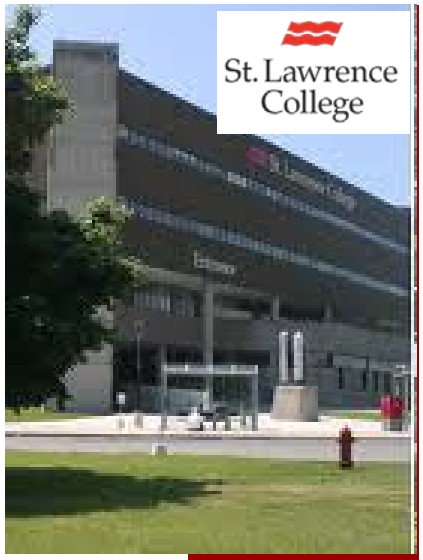


Issues in Haemostasis and Pregnancy

Dr. Maha Othman MD MSc PhD

- Associate Professor, Biomedical and Molecular Science, School of Medicine, Queen's University, Kingston, Ontario, Canada
- Professor, School of Baccalaureate Nursing, St Lawrence College, Kingston, Ontario, Canada
- Chairman of ISTH SSC on Women's Health Issues in Thrombosis and Hemostasis

ISth
International Society on Thrombosis and Haemostasis

Outline

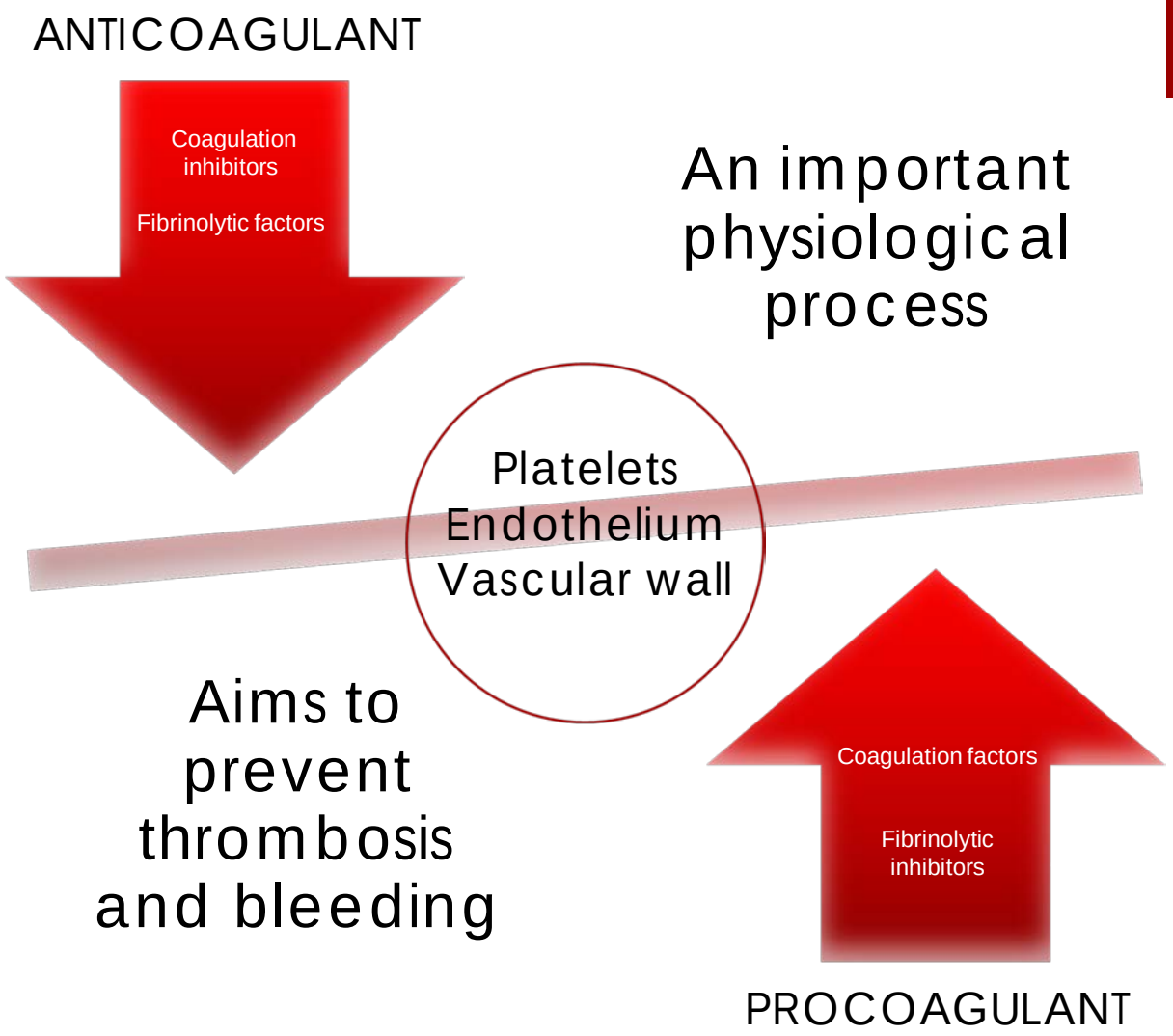
- Basics at a glance & haemostasis/coagulopathies in pregnancy
- Haemostasis testing in pregnancy and puerperium:
  - Conventional vs global viscoelastic testing (TEG, RoTEM)
  - Thromboelastography (TEG)
- Our research around coagulopathies and inflammation in pregnancy related conditions
- Current international projects around women, pregnancy and haemostasis

