

Diagnosis and Treatment of Females with Bleeding Disorders

Coagulation Updates 2001

Virginia Biotechnology Center

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Introduction

- Problem has been often unrecognized or misdiagnosed
- Increasing interest in this topic over the past decade
- Impact on management of such common problems as menorrhagia, pregnancy, iron deficiency anemia
- Improvement of quality of life



What are the Requirements of an Effective Hematostatic System?

- Must stop blood loss
- Must work at any point in the vascular bed
- Must be rapid
- Must be confined to the point of injury
- Must be removeable once hemostasis is established

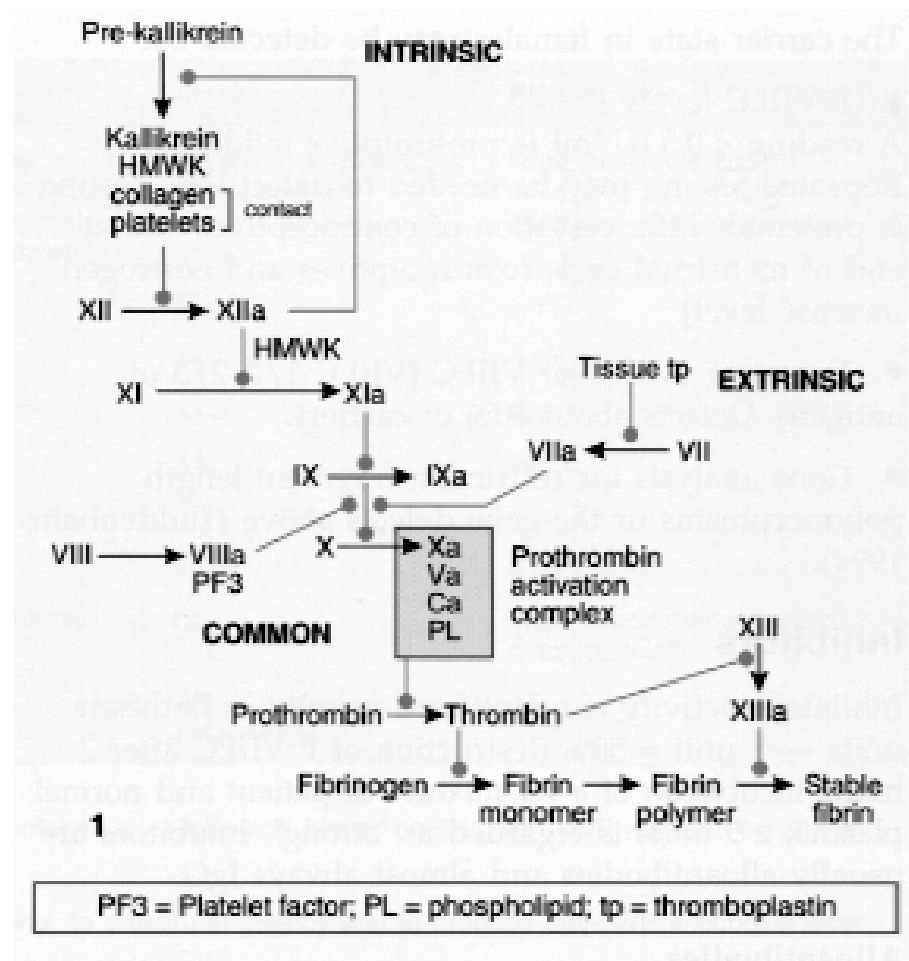


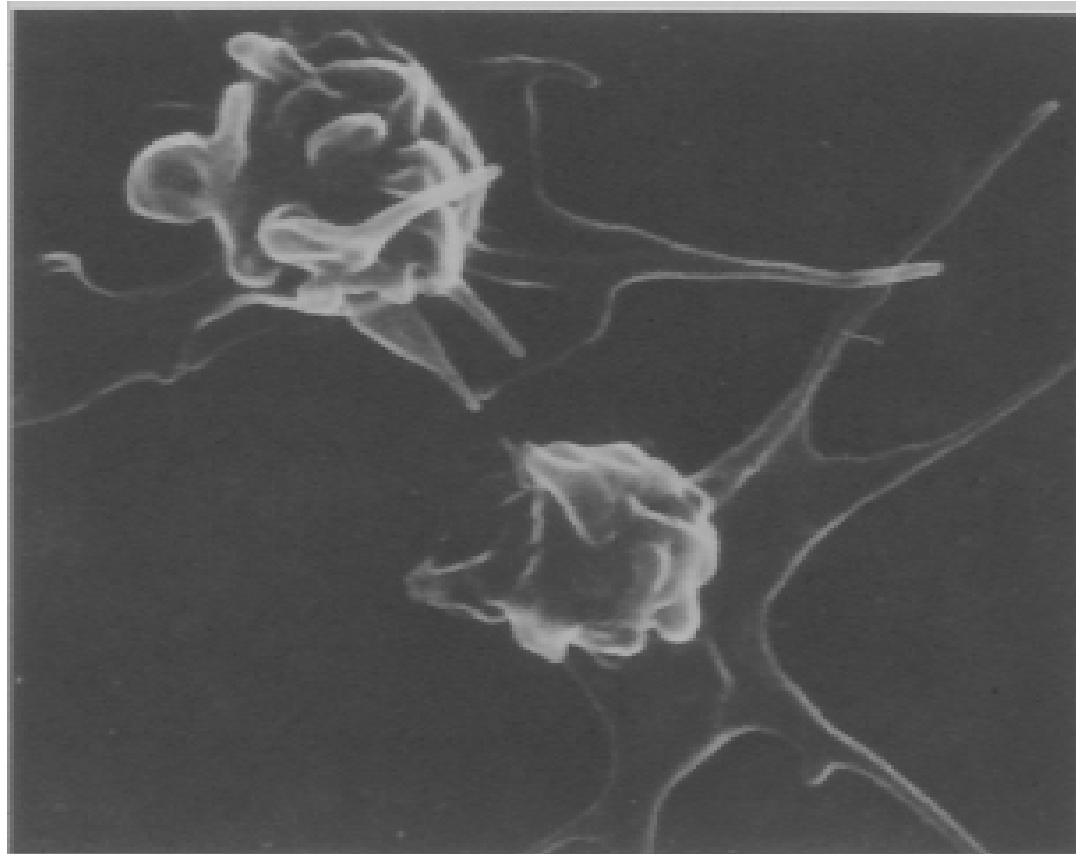
Simplified Review of Hemostasis

- Vasoconstriction
 - subendothelium exposed
- Platelet plug formation
 - platelet adhesion and aggregation
- Fibrin clot formation
 - activation of the coagulation cascade (factors I-XIII)
- Fibrinolysis
 - degradation of clot



