

Part 3: Coagulation and Fibrinolytic Systems (Barbara Konkle and David Ginsburg)

- What is the evidence that *the coagulation and fibrinolytic systems and susceptibility to thrombosis* are altered:
 - (a) across the menopausal transition?
 - (b) *from initiation and/or maintenance of HRT?*
- What are the *potential underlying biologic mechanisms* by which *the coagulation and fibrinolytic systems and susceptibility to*

Biology of the Perimenopause

Changes in Hemostasis with Menopause and with Hormone Replacement Therapy

Barbara A. Konkle, M.D.

University of Pennsylvania

David Ginsburg, M.D.

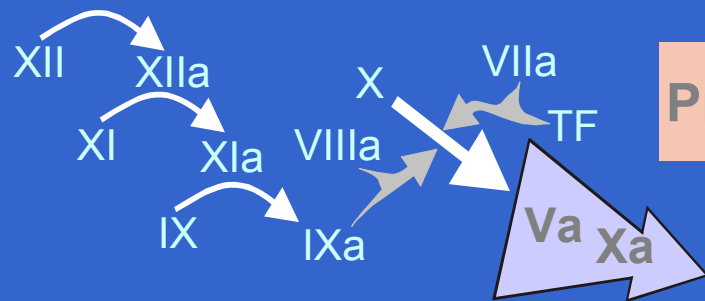
University of Michigan

Bleeding

Thrombosis



COAGULATION CASCADE



Prothrombin

Thrombin

Fibrinogen

Fibrin
Clot

PA

Plasminogen

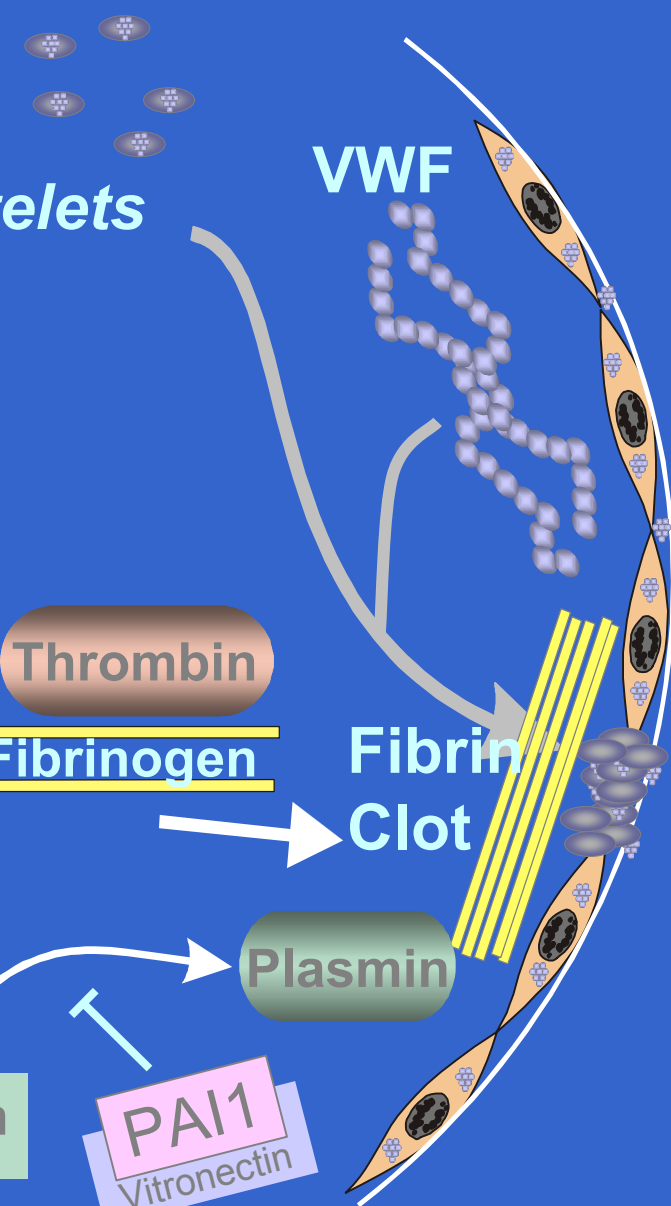
Plasmin

PAI1
Vitronectin

FIBRINOLYSIS

Platelets

VWF



Changes in Hemostasis with Aging

- Increase in procoagulants
 - Fibrinogen, FVIII, IX, VII
- Increase in natural inhibitors
 - Antithrombin, tissue factor pathway inhibitor
 - Variable observation; more in women than men
- Increase in platelet reactivity (greater in women), VWF
- Decrease in fibrinolysis (\uparrow tPA Ag and PAI-1, but overall decrease in tPA activity)
- Increase in coagulation-activation products
 - D-dimer, F 1.2, TAT
- Local effects of changes in endothelium

***Evidence for pro-inflammatory and genomic influences

Magnitude of Changes with Aging

Analyte	Increase per Decade	Reference
Fibrinogen	8.1-9.8 mg/dL	Tracy et al
Factor V	6 %	Brozovic et al
Factor VIII	9.4 – 10 %	Conlan et al
Factor IX	9.9 – 12.6 IU/L	Sweeney and Hoerning
D-Dimer	25.9%	Pieper et al
Factor XIII -A	3.7%	Ariens et al
VWF	13.1-15.4%	Conlan et al

Effects of HRT on Coagulation

- Increase in procoagulant factors
- Decrease in natural anticoagulants (AT, PS*)
- Increase in markers of coagulation activation
- ? Increase in fibrinolysis
- Overall procoagulant effect:
 - Increased APC resistance*; thrombin generation

**Differs from that seen with aging*

Note: All effects less or not present with transdermal preparations

Is Menopause Associated with an Increase in Venous Thrombosis ?

- Risk increases with age; 1/10,000 per year for young adults vs. 1/1,000 per year for middle-aged adults
- A specific effect of menopause has not been shown

Is HRT Associated with an Increased Risk of Venous Thrombosis ?

- 2 –4 fold increase of venous thrombosis
- Risk increased in women with underlying inherited thrombophilias
- Risk greatest with initiation of treatment
- Risk is less (or absent) with transdermal preparations

Research Questions

- What are the differences in biologic effects of natural versus exogenous estrogens and other hormones ?
- How do hormones regulate genes encoding hemostatic proteins ?
- What are the links between inflammation, atherosclerosis and hemostasis ?
- What role does coagulation play in the HRT-associated increase in arterial thrombosis ?