

# **Guidelines for PBM in obstetrics: what we have & what is on the horizon**

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# Disclosure

SPEAKERS BUREAU: CSL Behring, Masimo, Merck

CONSULTANT: AMAG Pharmaceuticals, Inc., CSL Behring, Gauss Surgical, Masimo Corporation, Vifor Pharma

GRANT/RESEARCH: CSL Behring, Masimo, HbO2 Therapeutics, LLC

# OVERVIEW

- What we have:
  - Current data on M&M
  - What do we know about prevention of maternal hemorrhage?
  - AWHON data and initiative
  - Assessing blood loss
  - Do we need MTP or MHP?
- What we need - the future
  - Understanding the physiology of coagulopathy in maternal hemorrhage
  - Is it DIC or something else?
  - The holy grail - antifibrinolytic therapy, does it work for all or just for some?

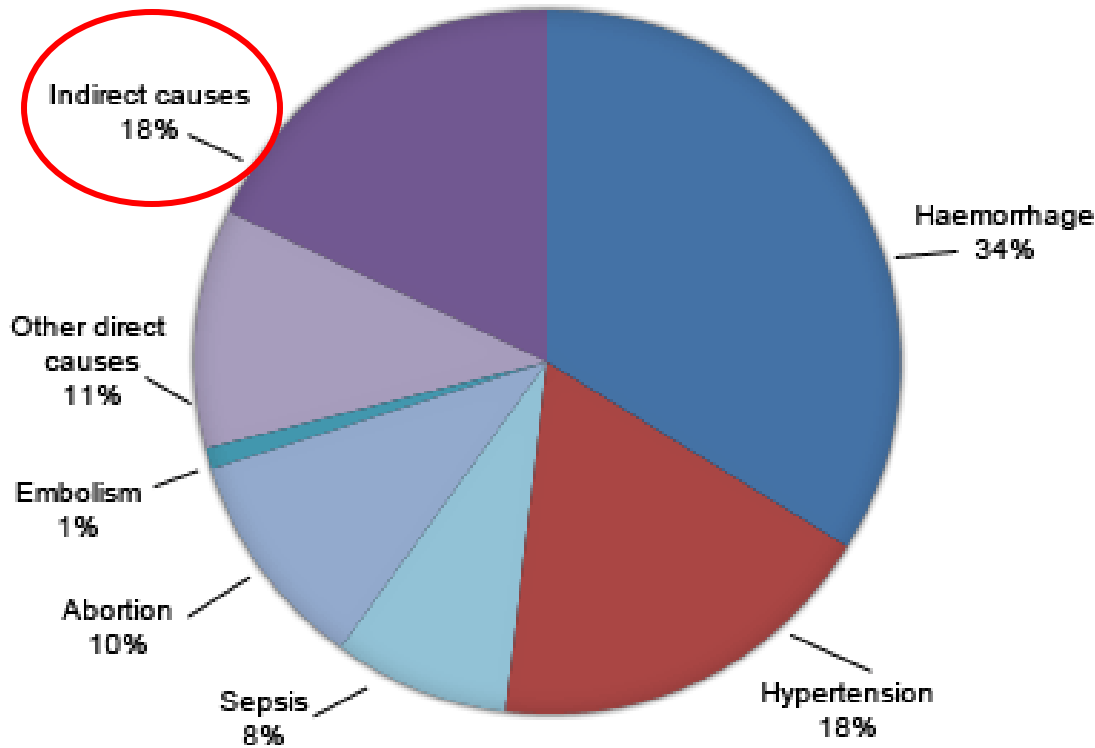
# Anemia in Pregnancy – Facts and more

- Prevalence of anemia during pregnancy:
  - 53%–61% for Africa
  - 44%–53% for South-East Asia
  - 17%–31% for Europe and North America
- Iron and folate deficiency are the most common etiological factors
- 20% of pregnant women have hgb levels of <8 g/dL,
- Between 2% and 7% have a value of <7 g/dL
- ACOG estimated that 5% of women who give birth lose 1,000 mL of blood or more during delivery

# LEADING CAUSES OF MATERNAL MORTALITY

Haemorrhage is the leading worldwide cause of maternal death

Cause of maternal death (Percentage)



Source: WHO systemic review of causes of maternal death (preliminary data). 2010

# Indirect causes of severe adverse maternal outcomes: a secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health

P Lumbiganon,<sup>a</sup> M Laopaiboon,<sup>b</sup> N Intarut,<sup>b</sup> JP Vogel,<sup>c,d</sup> JP Souza,<sup>d</sup> AM Gülmezoglu,<sup>d</sup> R Mori,<sup>e</sup>  
on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network

- 359 health facilities in 29 countries (N = 314,623 pregnant women)
- 2822 /314,623 reported to suffer from severe maternal outcomes
- 20.9% (589/2822) were associated with indirect causes
- **Most common indirect cause was anemia (50%)**
- Women with underlying indirect causes showed **significantly higher risk** of obstetric complications, severe maternal outcomes and perinatal mortality

# Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health

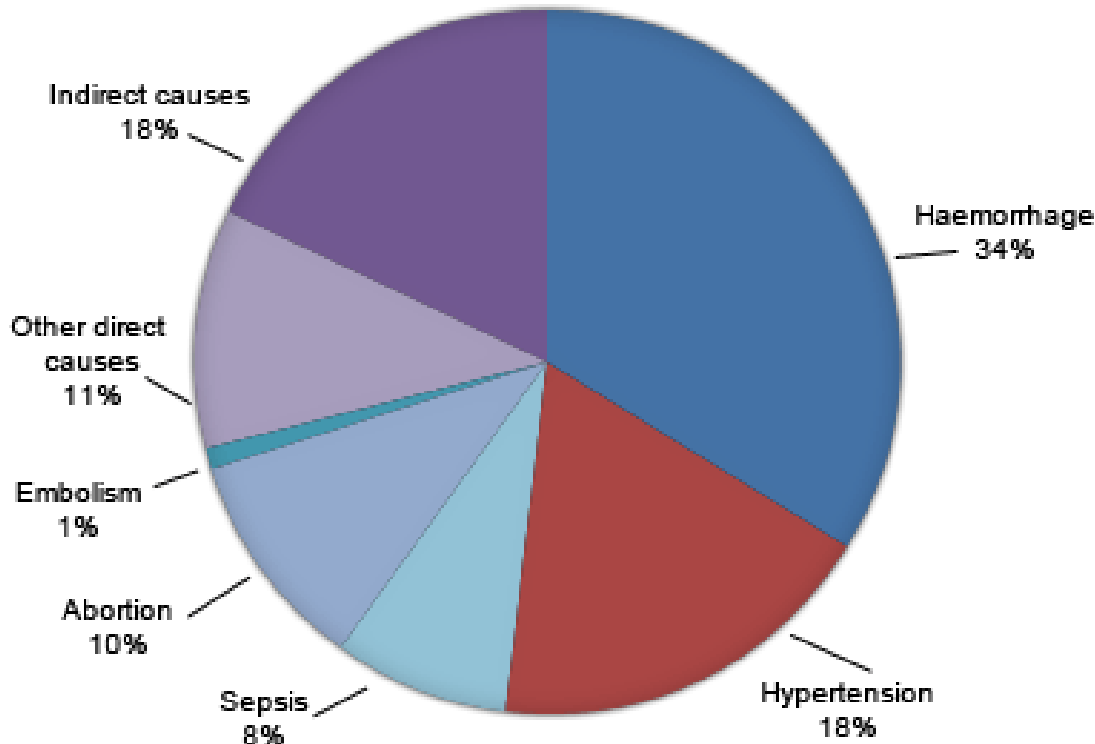
JP Vogel,<sup>a,b</sup> JP Souza,<sup>b</sup> R Mori,<sup>c</sup> N Morisaki,<sup>c,d</sup> P Lumbiganon,<sup>e</sup> M Laopaiboon,<sup>f</sup> E Ortiz-Panoso,<sup>g</sup> B Hernandez,<sup>h</sup> R Pérez-Cuevas,<sup>i</sup> M Roy,<sup>j</sup> S Mittal,<sup>k,l</sup> JG Cecatti,<sup>m</sup> Ö Tunçalp,<sup>b</sup> AM Gülmezoglu,<sup>b</sup> on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network

- 359 participating facilities in 29 countries (N = 308,392 singleton deliveries)
- Maternal complications were present in 85.6, 86.5, and 88.6%% of macerated LFDs, fresh LFDs, and ENDs, respectively.
- Risks of all three perinatal mortality outcomes were significantly increased with:
  - Placental abruption, ruptured uterus, systemic infections/sepsis, pre-eclampsia, eclampsia, and **severe anemia**

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# Medical Advances in the Treatment of Postpartum Hemorrhage

Anne-Sophie Ducloy-Bouthors, MD,\* Sophie Susen, MD, PhD,†‡ Cynthia A. Wong, MD,§  
Alex Butwick, MBBS, FRCA, MS,|| Benoit Vallet, MD, PhD,\* and Evelyn Lockhart, MD¶

- Monitoring and Rapid laboratory assessment of coagulopathy in the setting of PPH
- “Modern” approach to transfusion therapy
- Pro-hemostatic pharmacotherapy as an adjunct to transfusion

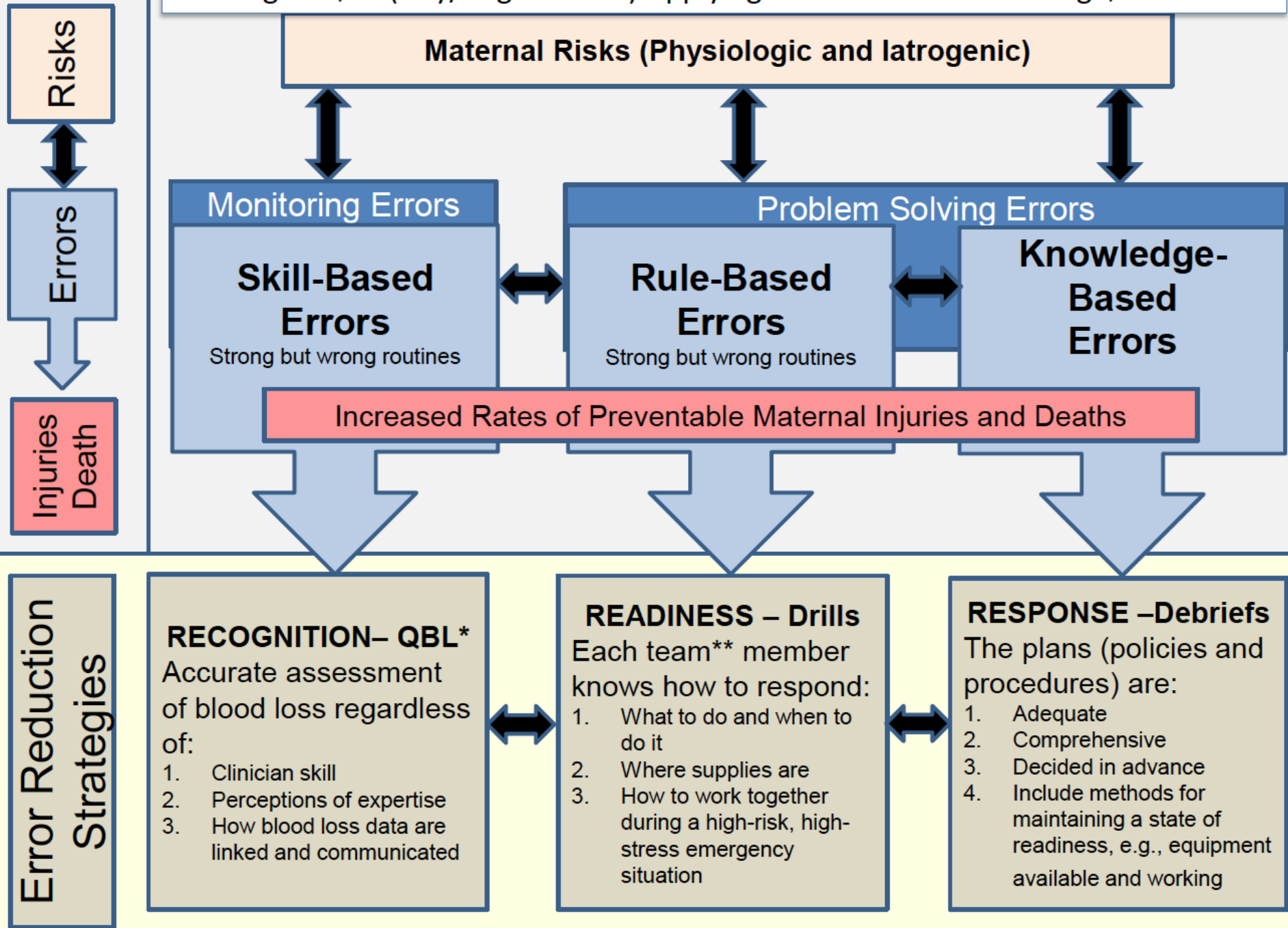
# Clinical and pharmacological measures for PPH prevention