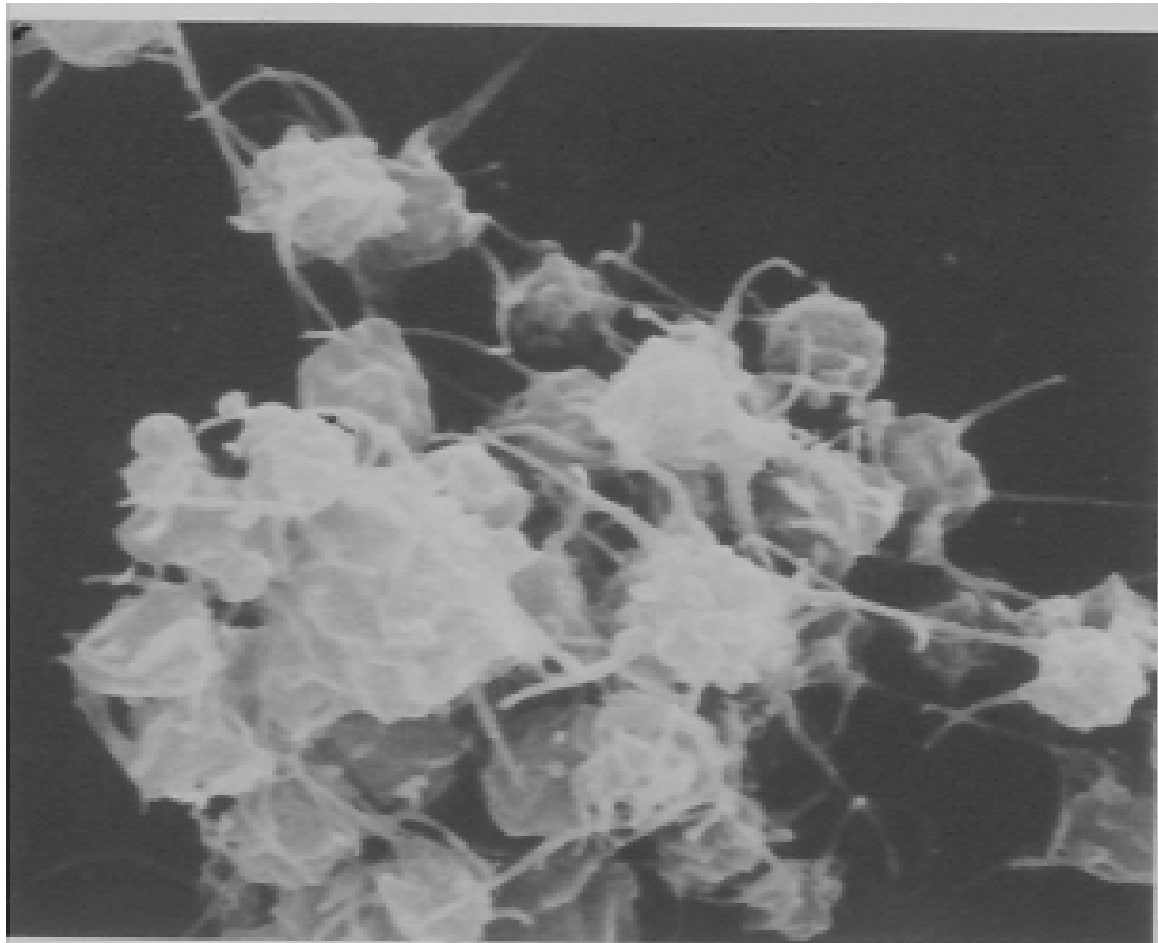
The Coagulation Cascade





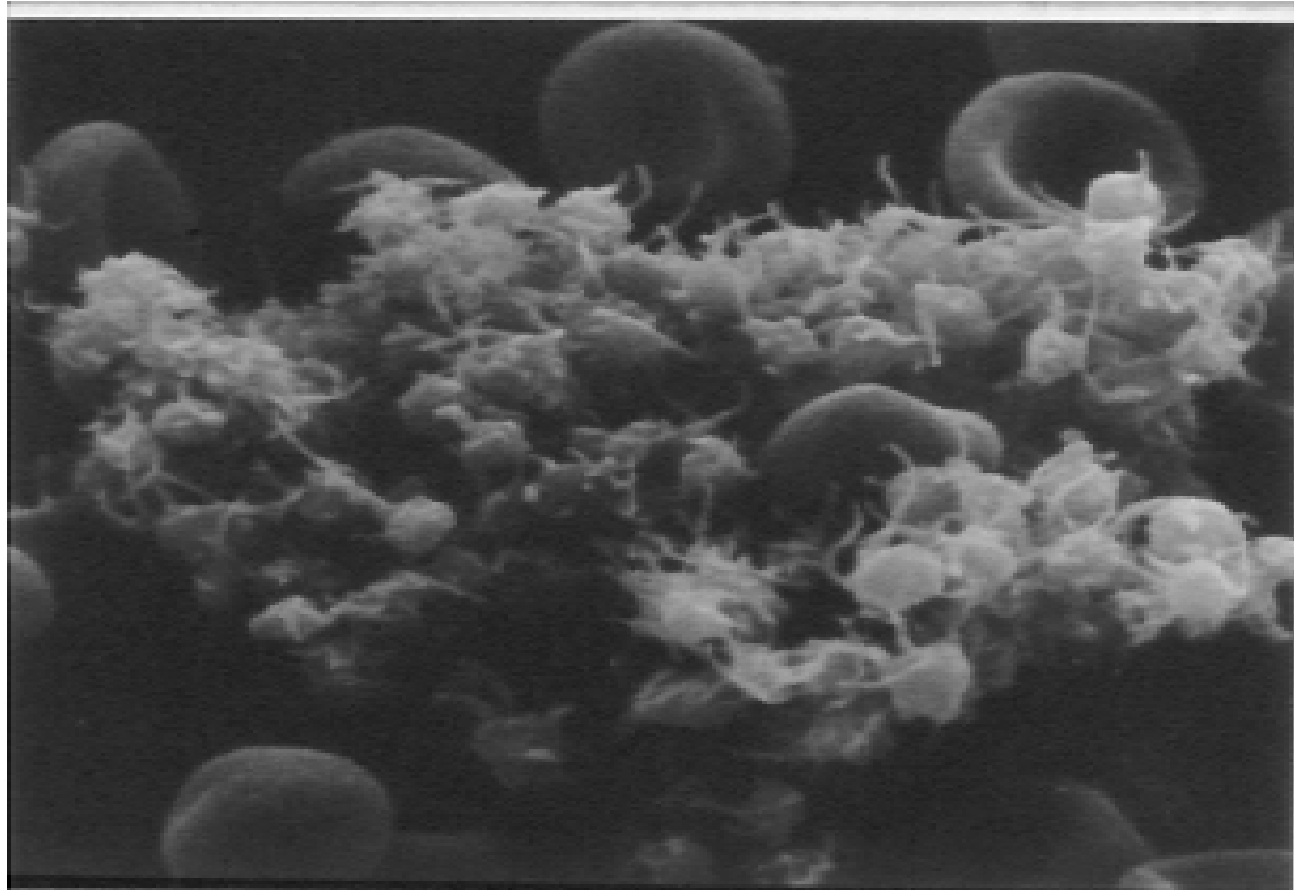
1. In response to local injury two platelets reach out their pseudopodia to stick together.





