Uterine Hemostasis is Achieved When There is Normal Coagulation

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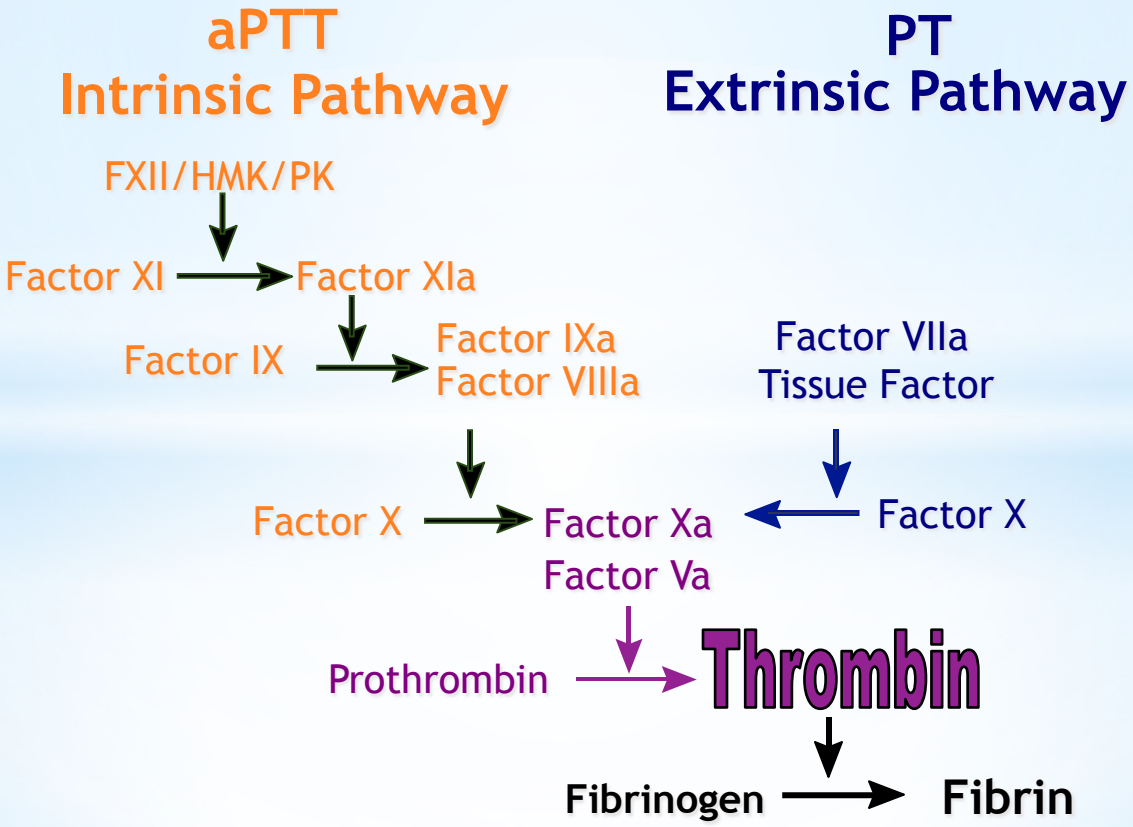
First let's talk about coagulation a little