Prevention	WHO (2012)	FIGO (2012)	RCOG (2011)	ACOG	SOGC	RANZCOG (2016)	CNGOF (2015)
Uterotonic	+	+	+	-	+	+	+
Controlled cord traction	+	+	+	-	+	+	-
Cord clamping	+	+	+	-	+	+	-
Uterine massage	-	+	-	-	-	-	-
Management of retained placenta in absence of bleeding	+	+	-	-	+	-	+
Surveillance and reporting of blood loss and vital signs after delivery	-	+	-	-	-	-	+



# AWHONN PPH Project

- Ca, NJ, DC and GA
- 1999 Maternal mortality from PPH – 9.9% (46<sup>th</sup>)
- 2010 Maternal mortality from PPH – 16.8%
- 184% increase in blood transfusions
- Leading cause of maternal morbidity
- Project revolves around:
  - Risk assessment – PBM
  - ‘Right’ blood products – Transfusion Medicine
  - Team work, simulation and “dry runs” – PBM



# Methods of Blood Loss Estimation

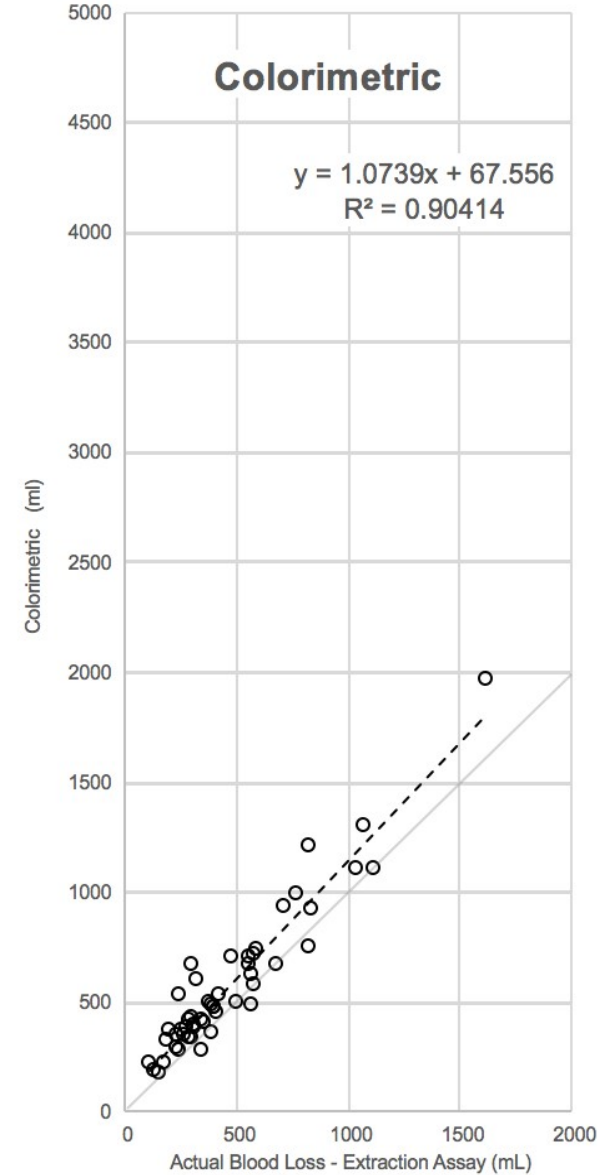
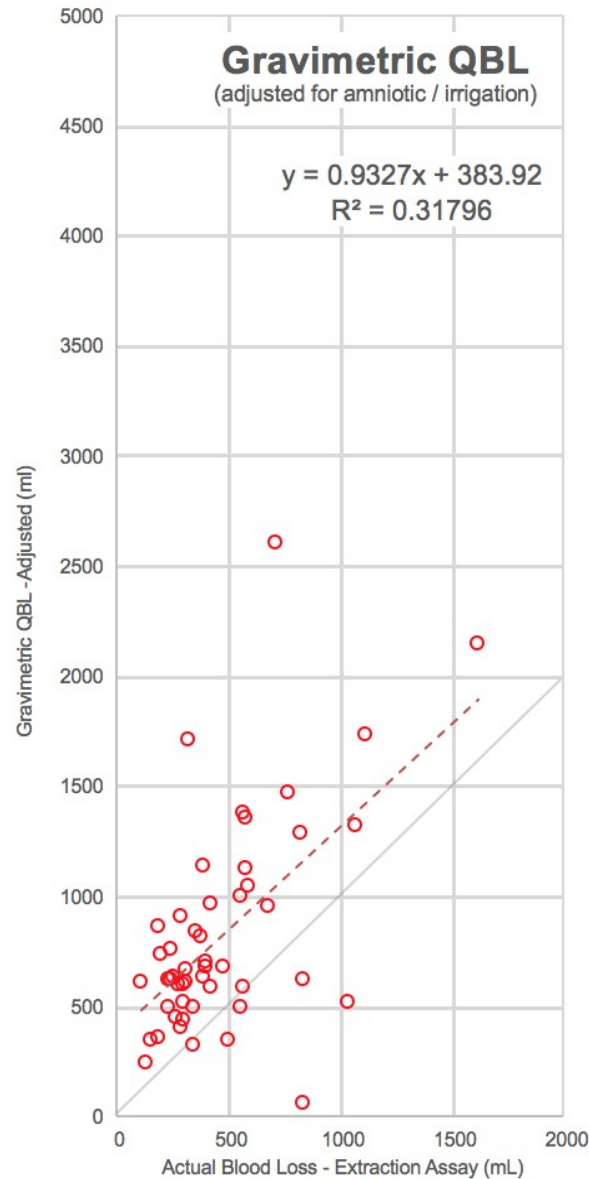
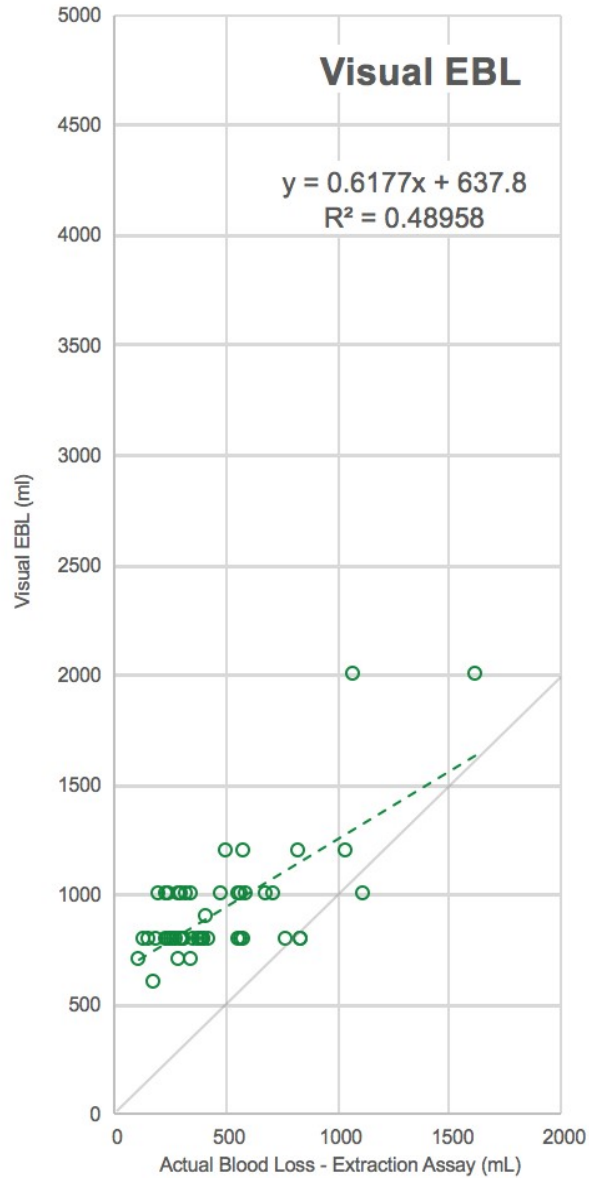
- Visual assessment
- Direct collection of blood
- Gravimetric method
- Determination of plasma volume changes
- Acidhematin method (spectrophotometric analysis)
- Plasma volume changes (radioactive tracers/elements)
- Measurement of Cr-tagged erythrocytes