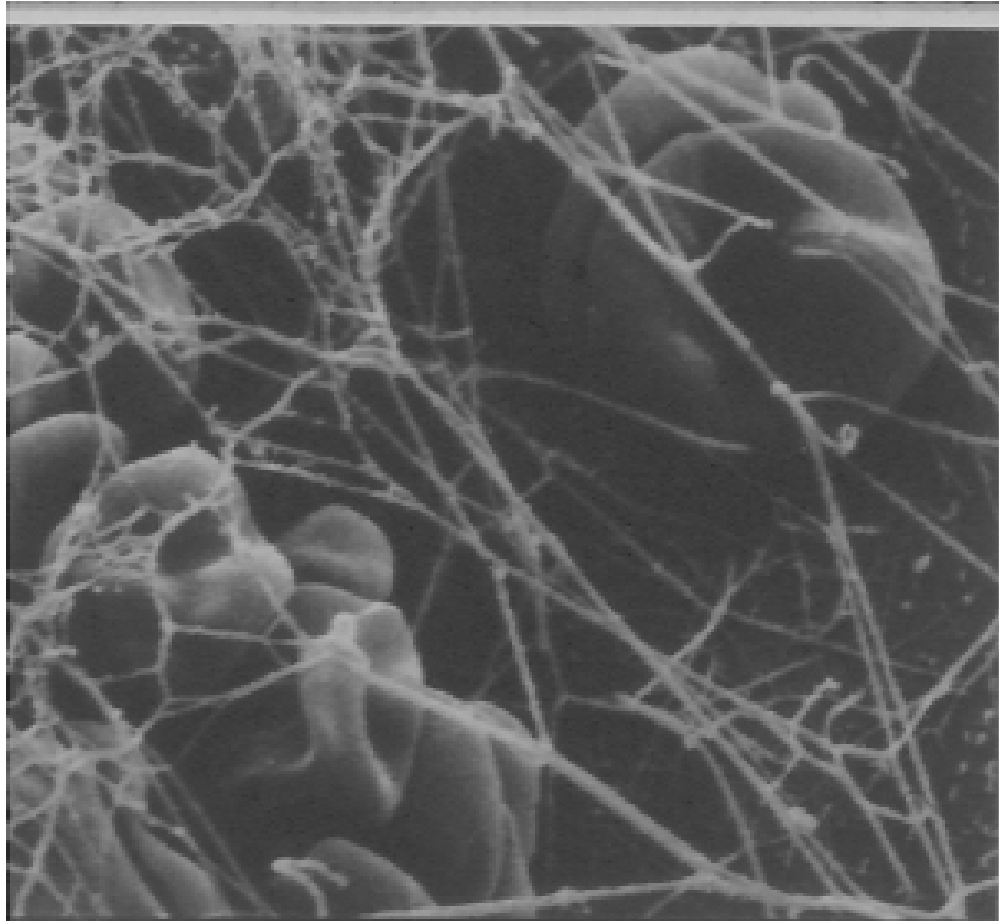
2. More platelets join in.