Societat Catalana d'Hematologia i Hemoteràpia

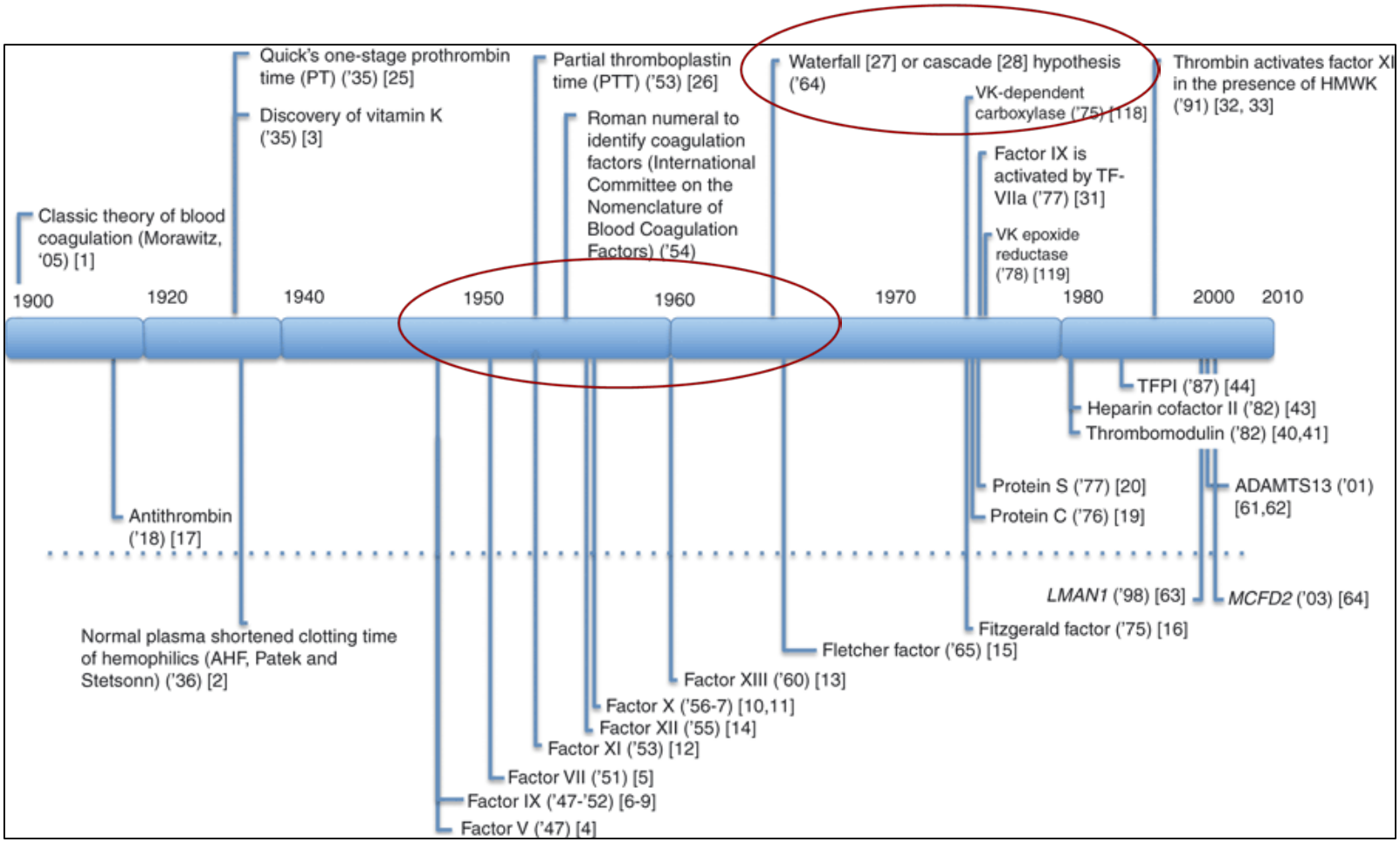
Divendres, 31 de maig de 2019

Auditori de l'Acadèmia, Barcelona

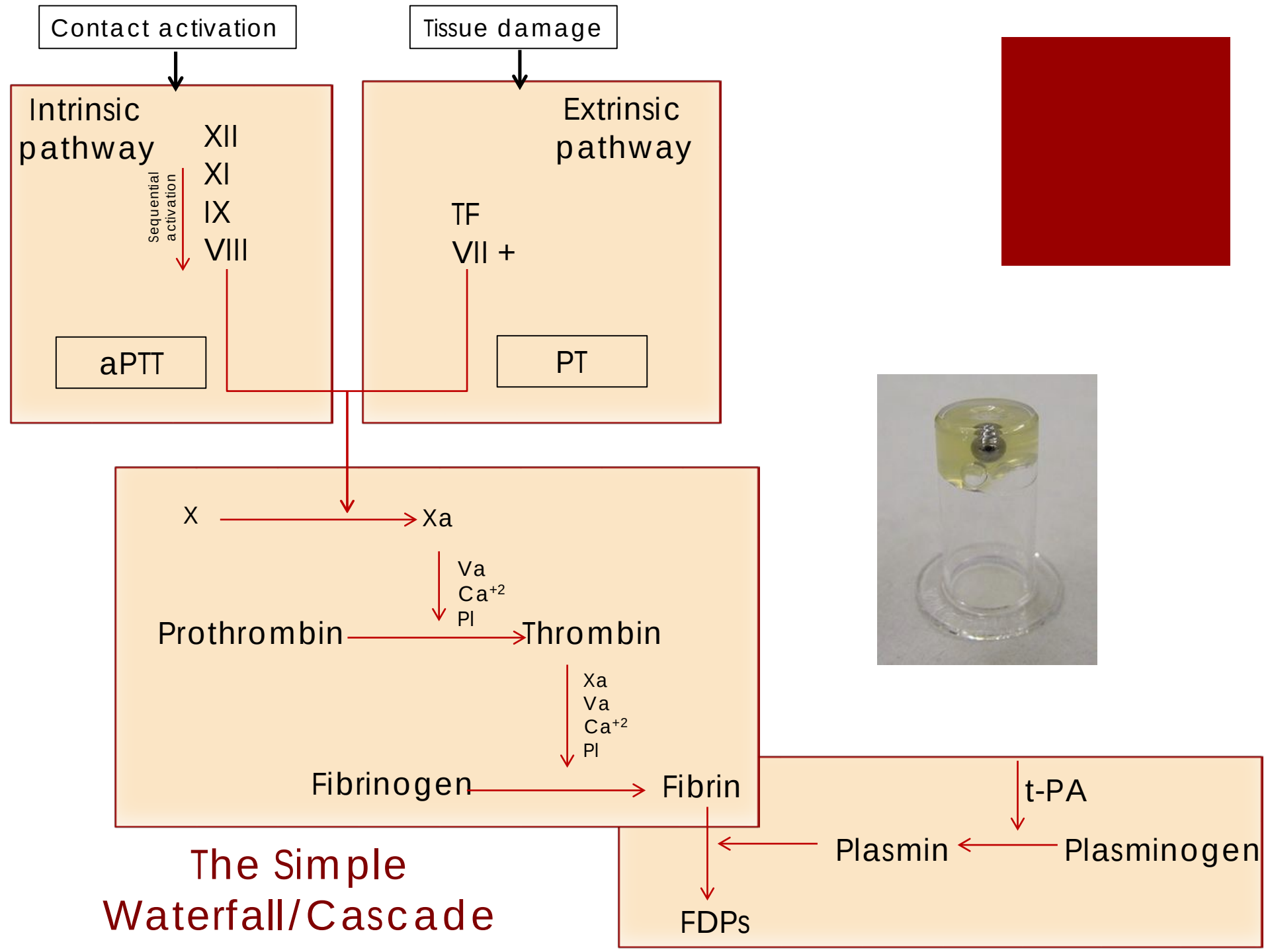
Haemostasis



Historical Perspectives

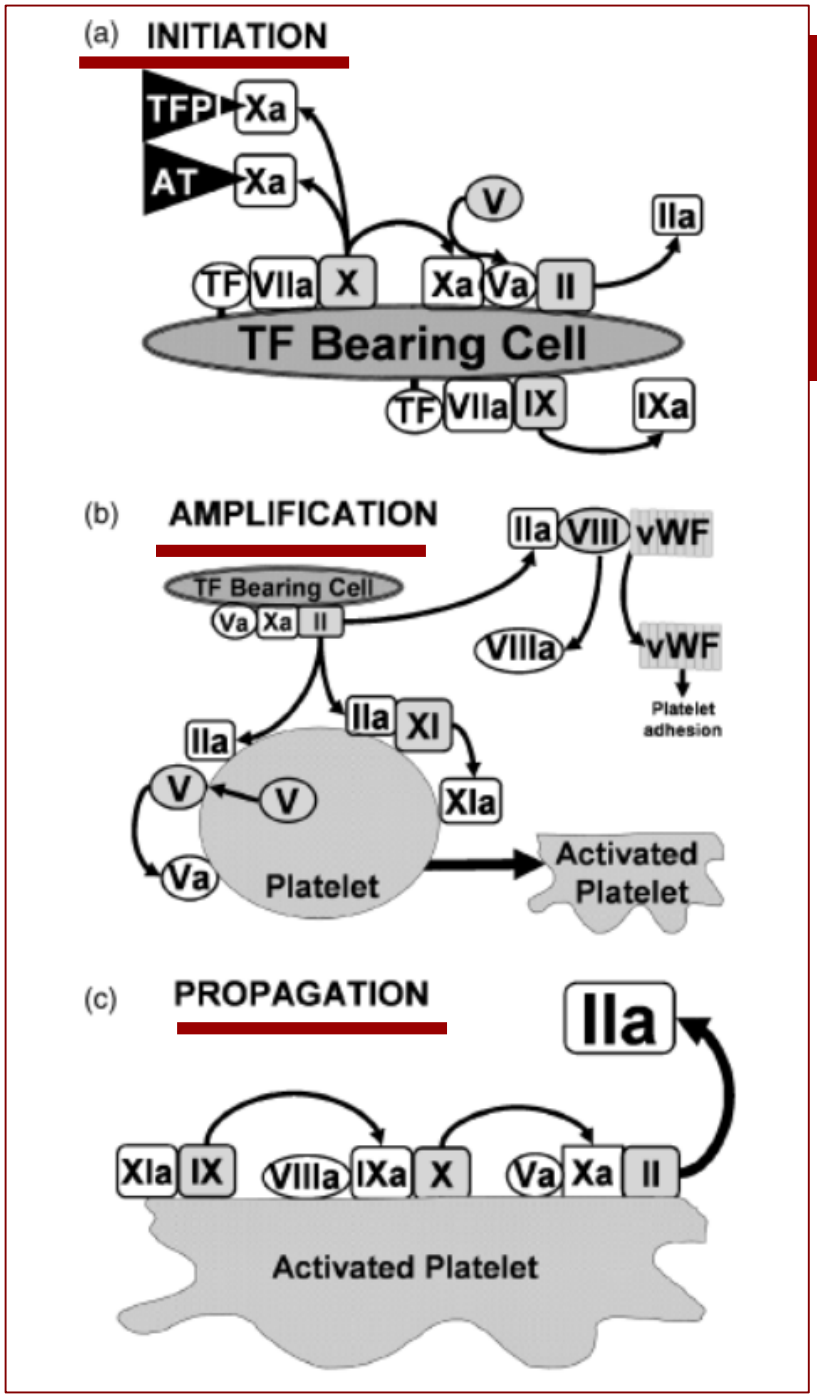


SAITO et. al., JTH 2011; 352-363
Davie JBC 2003;278 (5): 50819–50832, 2003



The Simple Waterfall/Cascade

Cell Model Theory



Smith SA. J Vet Emerg Crit Care San Antonio Tex 2001. 2009 Feb;19(1):3–10.

Pregnancy is a Physiological Hypercoagulable State

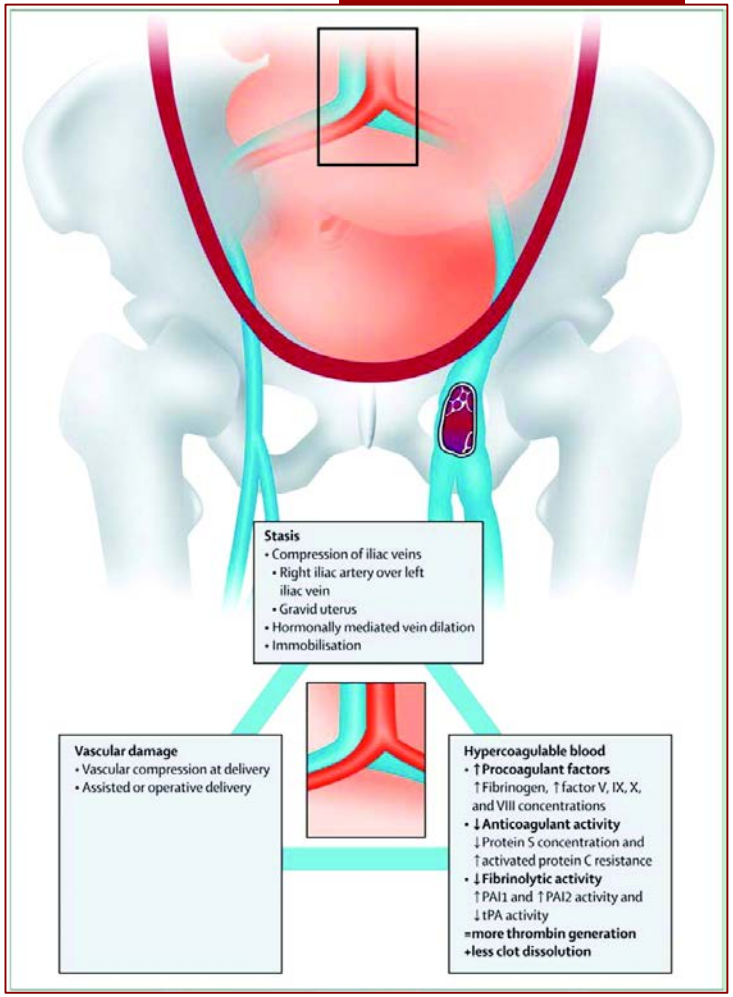
↑Fibrinogen, FVII, FVIII, FIX, FXII, VWF