Coagulation = blood clotting

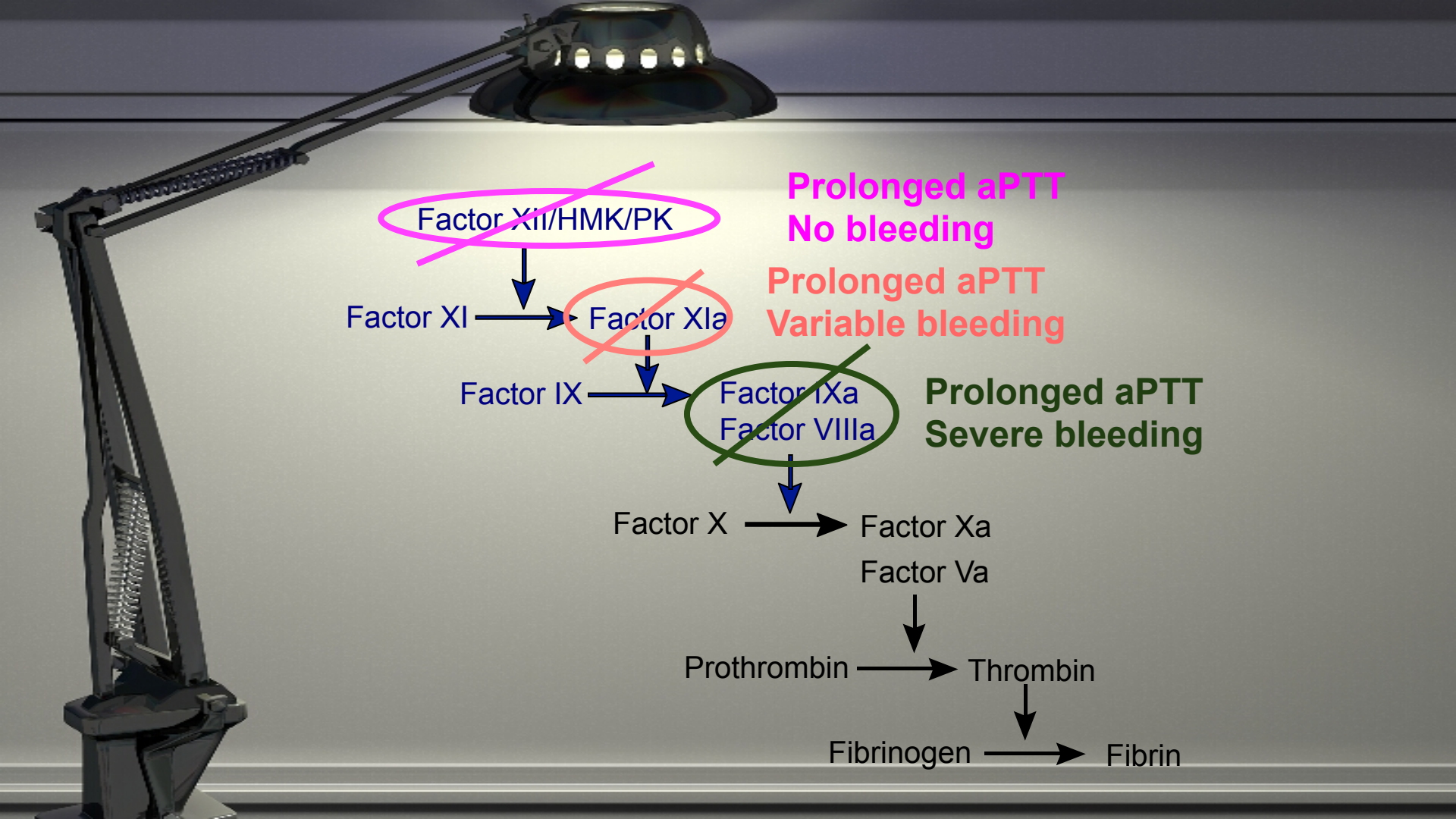
Hemostasis = stopping bleeding

Thrombosis = blood clotting in the wrong place i.e. inside a blood vessel

The Coagulation Cascade



The “Cascade” model leads us to believe that the clotting time in the PT or PTT should predict hemostatic function *in vivo*


Factor XII/HMK/PK
Prolonged aPTT
No bleeding
Factor XI
Factor XIa
Prolonged aPTT
Variable bleeding
Factor IX
Factor IXa
Factor VIIIa
Prolonged aPTT
Severe bleeding
Factor X
Factor Xa
Factor Va
Prothrombin
Thrombin
Fibrinogen
Fibrin

The clotting time is not a reliable predictor of clinical bleeding

Including cells in a model of hemostasis can explain some clinical observations better than the “Cascade” model