3. The platelet plug builds up to stem bleeding. In the background are red blood cells.





4. After a while strands of fibrin appear and strengthen the repair.



Simplified Review of Hemostasis

- PRIMARY
 - vascular endothelium
 - platelets
- SYMPTOMS
 - superficial bleeding sites
 - mucosal (epistaxis, gingival bleeding, menorrhagia)
 - bruising
- SECONDARY
 - plasma clotting factors
- SYMPTOMS
 - hematomas
 - muscles
 - joints



Simplified Review of Hemostasis

- Disorders of Primary Hemostasis
 - Vascular (vasculitis, abnormal collagens, vitamin C)
 - Platelet disorders (quantitative and qualitative)
- Disorders of Secondary Hemostasis
 - Factor deficiencies (the hemophilias)



Simplified Review of Hemostasis

- Congenital
 - Ehler's Danlos
 - Qualitative platelet abnormalities
 - Quantitative and qualitative factor abnormalities
 - von Willebrand disease
- Acquired
 - Medication (ASA, NSAID)
 - Malignant
 - Autoimmune (ITP, acquired hemophilias)
 - Diet (Vitamins C, K, B12, folate)
 - Other (DIC, TTP, liver disease)



What symptoms in women should make you suspect a bleeding disorder?

- Menorrhagia/Metrorrhagia
- Dysmenorrhea/Mid-cycle pain
- Conception/Fertility problems
- Post-partum hemorrhage




Menorrhagia

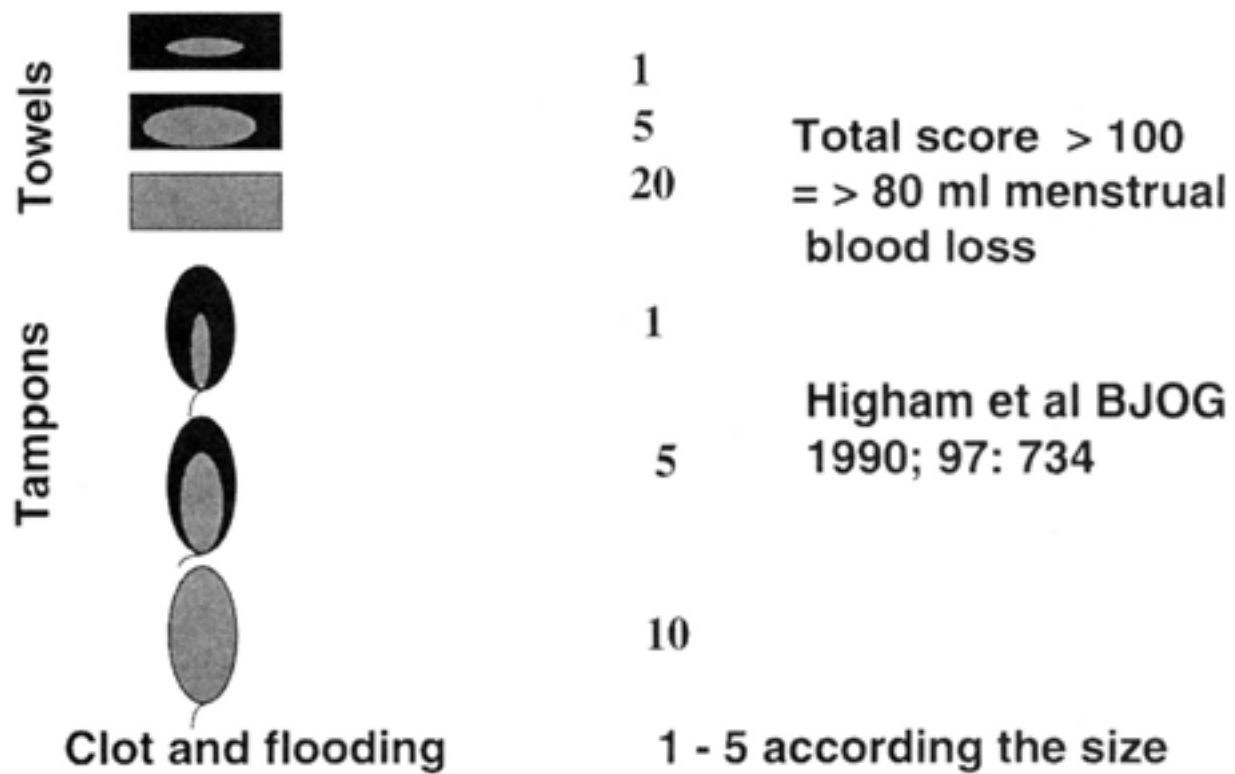
- Defined as blood loss in excess of 80 cc per cycle (pictorial assay for assessment)
- Occurs in 65-93% of women with inherited bleeding disorders compared to 10% of general population (*Kadir RA; Lancet 1998*)
- 20% of women with menorrhagia have underlying bleeding disorder (*Kadir RA; Haemophilia 1999*)



