caesarean section, oxytocin (5 IU slow IV) should be used to encourage contraction of the uterus and to decrease blood loss.
- Ergometrine–oxytocin may be used in the absence of hypertension in women at increased risk of haemorrhage as it reduces the risk of minor PPH (500–1000 ml).
- For women at increased risk of haemorrhage, it is possible that a combination of preventative measures might be superior to syntocinon alone to prevent PPH.
- Clinicians should consider the use of intravenous tranexamic acid (0.5–1.0 g), in addition to oxytocin, at caesarean section to reduce blood loss in women at increased risk of PPH

# Coagulopathy associated with PPH





# What do we know and what can we measure?

## Initial Stages of PPH

- Decrease of PT and Increase of INR
- Decrease of Fibrinogen
- Decrease of Factor II
- Increase of D Dimers

## More Advanced Stages of PPH

- Further decrease of Fibrinogen
- Decrease of Factor V
- Decrease of Platelets
- Increase of aPTT
- Increase of D dimers

**The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage**

B. CHARBIT,\*† L. MANDELBROT,‡ E. SAMAIN,§ G. BARON,¶ B. HADDAOUI,‡‡‡ H. KEITA,‡¶ O. SIBONY,\*\* D. MAHIEU-CAPUTO,¶ M. F. HURTAUD-ROUX,\*\* M. G. HUISSE,¶‡‡ M. H. DENNINGER,‡‡‡ and D. DE PROST‡‡‡‡‡ FOR THE PPH STUDY GROUP

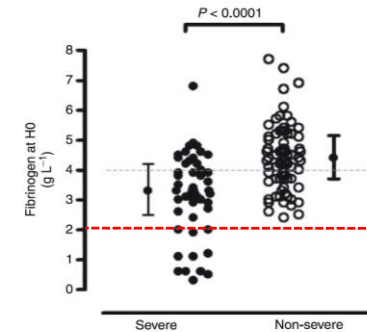


Fig. 2. Individual fibrinogen plasma concentrations at H0 in women with severe (●) or non-severe (○) postpartum hemorrhage. Mean ± SD values are reported for both groups.

- ↓ Hemoglobin (drop > 4 g/dL)
  - ↓ Fibrinogen (< 2 g/L)
- Negative predictive value if Fib > 4 g/L: 79 %

Positive Predictive value for severe PPH



# Fibrinogen

- Level  $<1.5\text{g/L}$  is too low for adequate haemostasis during ongoing PPH
- Fibrinogen can be replaced by cryoprecipitate or fibrinogen concentrate
- Cryo (2 pools) increases level by about  $1\text{g/L}$  (varies depending on consumption)
- Concentrate (unlicensed) corrects deficit more rapidly
- Concentrate reduces need for blood product usage and TACO (overload)
- Strong evidence that a low Clauss fibrinogen is a good biomarker for progression from moderate to severe PPH
- Level  $<2\text{g/L}$  taken 4hrs after onset of PPH predicted progression to invasive procedures and admission to level 3 ICU



# Ideal properties for me as an anaesthetist with wet socks!!



- Instantly available (every second counts)
- Safe (minimal side effects, reactions)
- Easy to administer/ mix
- Something that works!
- Cost consideration
- Readily measurable – titratable
- Not all fibrinogen conc is the same!!