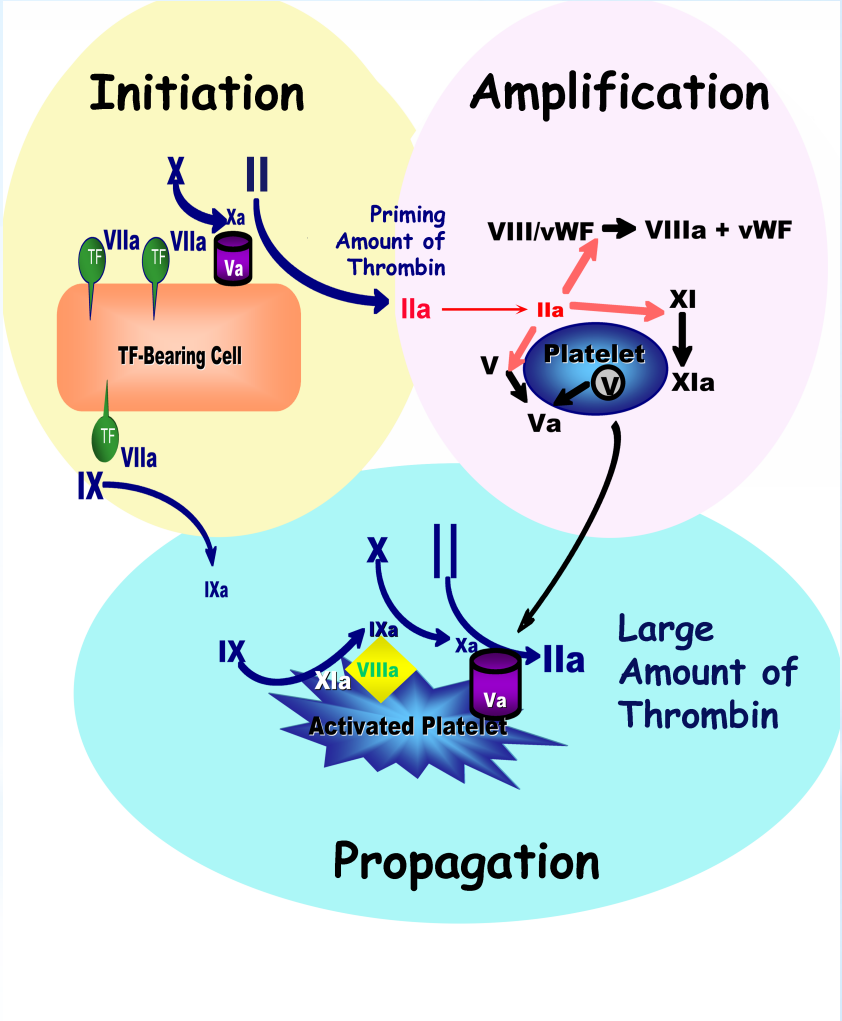
Cell-based experimental model

cells	monocytes (TF)	1 pM TF	15/uL
	platelets		100,000/uL
proteins	prothrombin	1400 nM	100 ug/mL
	factor VII	10 nM	0.5 ug/mL
	factor IX	70 nM	4 ug/mL
	factor X	135 nM	8 ug/mL
	factor XI	30 nM	5 ug/mL
	factor V	20 nM	7 ug/mL
	factor VIII	0.3 nM	0.1 ug/mL
inhibitors	antithrombin	3000 nM	200 ug/mL
	TFPI	3 nM	0.1 ug/mL