Menorrhagia (cont.)

- Menorrhagia since menarche reported in 53-65% of women with bleeding disorders
(Kadir, RA; Clin. Lab. Haem, 2000)
- History of iron deficiency anemia
- History of transfusion (especially after D&C)
- History of hysterectomy 
- History of significant quality of life impact







Assessment of Menorrhagia Using PBAC



Score Sheet Using Assessment in PBAC

Name: M.V.B.
LMP: 15/1/99

SCORE: 204

TOWEL	1	2	3	4	5	6	7	8
								
								
								
CLOT FLOODING	1P X2	50P X2						
TAMPON	1	2	3	4	5	6	7	8
								
								
								
CLOT FLOODING								




Dysmenorrhea and Mid-cycle Pain

- No good scientific data to associate these symptoms with underlying bleeding disorders
- Endometriosis
- Ovulation



Conception and Fertility Problems

- Association with thrombotic disorders
- No good scientific data for association with increased bleeding disorders
- Possible implications;
 - prolonged hormonal therapy
 - excessive bleeding with intercourse
 - anecdotal reports of higher miscarriage rate in patients with von Willebrand 

Post-partum hemorrhage (PPH)

- Defined as blood loss greater than 500cc in the first 24 hours post-partum
- Primary (uterine atony and trauma) and secondary (retained placental tissue and infection) PPH
- Risk of primary PPH is approximately 20% in patients with coagulopathy (*Kadir RA; Br J Ob Gyn; 1997*)
- Risk of secondary PPH is up to 28% in patients with coagulopathy (*Kadir RA; Br J Ob Gyn; 1998*)




Bleeding Disorders Affecting Women

- Von Willebrand Disease (vWD)
- Hemophilias
- Immune thrombocytopenic purpura
- Miscellaneous