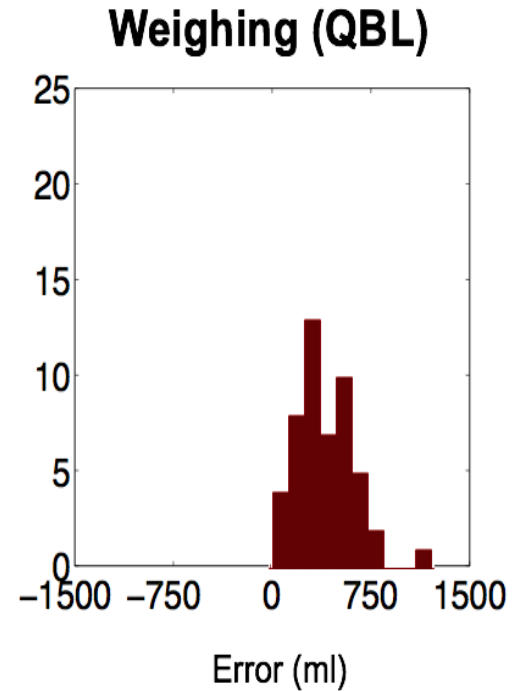
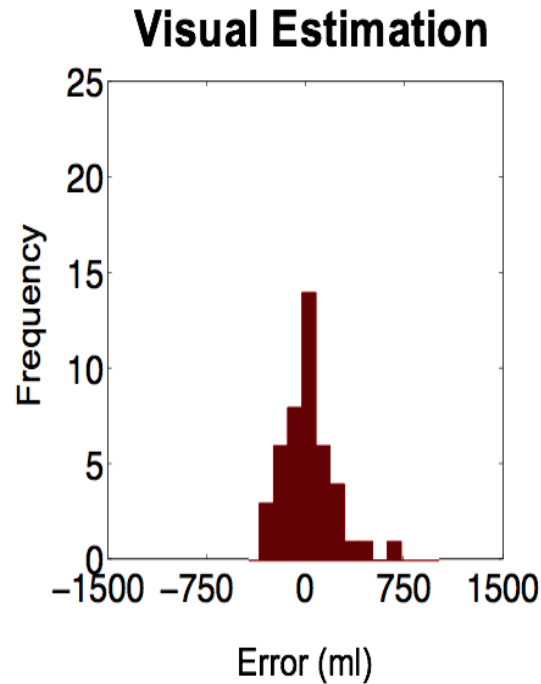
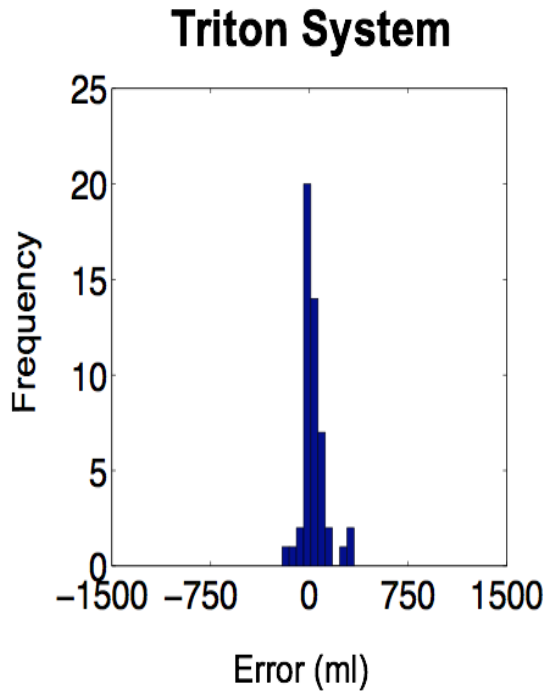
**Failures of each method**