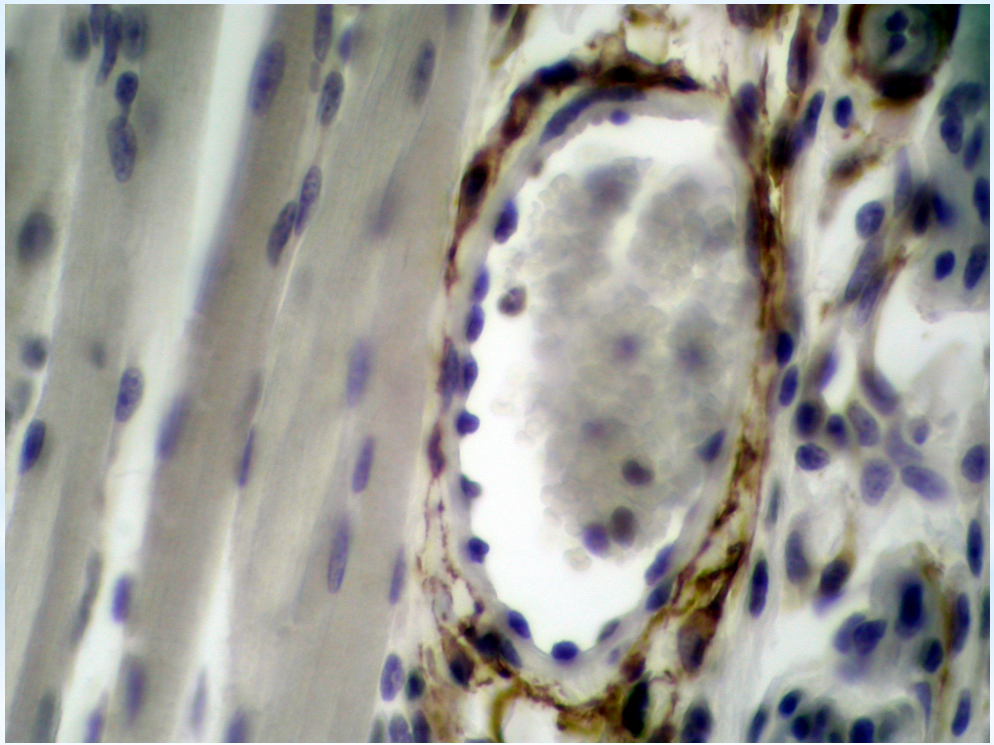
A Cell-Based Model of Hemostasis

Hemostasis proceeds in overlapping steps on two cell surfaces:

TF-bearing cells and platelets



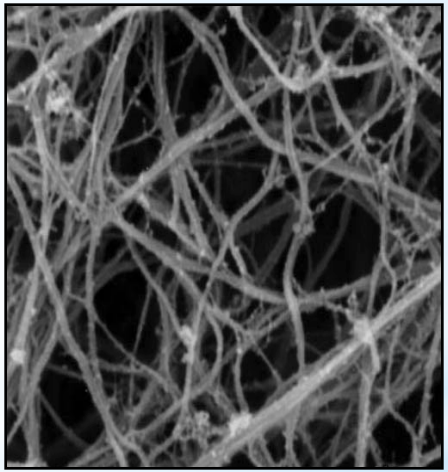
TF (brown stain) normally surrounds vessels