↑ Platelet aggregation

Placenta expresses high levels of TF

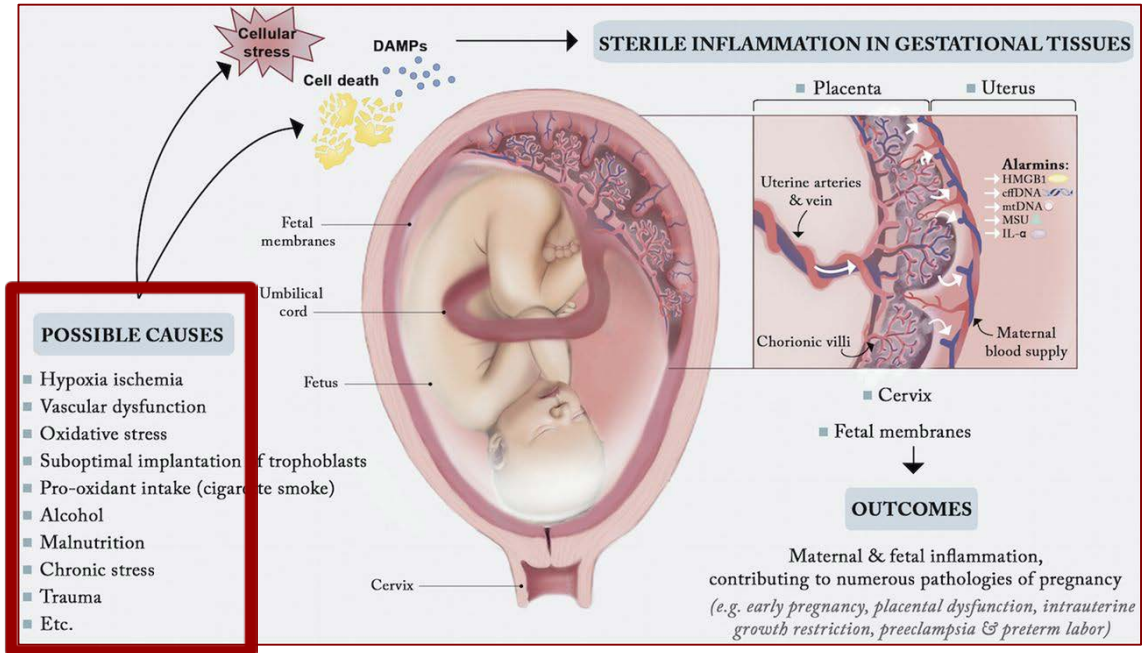
↓ t-PA
↑ PAI-1 & PAI- 2

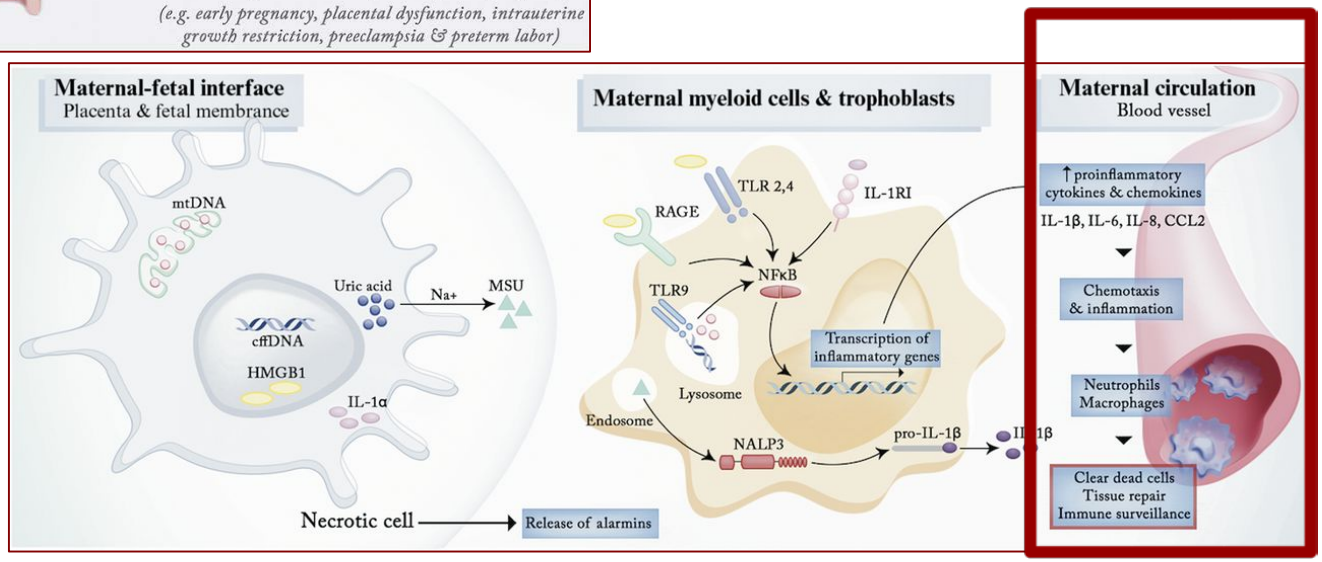
State of inflammation



Virchow's triad in pregnancy. Bourjeily etal., Lancet. 2010;375(9713):500–512.
Othman etal., Semin Thromb Haemost 2010; 36(7):738-46 *Sood et al, Blood. 2006 Apr 15;107(8):3173-80*

Maternal Inflammation Contributes to Various Pathologies in Pregnancy





Nadeau-Vallée etal., Reproduction 2016 152, 6; 10.

Coagulopathies in Pregnancy

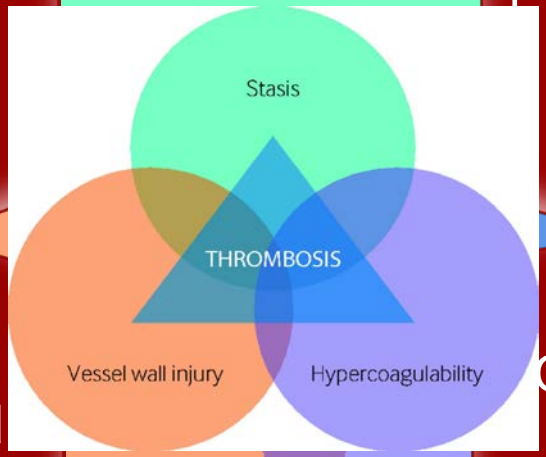
Thrombotic risk :

4-10 fold during gestation

22 fold risk postpartum

DVT &PE

PE: ~ 20% of pregnancy-maternal deaths



Impaired fetal and maternal outcomes

+

Long term complications

Coagulopathies are seen in association with PE, FGR, Recurrent miscarriage

Pomp etal., J Thromb Haemost 2008; 6(4):632-637.
Stirling etal., Thromb Haemost. 1984;31(2):176–82.
Sultan etl., Br J Haematol 2012;156(3):366-373.
Heit etal., Ann Intern Med 2005;143(10).

Laboratory Assessment of Haemostasis in Pregnancy

Normal values shift during pregnancy and puerperium

Sensitive tests are unavailable

Poor applicability and interpretation

Conventional routine tests are insufficient to represent the in vivo conditions

Complexity of some pregnancy haemostatic complications eg. PE, DIC

Othman M, McLintock C, Kadir R.. Semin Thromb Hemost. 2016 Oct;42(7):693-695.

Conventional Testing

- PT/INR, APTT
- Fibrinogen
- Platelets number & function
- Coagulation factors/inhibitors
- Fibrin degradation
- Plasminogen, t-PA and PAI

- Test various parts of hemostasis, but in isolation
- Plasma based:
  - may not reflect accurately in-vivo situation
- Platelet function: difficult to assess
- Static not real time tests
- Take time to complete results ∴ best guess or delay management

	Pregnant reference ranges		
	Pre-operative (n = 47)	Postoperative (n = 49)	Non-pregnant reference range
PT; s	9.5 (9.1–9.9)[a]	9.8 (9.2–10.4)[a]	9.6–11.6
APTT; s	27.1 (22.5–31.7)[b]	28.4 (19.3–36.5)	24.0–32.0
Fibrinogen; $g.l^{-1}$	5.0 (3.7–6.4)[a]	4.4 (3.0–5.7)[a]	1.5–4.0

Macafee etal., Anaesthesia 2012, 67, 741–747

Hartert H. Klin Wochenschr. 1948;26:577–583

KLINISCHE WOCHENSCHRIFT

26. JAHRGANG, HEFT 37/38 — 1. OKTOBER 1948

ORIGINALIEN.