**Underestimation of perioperative/  
peripartum bleeding!!!**

# Assessing blood loss



# C – Section, visual estimation and weighing sponges provide inaccurate results



# Capturing blood loss in the OR

## sponge



Captures blood loss on each sponge used during c-section

## canister



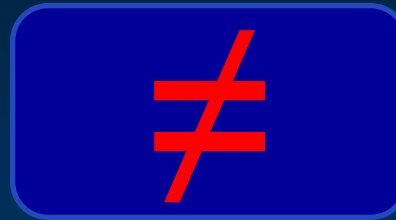
Analyzes image to determine blood loss in suction canister



# Protocols for massive bleeding

## Blood products transfusion RATIO in massive trauma

**PC : FFP: Plate - 1 : 1:1**



- Some obstetric centers have adopted formulaic protocols for PPH on data derived from massive trauma.
- Or **1:1:1:1 PC:FFP:PLT:CRYO**

# The **DISADVANTAGE** of unmonitored “shock packs” transfusion

- FFP is donated from non-pregnant population
  - Fibrinogen < 2g/L
  - Relative low Factor VIII and von Willebrand
- Do not distinguish between the underlying etiology of bleeding
  - Early empirical FFP transfusion **useful** for placental abruption and amniotic fluid embolism (consumption mechanism) and **unnecessary** for atonic bleeding or genital tract trauma
- The coagulopathy of MTP

# The Use of Postpartum Hemorrhage Protocols in United States Academic Obstetric Anesthesia Units

Rachel M. Kacmar, MD,\* Jill M. Mhyre, MD,† Barbara M. Scavone, MD,‡ Andrea J. Fuller, MD,§ and Paloma Toledo, MD, MPH\*

- 58% response rate (60 from 104)
- 67% of all academic obstetric units had PPH protocols and Massive Transfusion Protocol as a part of PPH protocol
- 79% “Obstetric hemorrhage packs”  
PC:FFP:CRYO:PLT 6:4:5:6

# Limitations of the Ratio-Driven Concept for TIC

- Survivor Bias
  - Skews data in observational studies
- Timing of Intervention
  - Early intervention required to improve the hemostatic capacity of exsanguinating patients
- Potential Adverse Events
  - High-volume transfusions are associated with a risk of complications
- Platelet Administration
  - Role of platelet transfusion in the management of TIC is currently unclear

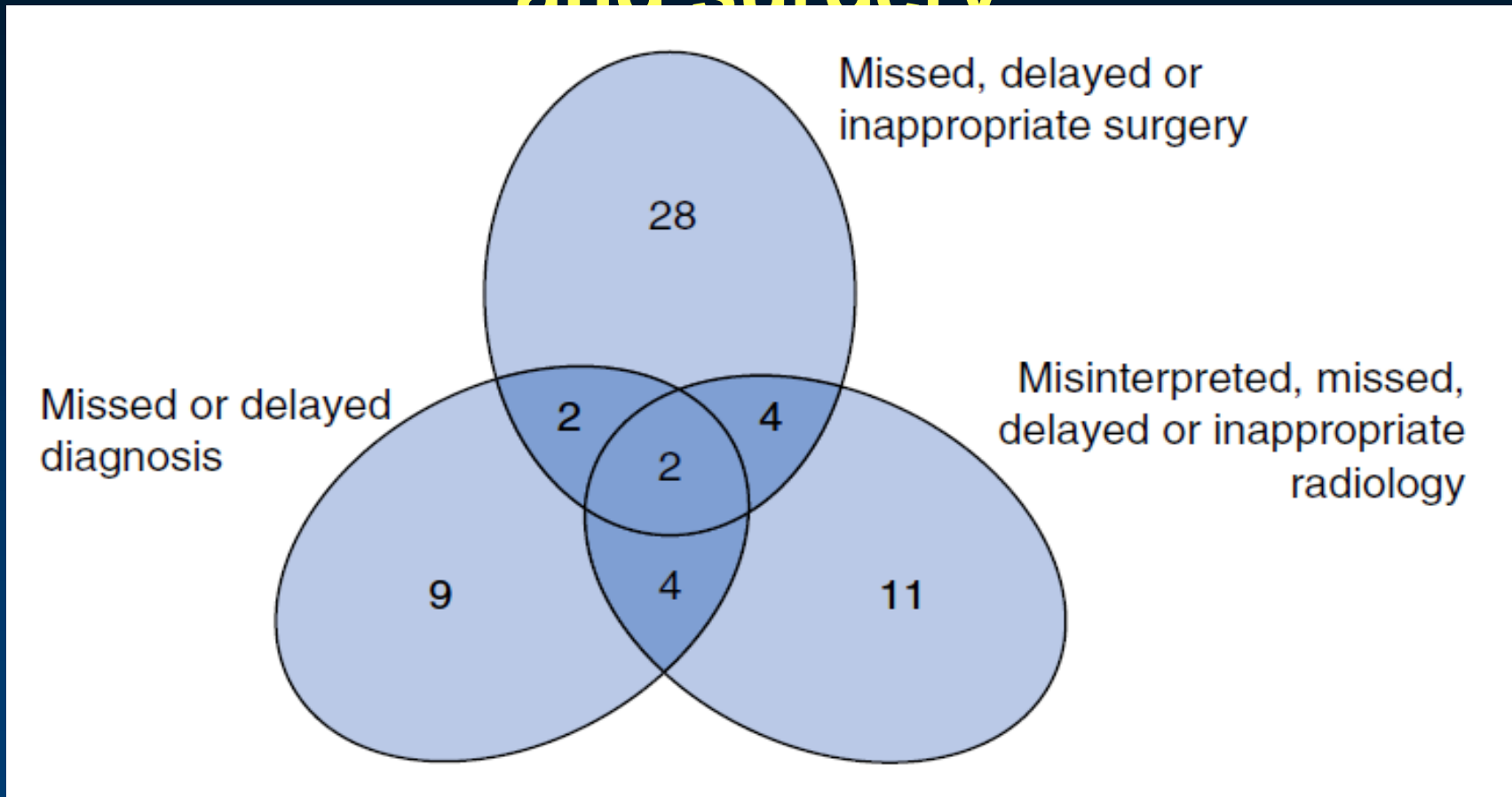
# Opportunities for improvement in the management of patients who die from haemorrhage after trauma