Clot Formation/Stabilization

IIa

Fibrinogen →



There Really Are “Intrinsic” and “Extrinsic” Pathways

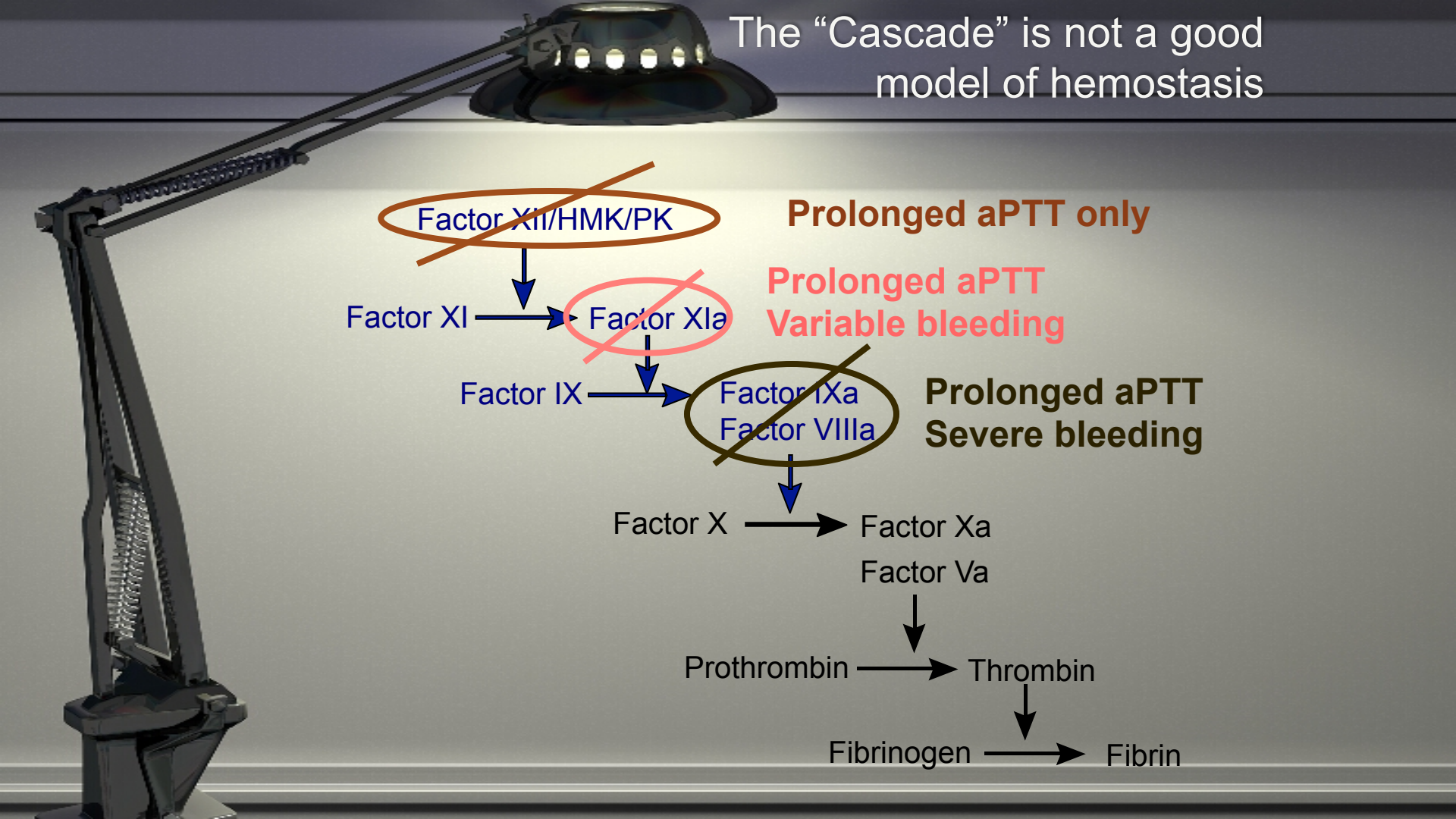
They are not redundant - they operate on different surfaces to do different jobs

* The “extrinsic” or TF pathway works on the initiating cell

* The “intrinsic” pathway works on platelets to produce the thrombin “burst”

Hoffman & Monroe: A Cell-Based Model of Hemostasis. *Thromb Haemostas*. 2001; 85:958-65

The “Cascade” is not a good model of hemostasis



Why do I think coagulation is important for uterine hemostasis?

- Women with coagulation defects have excessive uterine bleeding

- Mother nature thinks coagulation is important enough to give pregnant ladies extra coag factors – even at the risk of postpartum thrombosis

* The placenta expresses high levels of tissue factor

Excess menstrual bleeding is associated with coag defects

A consensus statement notes that in congenital bleeding disorders such as von Willebrand disease (vWD), “there is an increased incidence of pathological bleeding”.