Von Willebrand Disease

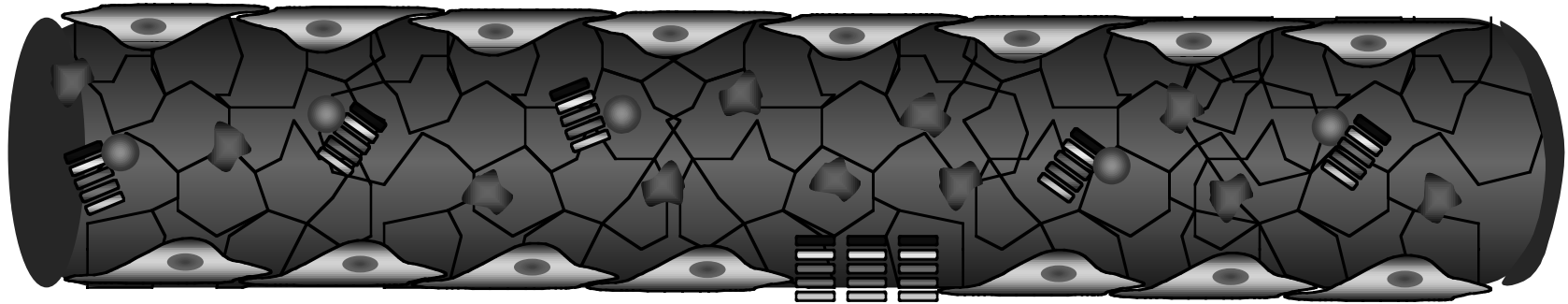
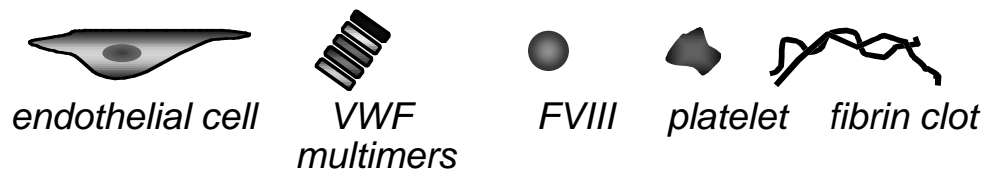
- The most common inherited coagulopathy (may affect >1% of population)
- Initial report by Dr. Erik von Willebrand (1926) -16 of 23 affected members were females; index case exsanguinated from menstrual blood loss)
- Worldwide distribution
- Three main types (>80% mild type I) 

Von Willebrand Disease

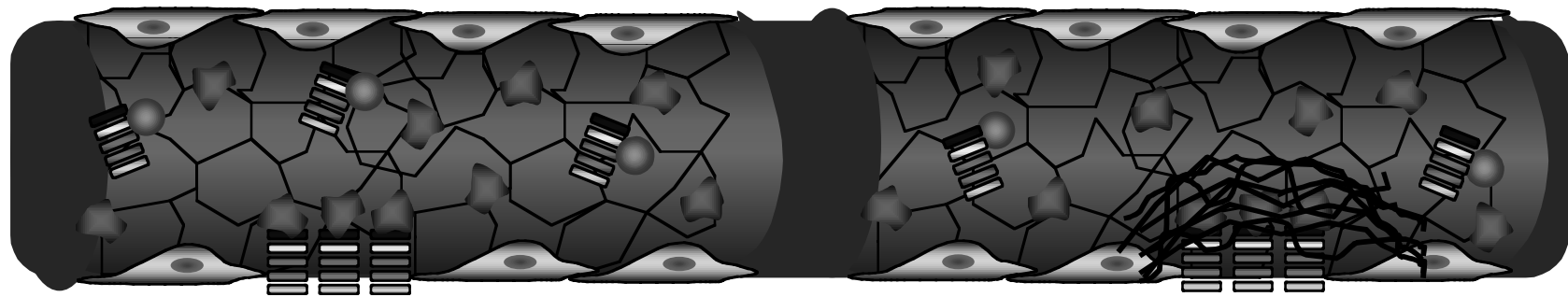
- Gene located on chromosome 12
- Usually autosomal dominant pattern of inheritance
- vW protein: (functions in primary and secondary hemostasis)
 - bridge between platelets and injury site
 - protects factor VIII from proteolytic degradation



Following vascular injury:



VWF binds to subendothelial matrix



Platelets adhere to bound VWF

fibrin clot formation is catalyzed by platelet surface



Symptoms of vWD

- Most symptoms related to inability to form platelet plug
 - bruising, epistaxis, menorrhagia, bleeding following dental work
- Severe type III may mimic classic hemophilia
- Significant predictors of menorrhagia and vWD are age, surgical or dental bleeding, history of anemia, diminished quality of life in relation to family activities (*Kouides, PA; Haemophilia, 2000*)



BLEEDING SYMPTOMS IN WOMEN WITH MENORRHAGIA


(Kadir et al; Clin and Lab Haematol; 2000)