D. O'Reilly<sup>1</sup>, K. Mahendran<sup>1</sup>, A. West<sup>1</sup>, P. Shirley<sup>2</sup>, M. Walsh<sup>1</sup> and N. Tai<sup>1</sup>

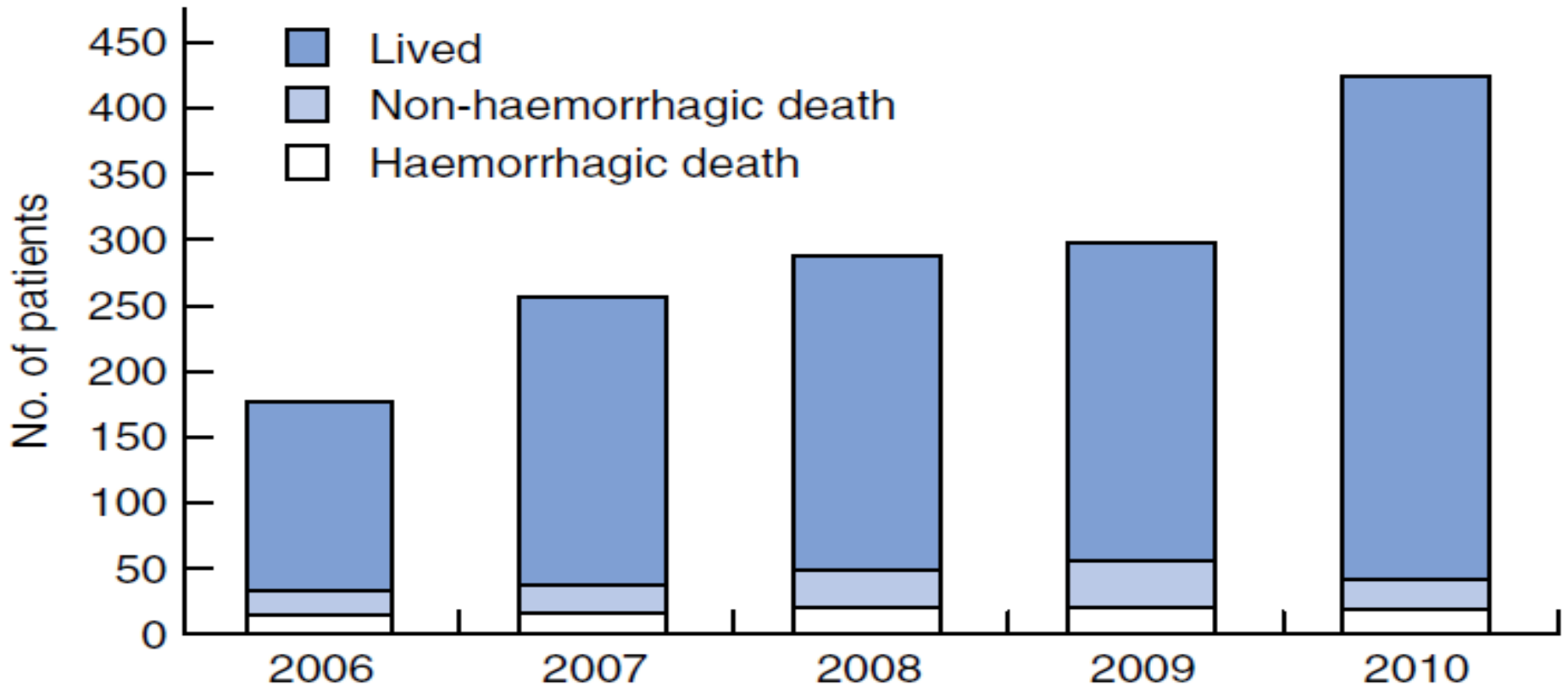


- N = 7511 trauma team activations; 423 patients died
- N = 112 – Hemorrhage 2<sup>nd</sup> most common cause of death (Substantial contributor to death in 15 cases )
- N = 84 of these 127 patients, a total of 150 OPIs were identified
- OPIs frequently involved - the decision between surgery, radiology and further investigation
- The **mortality rate among shock patients fell significantly** over the study interval (P < 0.026)
- Death from traumatic hemorrhage is associated **with identifiable, remediable failures in care**

# Analysis of the interaction between active failures in diagnosis, radiology and surgery



# Survival and mortality from hemorrhage or other cause in patients presenting in shock, 2006–2010





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  - Assessing blood loss
  - Do we need MTP or MHP?
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  - The holy grail - antifibrinolytic therapy, does it work for all or just for some?



# Changes in the hemostasis at term

- Prothrombotic (Hypercoagulable) state
- Levels of **ALL** procoagulant factors (except factor XI) increased
  - Fibrinogen and factor VIII  up to 100% (4-6g/L)
  - Von Willebrand factor  up to 300%
  - **Shorter PT/aPTT**
  - **D-dimer level increase**
  - **Increase in viscoelastic parameters**
- Natural anticoagulants (protein C and S ) fall
  - Increase in fibrinolysis
- Gestational thrombocytopenia

Allard S et al. Br J Haematol. 2014

Thachil J et al. Blood Rev. 2009

O'Riordan MN et al. Best Pract Res Clin Obstet Gynaecol. 2003

Liu XH et al. Int J Gynaecol Obstet. 2009

Szecsí PB et al. Thromb Haemost. 2010

# Is it a Hypercoagulable state of pregnant patients is a risk factor for embolic event ?

- Recombinant activated factor VII was used in three patients with massive obstetric hemorrhage due to
  - placenta previa accreta
  - rupture of the uterus and
  - pre-eclampsia with HELLP
- rFVII decreased the bleeding and enabled control of the hemorrhage
- rFVIIa seems to be an adjunctive hemostatic measure for the treatment of severe obstetric hemorrhage.