BLUTGERINNUNGSSTUDIEN MIT DER THROMBELASTOGRAPHIE, EINEM NEUEN UNTERSUCHUNGSVERFAHREN*.

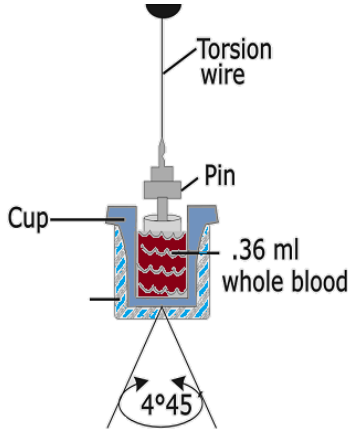
Von

HELLMUT HARTERT.

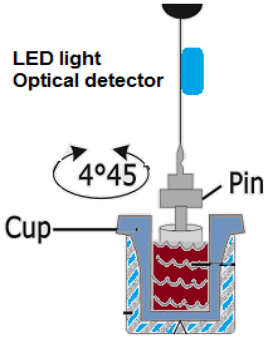
Medizinische Universitätsklinik Heidelberg (Direktor: Prof. Dr. R. SIEBECK).

Thromboelastogrpahy (TEG)

TEG®



ROTEM®

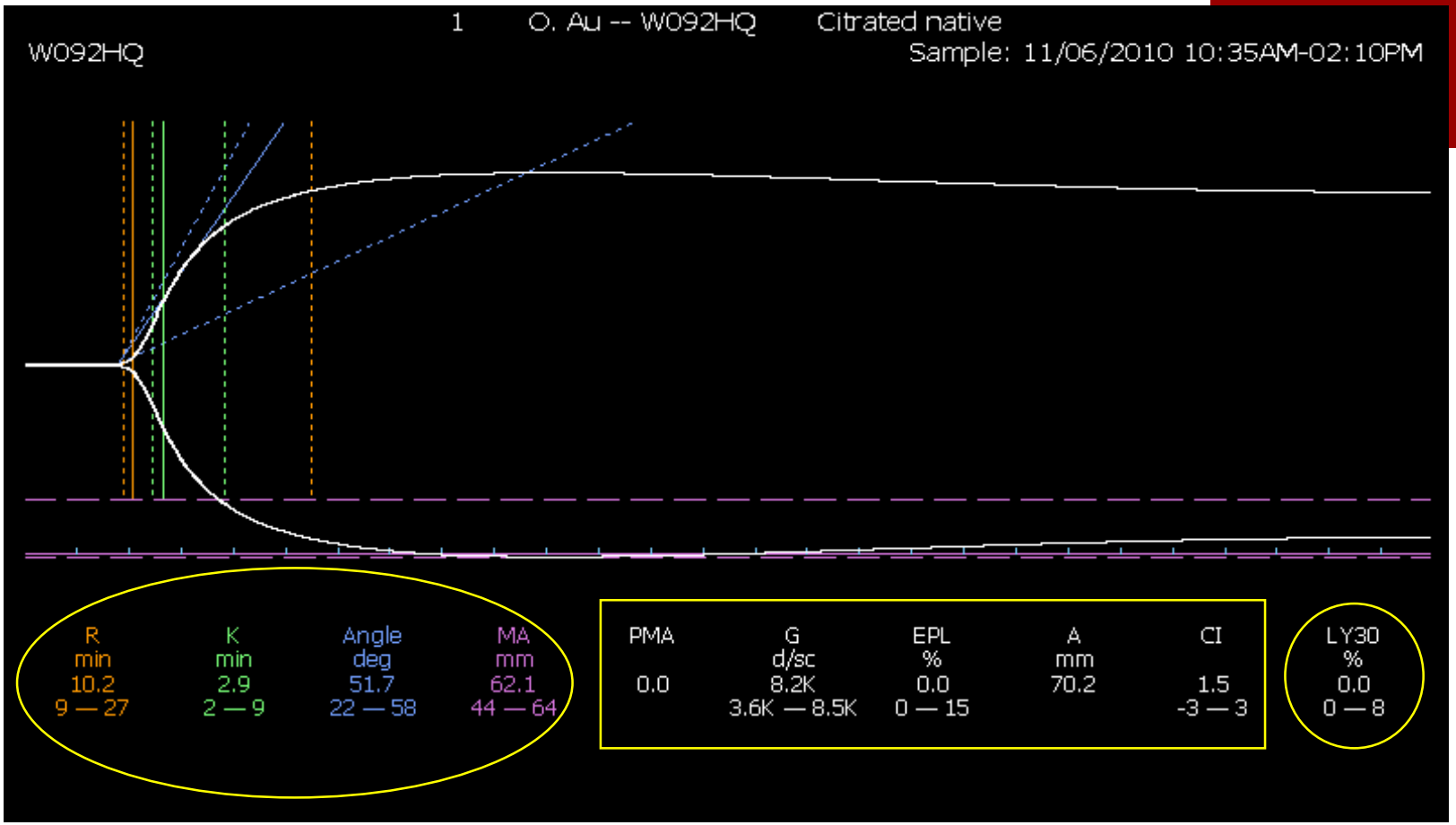


Thromboeastometry (RoTEM)

A Drop of Blood …

The Whole Picture!

TEG Trace



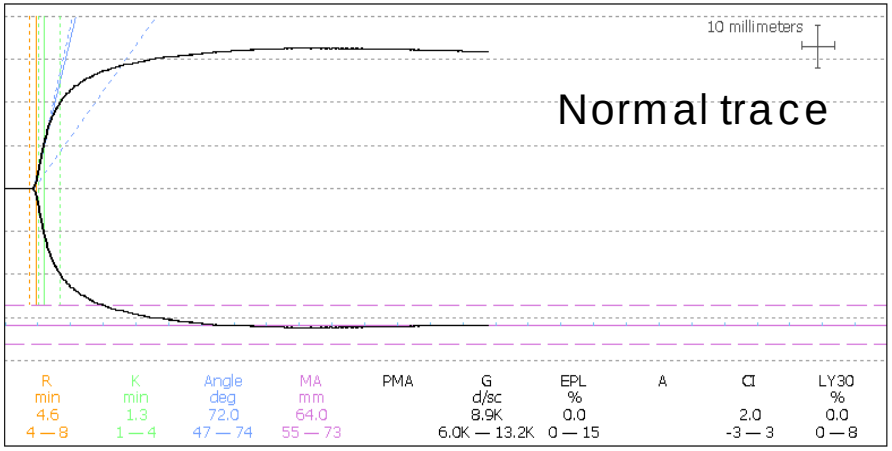
Coagulation

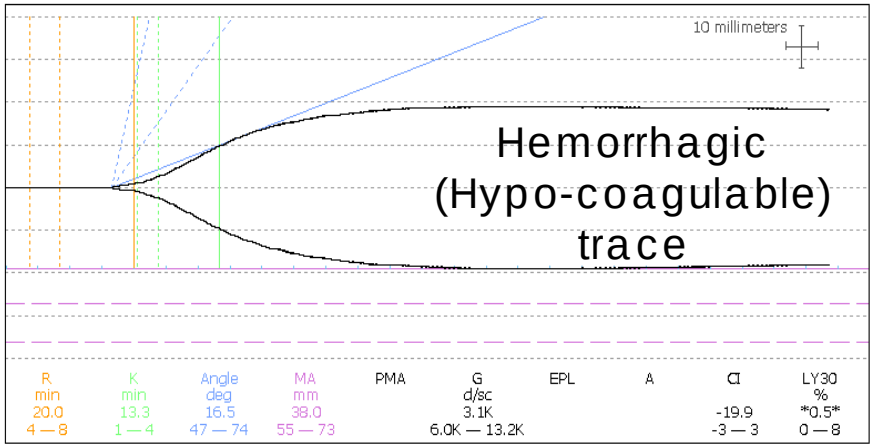
Calculated parameters

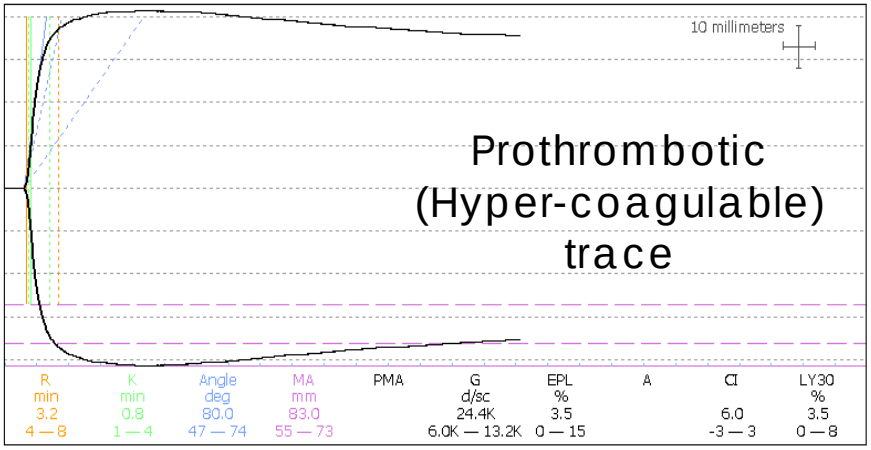
Fibrinolysis

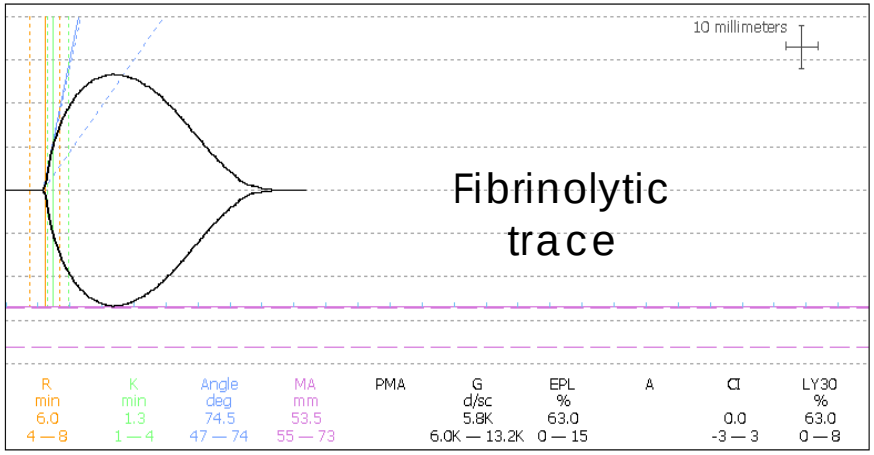
Thromboelastography/thromboelastometry. Clin. Lab. Haem. 2005, 27, 81–90