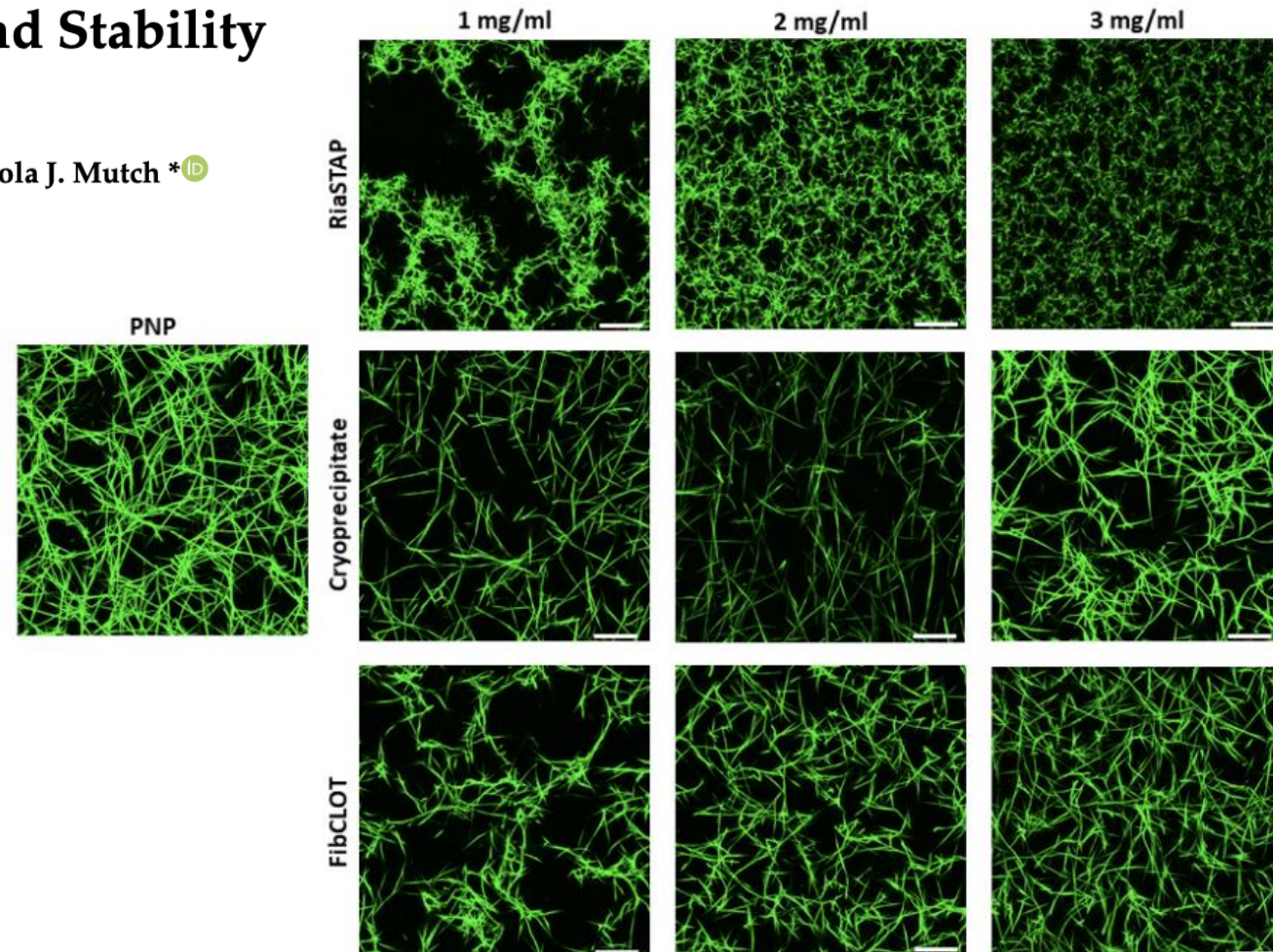




# Cryo vs RiaSTAP vs FibClot vs Fibryga

## The Efficacy of Fibrinogen Concentrates in Relation to Cryoprecipitate in Restoring Clot Integrity and Stability against Lysis

Claire S. Whyte , Akriti Rastogi, Ellis Ferguson, Michela Donnarumma and Nicola J. Mutch \*



# Differences in the biochemical composition of three plasma derived human fibrinogen concentrates

Andrea Neisser-Svae   • Oliver Hegener  • Klaus Görlinger 

Table 2 Amount/activity of tested components in a 3 g dosage.

|                                    | Parameter              | fibryga® | RiaSTAP®/<br>Haemocompletan® P | FibClot®/<br>Clottafact® |
|------------------------------------|------------------------|----------|--------------------------------|--------------------------|
|                                    |                        | Mean     | Mean                           | Mean                     |
|                                    | Total protein [g]      | 3.3      | 5.1                            | 3.2                      |
|                                    | Fibrinogen antigen [g] | 3.0      | 3.3                            | 2.6                      |
| Fibrinogen activity                | Fibrinogen Clauss [g]  | 3.6      | 3.9                            | 2.6                      |
|                                    | Clottable protein [g]  | 3.0      | 3.0                            | 2.8                      |
| Accompanying proteins              | Fibronectin [mg]       | 2.1      | 140                            | 25.6                     |
|                                    | VWF antigen [U]        | 30       | 570                            | 100                      |
|                                    | Vitronectin [µg]       | 2.1      | 6.0                            | 24.0                     |
|                                    | Albumin [mg]           | 63       | 1449                           | 0.7                      |
|                                    | FXIII activity [U]     | 585      | 165                            | 420                      |
| Activation and fibrinolysis marker | D-dimer [µg]           | 11       | 54                             | 24                       |
|                                    | Fibrinopeptide A [µg]  | 0.9      | 11.4                           | 19.4                     |
|                                    | Plasminogen [U]        | 6        | 6                              | 4                        |



**Table 2 Comparison of cost and quantity of FFP, fibrinogen concentrate and cryoprecipitate required to raise plasma fibrinogen concentration by 1 g/L in a 70-kg adult**

| Blood product                       | Predicted quantity required to increase plasma fibrinogen concentration by 1 g/L (volume, mL) | Cost to increase plasma fibrinogen concentration by 1 g/L |
|-------------------------------------|---|---|
| FFP <sup>7</sup>                    | 4 units (1000 mL)   | £384  |
| Cryoprecipitate <sup>7</sup>        | 13 units (260 mL)   | £478  |
| Fibrinogen concentrate <sup>9</sup> | 2 g (100 mL)  | £440  |

Quantities may vary according to ongoing consumption or dilution of fibrinogen. Prices obtained from the University Hospital of Wales Blood Bank, 2008.

FFP: fresh frozen plasma.

# Summary

- In MoH – blood loss rapidly gets out of control
- Non-clottable, non-oxygen carrying fluids have limited value
- Strong evidence to ensure fibrinogen > 2g/L
- Having products to hand on LW helps with the above 3 points
- Guide additional products with TEG/ ROTEM
- Make it MDT – involve Haematologists immediately.
- Care package and algorithm essential
- Choice of Fibrinogen concentrates – more studies needed
  - We started with Riastap and moved to FibClot:
    - Ease of constitution
    - 2 boxes, not 3
    - Overall cheaper
    - It appears to work