# Disseminated Intravascular Coagulation Syndromes in Obstetrics

- DIC common contributor to maternal morbidity and mortality and is associated with up to 25% of maternal deaths
- The etiopathogenesis of DIC is complex and currently thought to be initiated by tissue factor or thromboplastin
- Tissue factor activates the coagulation sequence to cause fibrin clotting and its dissolution by the fibrinolysin system
- Common disorders associated with DIC include:
  - Severe preeclampsia, hemolysis, elevated liver enzymes, and low platelet count syndrome, and massive obstetric hemorrhage

# DIC treatment in obstetrics

- Treatment of DIC is centered on two principles:
- The first is identification and treatment of the underlying disorder
  - Many women with consumptive coagulopathy also have massive hemorrhage
- The second tenet of treatment is that obstetric complications such as uterine atony or lacerations must be controlled simultaneously with prompt blood and component replacement for a salutary outcome

# Rules of treating coagulopathy

- Recognize that it is coming and try to prevent it
- Recognize the major mechanism of the developing coagulopathy and concentrate efforts on its treatment
- Recognize the general pace of the development of coagulopathy in normal patients
- Establish treatment goals for the administration of blood products
- In patients with established coagulopathy:
  - a steady hand on the blood product spigot can be expected to reduce both blood product waste and patient bleeding

# Monitoring (Laboratory diagnosis)

- “Classical” - laboratory-based method
  - PT/aPTT; Fibrinogen; PLT; Hgb
- “Modern” - Point-of-care testing
  - Tromboelastography (TEG)
  - Tromboelastometry (ROTEM)
- Clinical observation with empirical blood product replacement

# PT/aPTT



- During PPH PT/aPTT remain normal despite large amounts of bleeding
  - In a cohort of 456 women with PPH, most had normal PT/aPTT until blood loss reached 5000mL.

# Fibrinogen is an important predictor of severe PPH

- Fibrinogen concentration  $< 2\text{g/L}$  compared with fibrinogen concentration  $>3\text{g/L}$  was
  - Predictive of severe PPH with pos.pred.value of 100%
  - Specificity of severe PPH was 99.3%

Cortet M et al. Br J Anaesth. 2012  
Gayat E et al. Intensive Care Med. 2011



# Fibrinogen levels in non-pregnant women and in pregnant women during the 1<sup>st</sup>, 2<sup>nd</sup> & 3<sup>rd</sup> trimester

	Non-pregnant controls	1 <sup>st</sup> trimester	2 <sup>nd</sup> trimester	3 <sup>rd</sup> trimester
	Fibrinogen concentration (g/l)			
Huissoud et al	3.3 [3.1–4.6]	4.0 [3.7–4.3]	4.6 [4.3–4.8]	5 [4.4–5.8]
Adler et al	2.2 (0.4)	NA	NA	3.79 (0.78)
Uchikova et al	2.6 (0.6)	NA	NA	4.7 (0.7)
Cerneca et al	3.7 (0.8)	4.1 (0.7)	4.6 (0.8)	5.6 (1.1)
Oliver et al	NA	2.6 (0.3)	3.0 (0.2)	3.5 (0.2)
Manten et al	NA	3.5 (NA)	3.79 (NA)	5.1 (NA)
Choi et al	3.3 (0.5)	3.3 (0.5)	3.8 (0.5)	4.4 (0.5)

2.2 – 3.7

2.6 – 4.1

3.0 – 4.6

3.5 – 5.6

# Major obstetric haemorrhage: monitoring with thromboelastography, laboratory analyses or both?

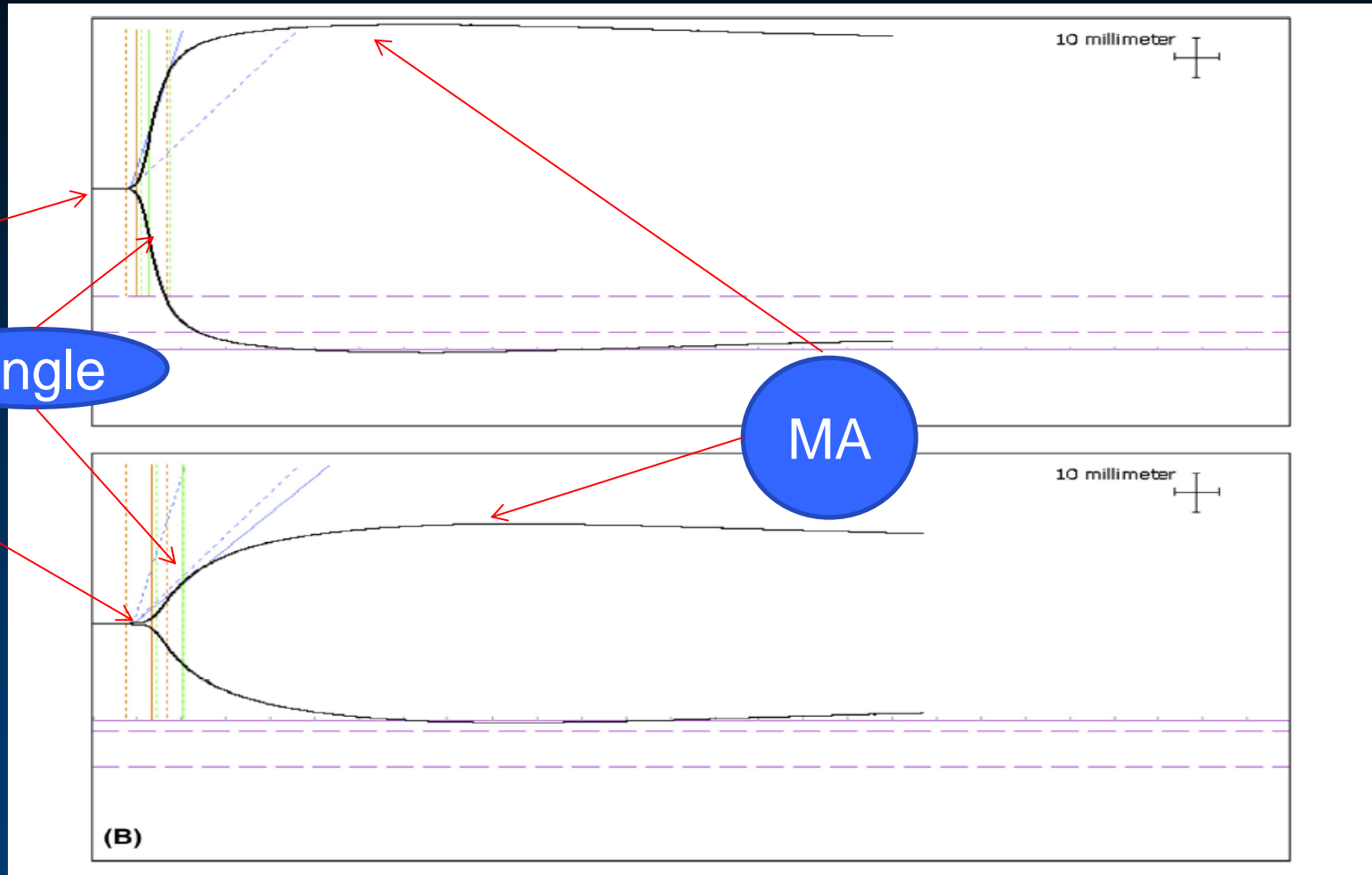
O. Karlsson,<sup>a</sup> A. Jeppsson,<sup>b</sup> M. Hellgren<sup>c</sup>