Normal & Abnormal TEG Traces

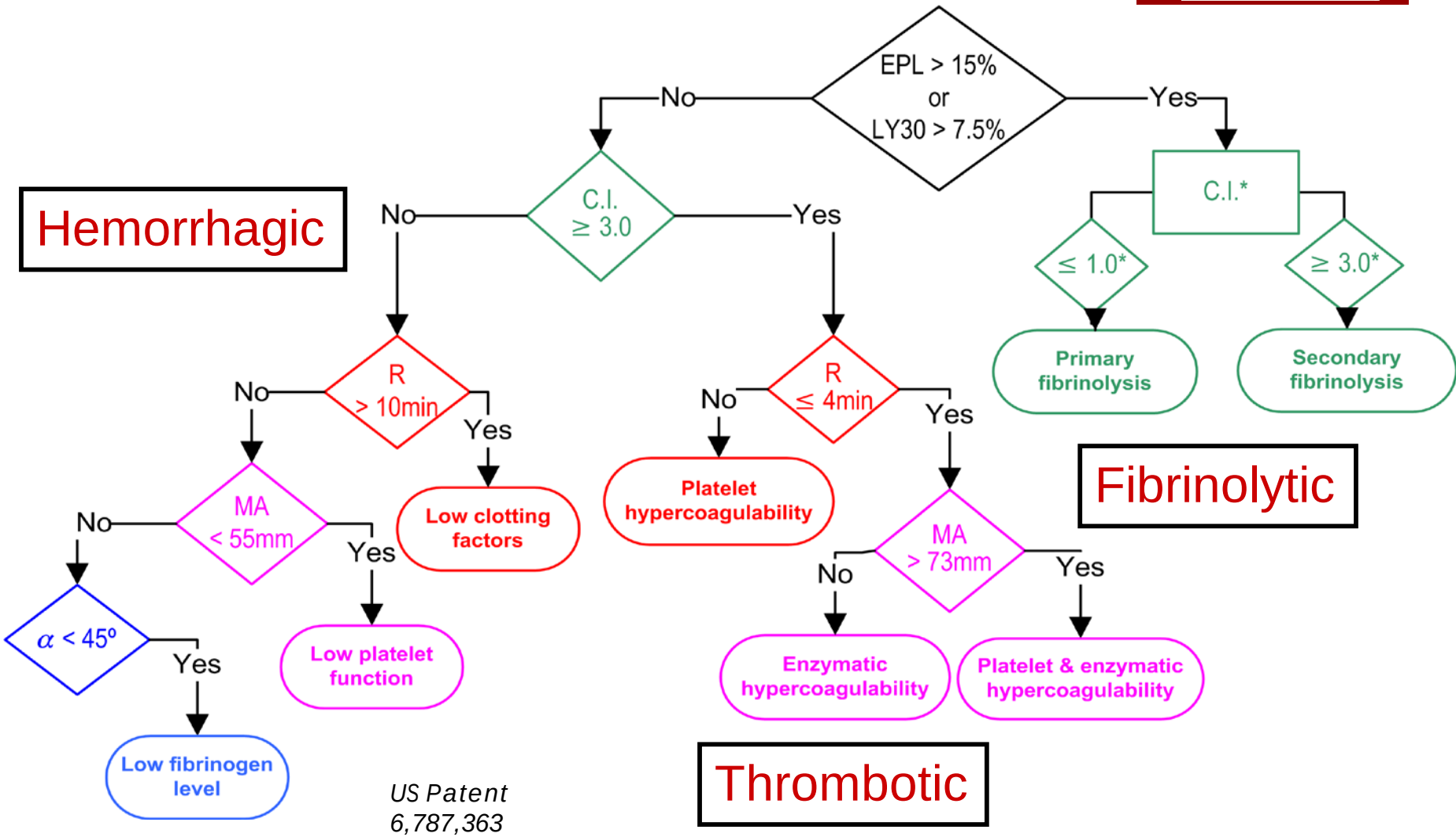








TEG Decision Tree
Quantitative



US Patent 6,787,363

Pregnancy Reference Range

New reference ranges for pregnant women.

	THROMBOELASTOGRAPHIC PARAMETERS*					
	r (min)	k (min)	AA (°)	MA (mm)	LY60 (%)	CI
Reference ranges for the general population	4 - 8	1 - 4	47 - 74	55 – 73	0 - 15	(−3) – (+3)
Our recommendation for pregnant women	2 - 8	1 - 3	60 - 77	64 – 76	0 - 3	0 - 5

*For kaolin-activated samples.

RoTEM Reference ranges
T1: EXTEM: CT 31–63 s, CFT 41–120 s, and MCF 42–78 mm.
INTEM: CT 109–225 s, CFT 40–103, and MCF 63–78 mm.
FIBTEM: CT 31–79 s and MCF 13–45 mm. APTEM: CT 33–62 s, CFT 42–118, and MCF 61–79 mm.

	Pregnant reference ranges				
	Pre-operative (n = 50)	Postoperative (n = 50)	Post-enoxaparin (n = 33) Uncorrected	Post-enoxaparin (n = 33) Corrected	Non-pregnant reference range
R time; min	7.0 (1.0–13.0)[a]	6.6 (2.4–10.8)	8.2 (3.2–13.2)[b]†	6.7 (2.3–11.1)	4–8
K time; min	2.0 (0.2–3.8)	1.8 (0.4–3.2)[c]	2.2 (0.4–4.0)	1.7 (0.5–2.9)[d]	0–4
MA; mm	75.4 (64.6–86.2)[b]	76.4 (66.8–86.0)[b]	72.8 (62.8–82.8)[b]‡	74.6 (65.4–83.8)[b]	54–72
Alpha angle; °	64.8 (47.6–82.0)[c]	67.3 (53.5–81.1)[b]	63.2 (45.0–81.4)	67.4 (54.6–80.2)[b]	47–74
Ly30; %*	1.6 (0–8.8)[b]	0.7 (0–4.9)[b]	0.7 (0–4.5)[b]	4.5 (0–13.9)§	0–8
CI	1.2 (−5.4–7.8)[e]	1.8 (−3.4–7.0)[b]	−0.2 (−6.4–6.0)¶	1.6 (−3.6–6.8)[b]	−3–3

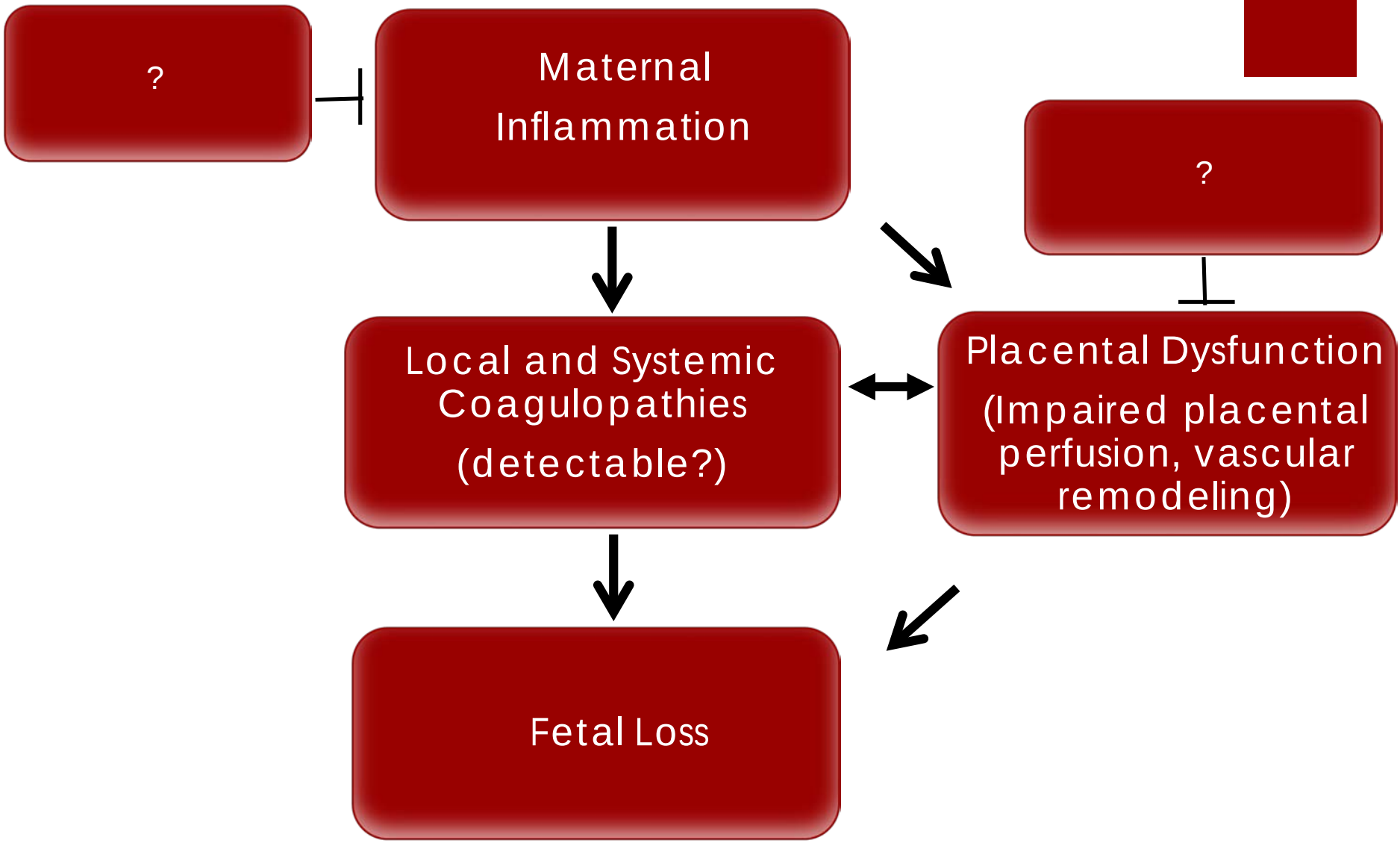
F. Polak et al. Thrombosis Research 128 (2011) e14–e17
Macafee etal., Anaesthesia 2012, 67, 741–747
De Lange etal., Br J Anaesth 2014; 112: 852–9.