(James, et al. *AJOG*, 2009)

Excess menstrual bleeding is associated with coag defects

Best evidence is available for vWD, because it is the most common inherited bleeding disorder

* Prevalence of menorrhagia (HMB) is 74-92% in women with vWD

Women with rare bleeding disorders also have a greater risk of uterine bleeding, though numbers were small

* Prevalence of menorrhagia (HMB) was 50% in a study of 101 women with FV, FVII, FX and combined FV/VIII deficiencies (Lukes, et al. *Fertil Steril*, 2005)

Excess menstrual bleeding is associated with anticoagulation

In one study of 90 women treated with Vitamin K Antagonists, VKA (vanEijkeren, et al, 1990)

* 17.8% had menorrhagia before starting VKA
* 29.5% had menorrhagia after starting VKA ($p<0.01$)

Excess menstrual bleeding is associated with anticoagulation

Non-vitamin K antagonist anticoagulants, NOACs, also associated with increased bleeding (Ferreira, et al, 2015; Myers, et al, 2016; Marten, 2015; Maas, et al, 2015)

* Rivaroxaban was associated with greater incidence of menstruation >8 days, medical or surgical intervention for bleeding, and need to modify anticoagulant therapy than was VKA

* Dabigatran was also associated with a higher incidence of bleeding than VKA

Excess menstrual bleeding is associated with anticoagulation

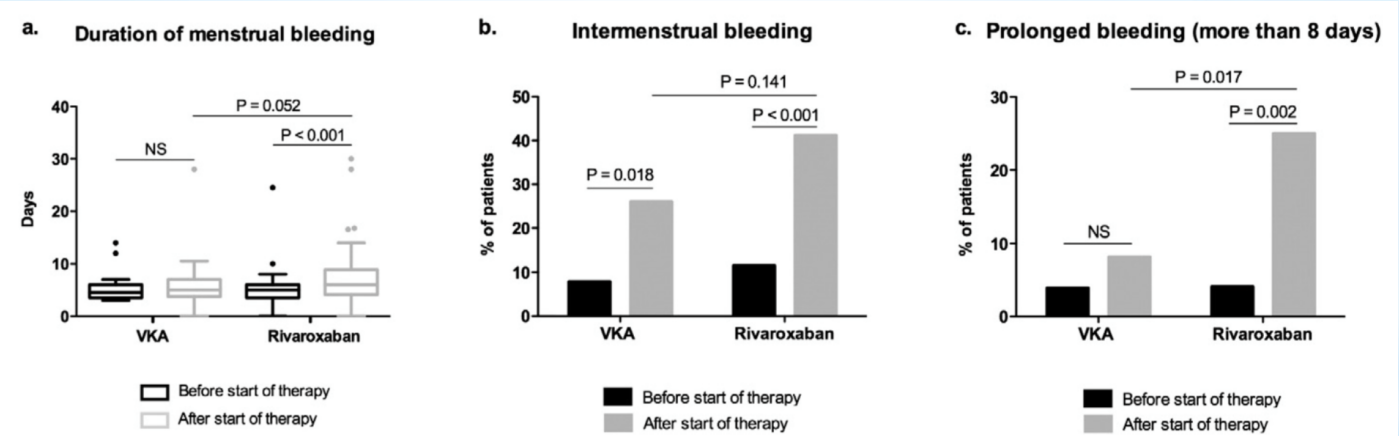


Fig. 2. Menstrual disturbances - objective parameters. a. Duration of menstrual bleeding; b. Intermenstrual bleeding; c. Prolonged menstrual bleeding (more than 8 days). VKA denotes vitamin K antagonists, NS = not significant.

De Crem, et al, 2015

Procoagulant activity increases during pregnancy

All aspects of hemostasis change during pregnancy

* Most of the clotting factors increase
* Anticoagulant and fibrinolytic activities decrease
* Placental TF increases during pregnancy

Table 1 Haemostatic changes in pregnancy[9–19]

Haemostatic parameter	Change at term pregnancy (% change)
Factors II and V	No change
Fibrinogen	Increases more than 100%
Factor VII	Up to 1000% increase
Factors VIII, IX, X, XII and VWF	Increase more than 100%
Factor XI	Variable
Factor XIII	Up to 50% decrease
Protein C	No change
Protein S	Up to 50% decrease
D-dimer	Up to 400% increase
Platelet count	Up to 20% decrease