Table 3 Thromboelastography variables

	Controls (n = 49)	MOH all (n = 45)	MOH 2-3L (n = 35)	MOH > 3L (n = 10)
R (min)	6.3 (5.8 to 6.9) [1.8-13.4]	5.1 <sup>†</sup> (4.5 to 5.7) [1.3-9.6]	5.2 (4.5 to 5.9) [1.6-9.6]	4.5 (3.2 to 5.9) [1.3-6.7]
K (min)	1.8 (1.6 to 2.1) [1.0-5.3]	2.0 (1.8 to 2.2) [1.2-3.7]	2.0 (1.8 to 2.2) [1.2-3.7]	2.1 (1.6 to 2.6) [1.3-3.3]
Angle (degree)	65.2 (62.7 to 67.6) [38.6-77.1]	61.3 <sup>*</sup> (58.7 to 63.8) [42.1-72.1]	61.4 (58.4 to 64.3) [42.1-72.1]	60.8 (55.0 to 66.7) [48.5-71.8]
MA (mm)	72.9 (71.4 to 74.4) [54.2-81.6]	64.8 <sup>Σ</sup> (62.4 to 67.3) [38.0-79.4]	65.1 (62.2 to 68.1) [38.0-79.4]	63.8 (59.7 to 67.9) [55.4-74.6]
LY30 (%)	1.5 (0.9 to 2.2) [0-9.3]	0.4 <sup>†</sup> (0.1 to 0.7) [0-5.9]	0.4 (0.1 to 0.8) [0-5.9]	0.2 (-0.06 to 0.4) [0-0.9]

Data are mean, (95% CI) and [range]. R: time to start of clotting; K: time to 20 min clot firmness; Angle: clot growth rate; MA: maximum clot amplitude; LY30: lysis 30 min after maximum amplitude. <sup>\*</sup>P < 0.05; <sup>†</sup>P < 0.01; <sup>Σ</sup>P < 0.0001 compared to controls.

# Two TEG profiles



Turnaround time PT/aPTT - TEG from  $35 \pm 37$  min to  $14 \pm 3$  min

# Tranexamic acid

- Antifibrinolytic agents strengthen fibrin clots by inhibiting enzymatic fibrinolysis.
- Blocks the degradation of fibrin clots by plasmin.
- Have moderate but significant effect on blood loss.
- Without significant adverse effects.

20000 adult trauma patient CRASH-2 trail

**The addition of TA (1g) is cheap, likely to be useful and appears safe.**

(Mercier FJ et al. Curr Opin Anaesthesiol. 2010)

## The **CRASH 2 trial** for trauma patients

Early administration of TXA safely reduced the risk of death in bleeding trauma patients.

# Trauma patient $\neq$ Obstetric patient

The WOMAN Trial: TA for the treatment of PPH:  
an international randomized, double blind placebo controlled  
trial. 20,000 women

**WHO and ESA guidelines recommend  
1gm TA for > 1L Bleeding  
or for suspected massive bleeding**

# PBM Recommendations in National and International Obstetric Societies' PPH Guidelines

	ACOG	SOGC	RCOG	RANZCOG	D-A-CH	IEP	NPM S	CNGO F
Transfusion Indications	+	-	+	+	+	+	-	+
RBC	+	-	+	+	-	-	+	+
Plasma	-	-	+	+	+	-	+	+
PLTs	-	-	+	+	+	-	-	+
MTP	-	-	-	+	-	+	+	-
Fibrinogen replacement	-	-	+	+	-	+	+	+
Pharmacological agents	-	-	-	+	+	+	-	+
RVIIa	-	-	+	+	+	+	-	-
Cell salvage	+	-	+	+	-	-	-	-
Other PBM strategies	+	-	+	+	+	+	+	+

# Summary

- Rate of Post Partum Hemorrhage (PPH) increasing
- **Massive PPH = ~~Massive~~ trauma-associated hemorrhage**
- EBL – the need for better objective measures
- **Lab monitoring (Fibrinogen; Viscoelastic)**
- Institutional protocol for PPH – MTP is not enough!
- **Blood components – use clinical judgment – goal directed**
- Identify PPH and act early and quickly!!!
- **Team Approach !!! PBM can lead the way**

**THANK YOU**