The use of viscoelastic hemostatic tests in pregnancy & puerperium: review of the current evidence - communication from the Women's Health SSC of the ISTH

- Hypercoagulable state of pregnancy increase towards the third trimester, labor, and up to 6 weeks post-partum
- Potential to reflect the higher risk of venous thromboembolism, particularly PP
- Rreference ranges are available. Profiles (pre and postoperative) for women undergoing caesarian delivery are also available
- TEG/RoTEM-guided transfusion during PPH
- Strong correlation with conventional coagulation parameters in normal, hypocoagulable, and hypercoagulable states
- Potential to guide safe neuroaxial anesthesia in obstetric emergencies
- Potential to detect hypercoagulability in various pregnancy-related conditions including gestational diabetes, preeclampsia as well as HELLP syndrome, recurrent pregnancy loss
- Larger studies needed to promote application particularity in thrombotic complications

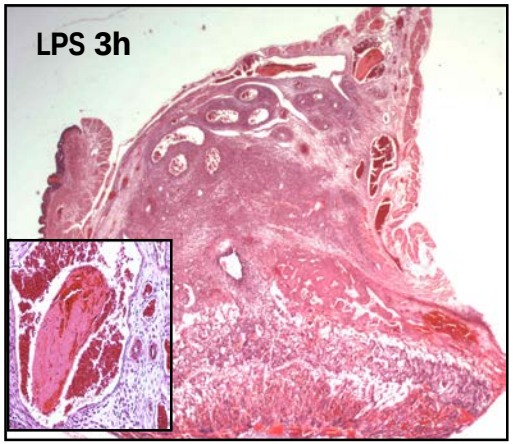
Othman etal., JTH 2019 First published April 25,

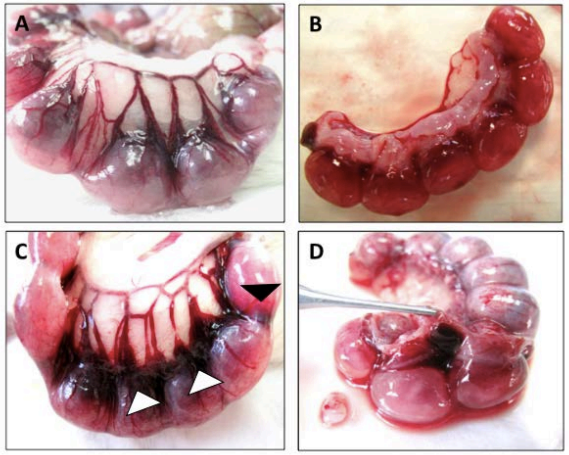
Hypothesis re Coagulopathies in Pregnancy

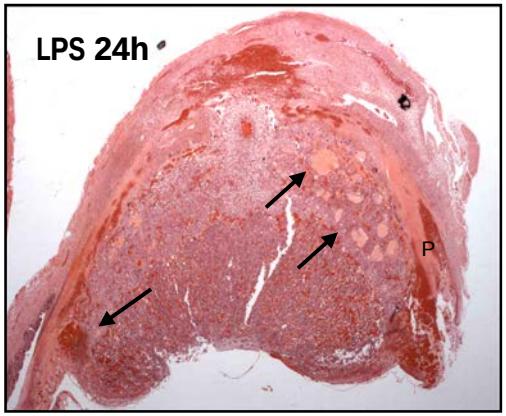


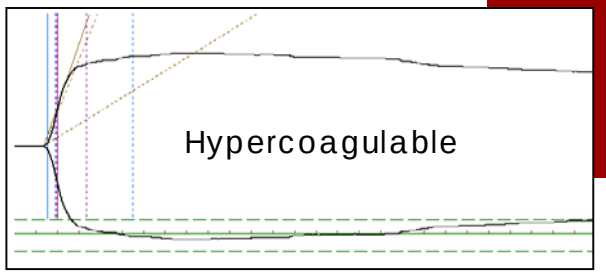
Inflammation Associates with Coagulopathies in a Rat Model of Preeclampsia/Fetal loss

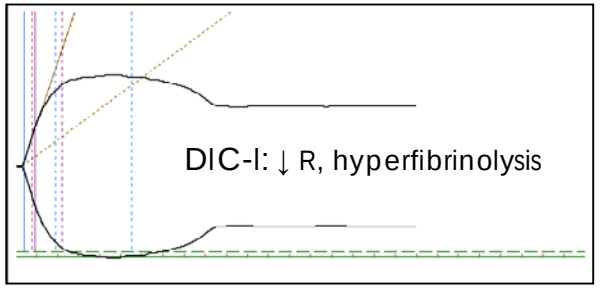
Rat Model of fetal loss GD: 14.5
LPS administration (100 µg/kg)
"Acute model"

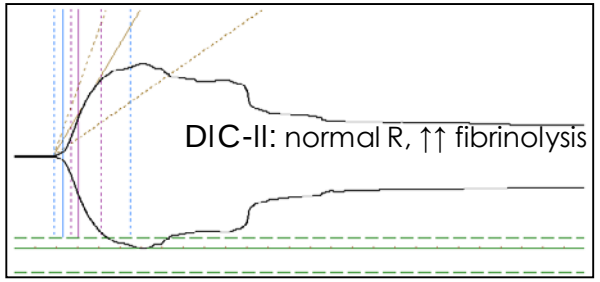


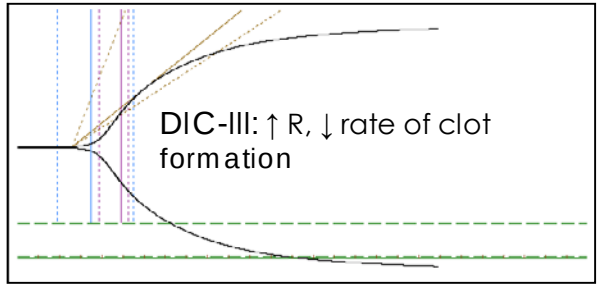






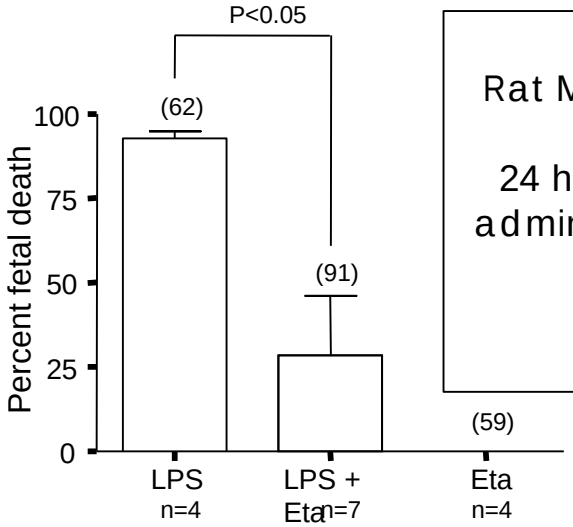






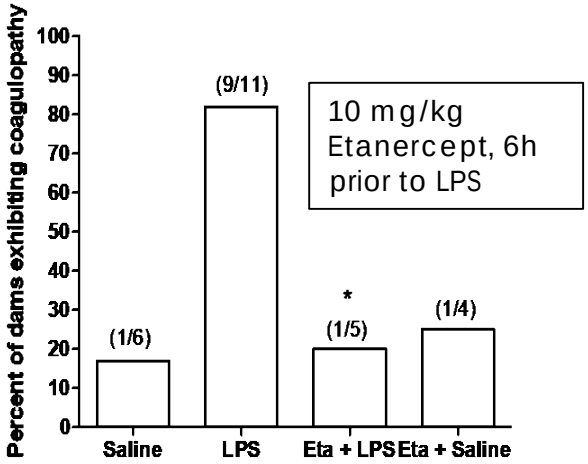
Falcón et al. Thromb Haemost 2012; 107: 438–447