Katz & Beilin. *Br J Anes.* 2015

Table 2. *Summary of TF Expression in Human Tissues*

Skin	Epidermis	+++
	Dermis	–
Gut	Mucosa	+++
	Submucosa	–
	Muscularis	V (+)
Vessels	Intima	–
	Media	V (+)
	Adventitia	++
	Capillaries	–
Heart	Myocardium	+++
	Endocardium	–
	Cardiac valves	–
Lung	Bronchial mucosa	++
	Bronchial submucosa	–
	Alveolar septae	+
	Alveolar epithelial cells	++
	Alveolar macrophages	V (++)
Brain	Meninges	+
	Cerebral cortex	+++

Drake, et al. *Am J Path.* 1989

TF in endometrium is upregulated around the time of implantation

(Lockwood, et al. 2009)

TF is strongly expressed by decidual cells

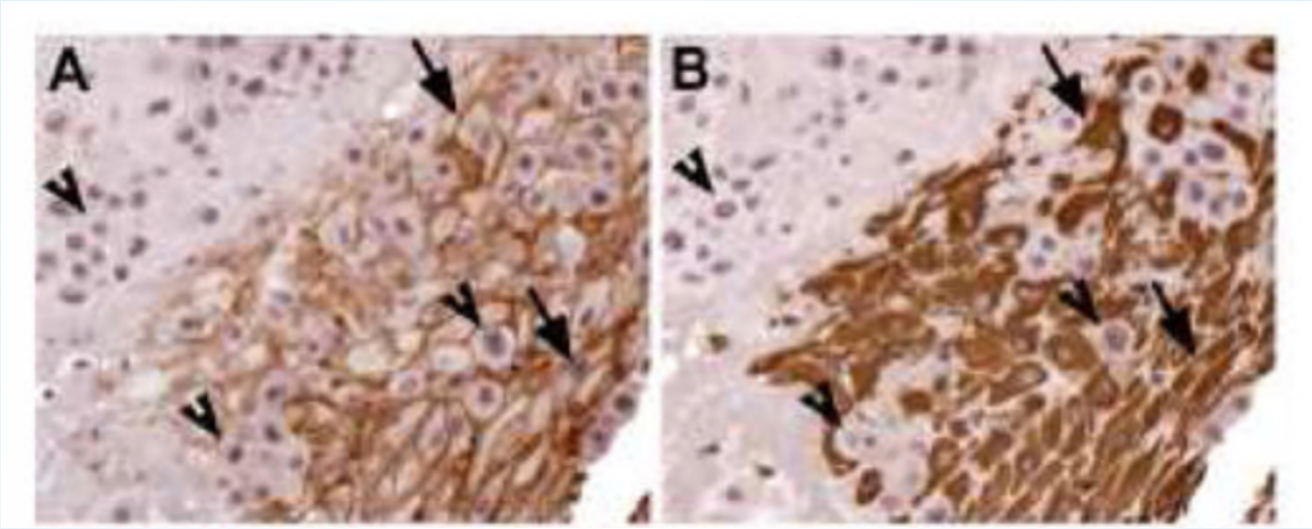


Figure 1. Immunohistochemical analysis of tissue factor (TF) expression at the decidual/placental interface

Serial sections of decidual basalis were immunostained for TF and vimentin in an idiopathic preterm specimen (A: TF, and B: vimentin). Decidual cells (DCs) (arrows), identified by positive vimentin staining, exhibited strong peri-membranous TF staining. TF staining was virtually absent in interstitial trophoblast (arrowheads). Similar results were seen in term

Lockwood, et al. *Thromb Res*. 2009

Adequate TF expression is essential for uterine hemostasis

Mice with reduced uterine TF suffer placental bleeding and about 16% suffer fatal post-partum hemorrhage

(Erlich, et al. *PNAS*. 1999)

In Summary -

While most uterine bleeding (menstrual or peripartum) is not due to disorders of coagulation - normal coagulation is required to maintain uterine hemostasis