Anti inflammatory & Nitroglycerin Prevents coagulopathies/Fetal Death

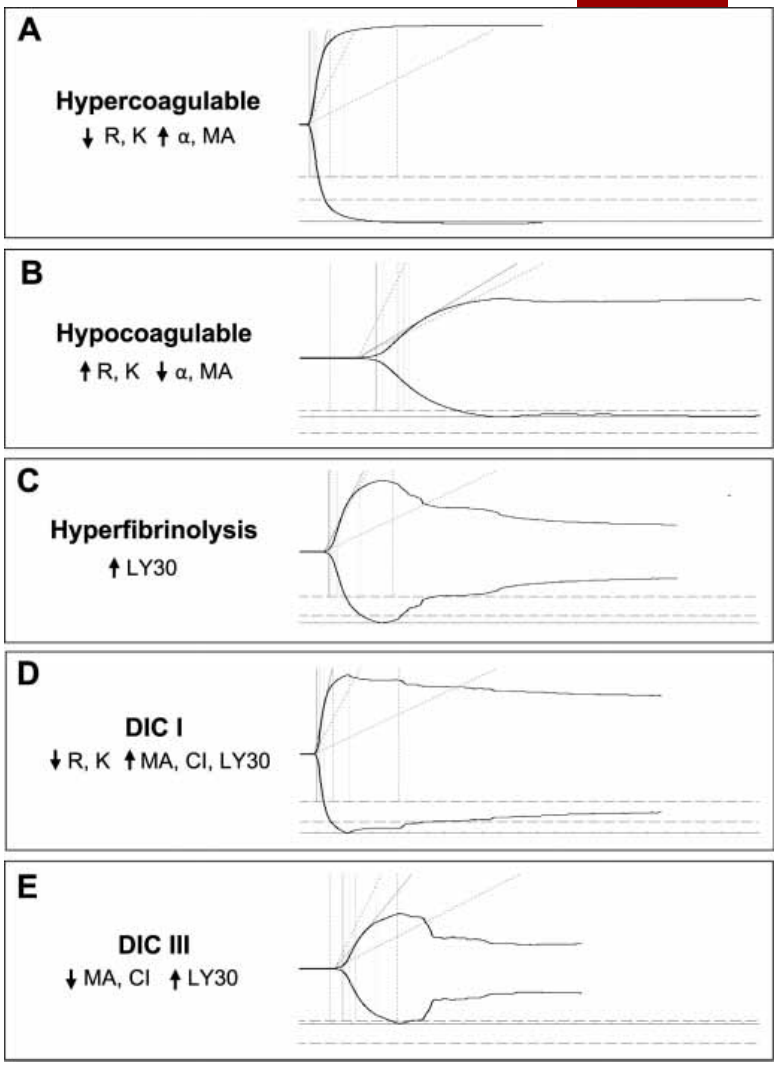


Rat Model of Pre-eclampsia GD: 17.5
24 h after the last of 4 daily LPS administrations (40 µg/kg) starting GD14.5

"Chronic model"

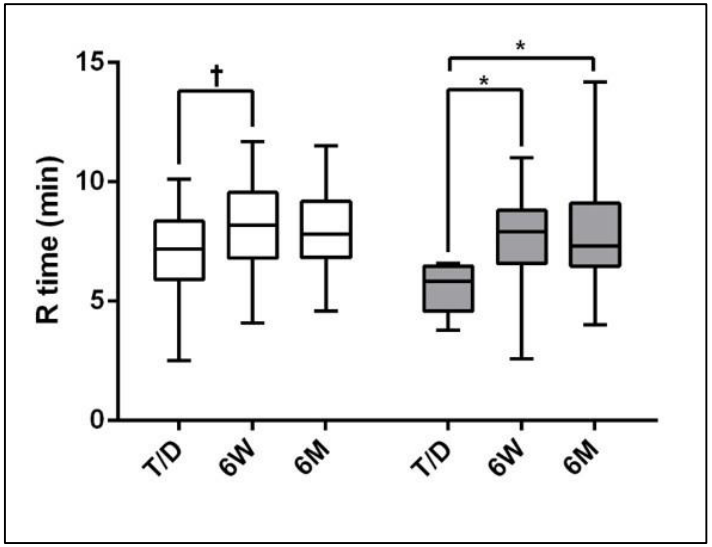


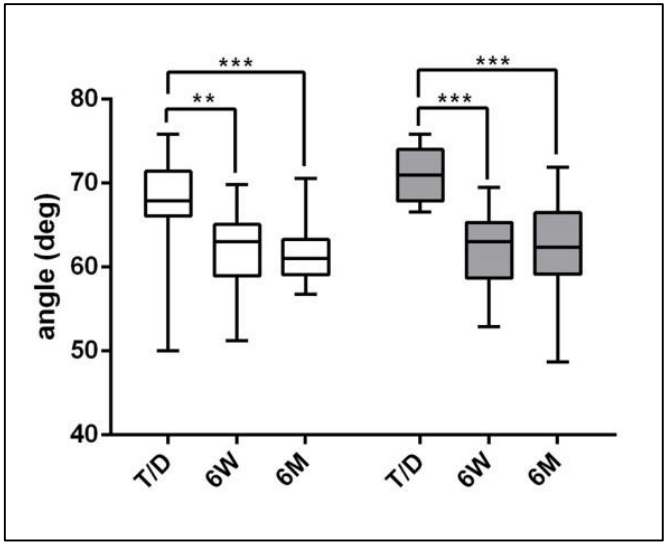
10 mg/kg Etanercept, 6h prior to LPS

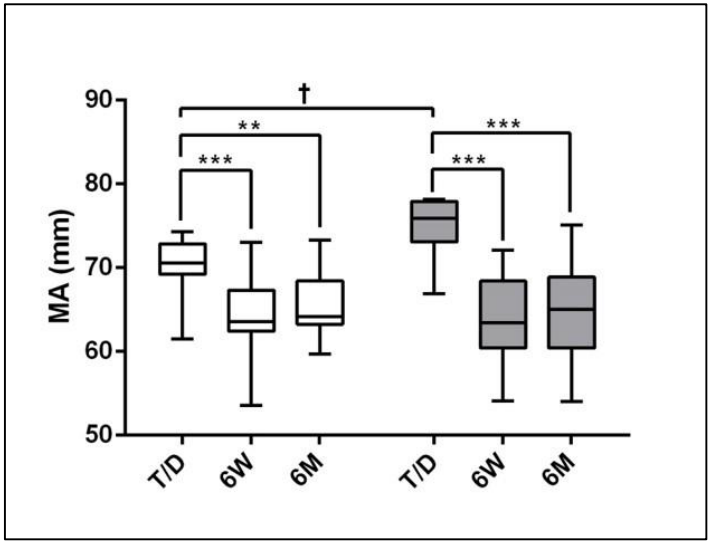


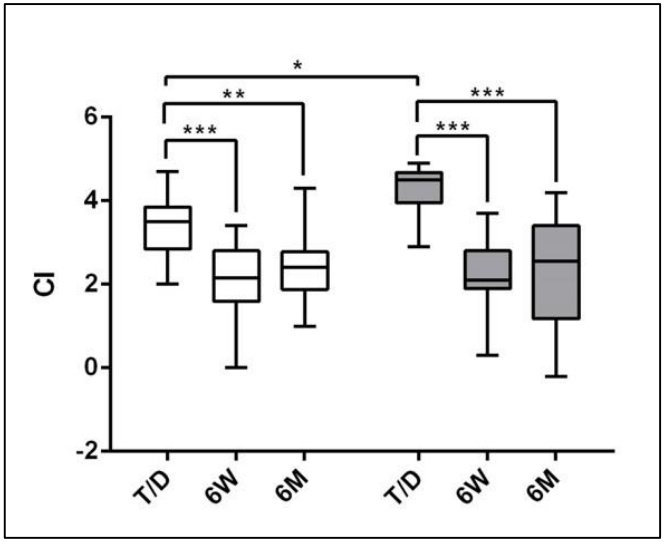
Cotechini et al. Thromb Haemost 2012; 107: 864–874

Coagulopathies (Evident by TEG) in Pre-eclamptic and Normotensive Women









Hypercoagulability:

↓ R

↑ Angle, MA, CI

Normal pregnancy

Pre-eclampsia

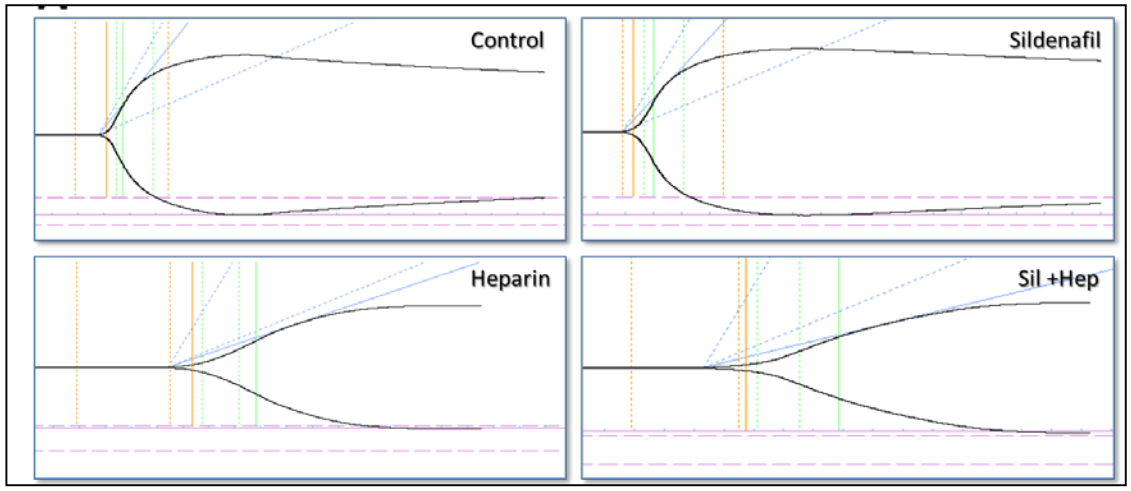
TD: term/ delivery

6w: 6w after delivery

6m: 6 moths after delivery

Murray etal., Blood Coagul Fibrinolysis. 2018 Sep;29(6):567-572

Sildenafil & Dalteparin as Therapeutics for Recurrent Pregnancy Loss



RPL **mouse model**
LPS 100µg/Kg at GD 15

Sil (50mg/kg)
LMWH 500IU/kg
Both Sil & LMWH
Saline control mice

n = 4	R (min)	MA (mm)	LY30 (%)	CI
Control	7.80	60.00	0.10	2.10
LPS	5.53#	58.01	4.80##	2.66
Sildenafil	5.75	40.03*	0.07**	1.44*
Heparin	12.33**	54.35	0.43**	00.00**
Sil + Hep	8.03*	64.05*	00.00**	2.90

Khalaj, et al., Unpublished data

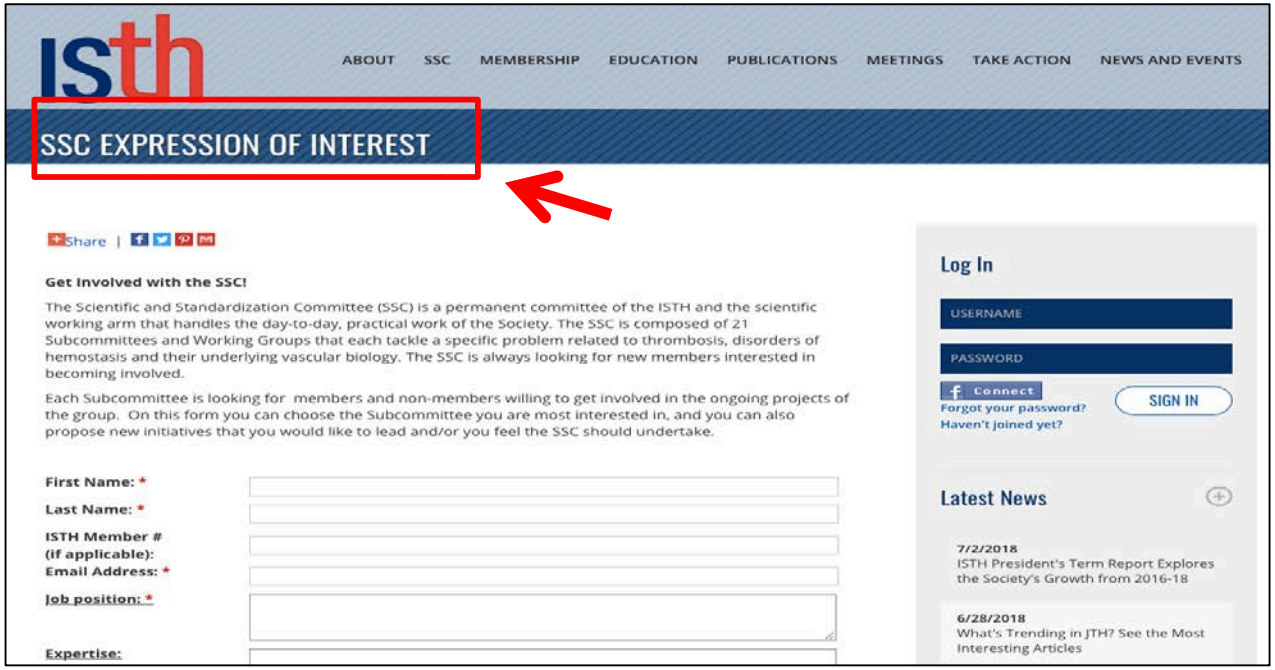
*compared to the LPS group, #compared to the control

ORAL

Kasra Khalaj, Rayana Leal Luna, Maha Othman, B. Anne Croy, Christina A. Peixoto

Promising maternal and fetal therapeutic outcomes from sildenafil and dalteparin treatments in a murine pregnancy loss Model

ISTH SSC on Women's Health Issues in T&H- Please Join Us!



- Active members can be nominated as a co-chairs
- Collaborative projects
- Registries / data collection
- Prospective studies
- Guidance documents and official communications
- Contribute to the program of SSC meetings

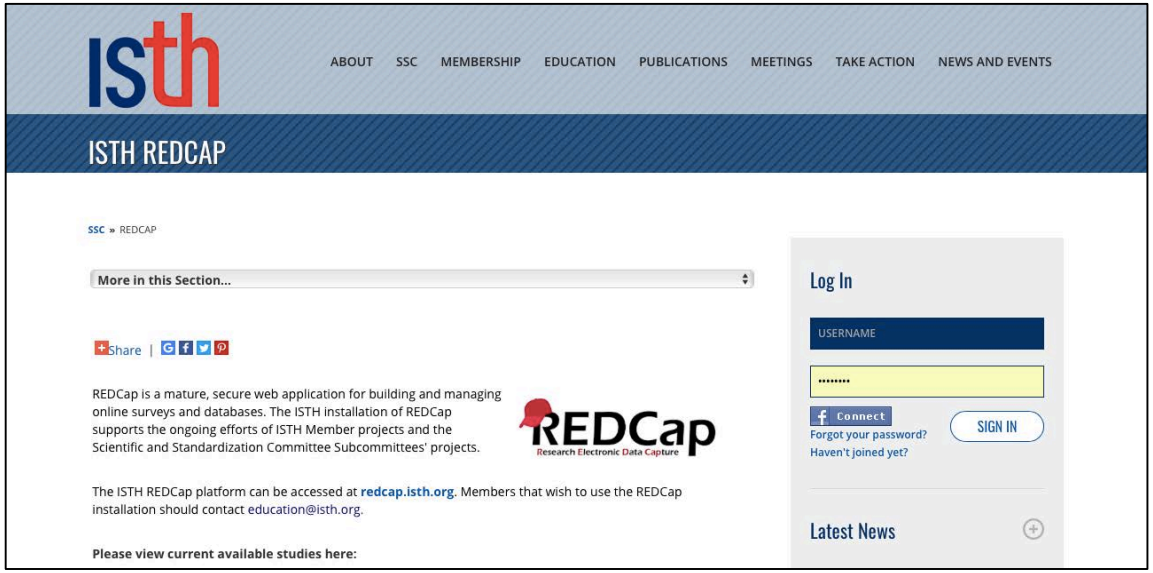
344 members registered and active members

www.isth.org/?page=ssc_get_involved

othman@queensu.ca

International Projects around Haemostasis and Pregnancy

- ISTH REDCap: Secure web application for building and managing online surveys & databases.
- All collected patient-related data are securely protected and are non-identifiable.



ISTH REDCap https://www.isth.org/page/redcap

https://www.isth.org/page/redcap

Registries on Women's T&H

- WiTEAM: A Registry Based Study on Thrombophilia and Placental-Mediated Obstetric Complications
- Global registry on DIC in pregnancy
- Obstetrics and Gynaecological Outcomes of Women with PFDs
- Retrospective Obstetric Study in Severe Congenital Protein C Deficiency
- The registry for thrombolysis and invasive treatments for MAssive Pregnancy-related Pulmonary embolism (MAPP)
- Registry of pregnancy in patients exposed to DOACs

Othman etal., 2019 RPTH –in revision

POSTER

Maha Othman, Amparo Santamaría, María Cerdá, Offer Erez, Adrian Minford, Deborah Obeng-Tuudah, Marc Blondon, Ingrid Bistervels, Saskia Middeldorp, Rezan Abdul-Kadir

Current ISTH Registries in Women´s Health Issues in Thrombosis and Haemostasis: Powerful Tools for Improved Data Collection and Outcome Measurement

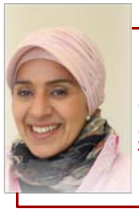
ISTH SSC on Women's Health Issues in T&H- The Committee!

Chair: Maha Othman, Canada
othman@queensu.ca

Robert Sidonio, USA
robert.sidonio@choa.org

Ian Greer, UK
ian.greer@qub.ac.uk

Predrag Miljic, Serbia
predragmiljic@yahoo.com



Susan Halimeh, Germany
susan_halimeh@gmx.de

Emmanuel Favaloro, Australia
emmanuelfav@gmail.com

Patricia Casais, Argentina
pcasais@hotmail.com

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Students/ Trainees

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Thursday May 23, 2019

By Communications Staff

A graduate of the School of Medicine is hooded by her parents as Tony Sanfilippo, Associate Dean, Undergraduate Medical Education, and Principal and Vice-Chancellor Daniel Woolf, look on.