Table 2 Bleeding symptoms in women with menorrhagia

	Total <i>n</i> = 150	No bleeding disorder <i>n</i> = 123	vWD <i>n</i> = 20	<i>P</i> -value
Bruising	88 (59%)	66 (54%)	16 (80%)	0.05
Nose bleeding	22 (15%)	17 (14%)	5 (25%)	0.20
Gum bleeding	54 (36%)	41 (33%)	9 (45%)	0.45
Bleeding after tooth extraction	13/98 (13%)	6/81 (7%)	6/13 (46%)	0.001
Postoperative bleeding	18/109 (17%)	7/90 (8%)	8/13 (62%)	<0.001
Postpartum bleeding	29/97 (30%)	17/80 (21%)	8/13 (62%)	0.005



Diagnosis of vWD

- DIFFICULT - history may be key in face of negative lab tests - no perfect test
- PT, aPTT, bleeding time (BT), platelet counts (traditional screening tests) may all be normal
- often prolongation of aPTT, BT
- decrease in factor VIII, vWAg, vWAct
- vW multimers on SDS gel electrophoresis 

Diagnosis of vWD

- Increased Levels
 - AB blood type
 - African-Americans
 - stress
 - DIC
 - hyperthyroidism
 - collagen-vascular disease
 - pregnancy (levels fall within 4-5 d post partum)
- Decreased levels
 - O blood type
 - hypothyroidism
- Normal variation during menstrual cycle
 - optimal testing time is 5-7 days after onset of menses (early follicular phase)



Therapy for vWD

- Oral contraceptives
- DDAVP
- Plasma products
- Anti-fibrinolytics
- NSAIDs
- Surgical



Oral Contraceptives

- Increase factors II, VIII, vWF (does not correct qualitative defect)
- >50% still have excessive bleeding
(*Kouides, PA; Haemophilia, 2000*)
- higher estrogen OCP may be more effective
- pure progestational agents may be indicated



DDAVP

- IV or intranasal form
- increases factor VIII and vWF (does not correct qualitative defect)
- adverse effects
 - flushing, head-ache
 - hyponatremia and water retention
 - convulsions



Plasma Products

- Indicated for severe vWD (type III)
- No recombinant vWF clinically available
- FFP and cryoprecipitate
- Pooled plasma products - virally attenuated
 - factor VIII concentrates containing HMW vWF
 - Humate P, Alphanate, Koate HS



Antifibrinolytic agents

- Efficacy of tranexamic acid in Europe
(*Ong, YL; Haemophilia, 1998*)
- Amicar (epsilon aminocaproic acid)



NSAIDs and Surgery

- Affect platelet function and may aggravate bleeding
- Trilisate and Disalcid
- Cox-2 inhibitors (Celebrex and Vioxx)
- Diagnosis of coagulopathy important before surgical intervention as these women are at higher risk for operative bleeding complications.



The “Hemophilias”

- After vWD, carrier status for factor VIII and IX accounts for the next most common inherited coagulopathy in women with bleeding disorders
- Factors XI and VII
- Acquired hemophilia (usually associated with severe PPH) may also occur



Inherited Factor VIII and IX Deficiency

- Low levels may be due to;
 - carrier status and extreme lyonization
 - the rare homozygote
 - abnormal karyotype (Turner's syndrome)
- Common symptoms;
 - menorrhagia
 - bleeding with procedures and PPH



Factor XI and VII Deficiency

- Factor XI
 - autosomal recessive
 - increased prevalence in Ashkenazi Jewish population
 - mild to moderate bleeding (often menorrhagia is only symptom)
 - symptoms do not correlate with factor level
- Factor VII
 - autosomal recessive
 - menorrhagia and PPH common



BLEEDING SYMPTOMS IN WOMEN WITH MENORRHAGIA

(Kadir et al; Clin and Lab Haematol; 2000)

	Total <i>n</i> = 150	No bleeding disorder <i>n</i> = 123	Factor XI deficiency <i>n</i> = 6	<i>P</i> -value
Bruising	88 (59%)	66 (54%)	4 (67%)	0.69
Nose bleeding	22 (15%)	17 (14%)	0	1.00
Gum bleeding	54 (36%)	41 (33%)	1 (17%)	0.66
Bleeding after tooth extraction	13/98 (13%)	6/81 (7%)	1/3 (33%)	0.23
Postoperative bleeding	18/109 (17%)	7/90 (8%)	3/5 (60%)	<0.008
Postpartum bleeding	29/97 (30%)	17/80 (21%)	3/3 (100%)	0.01




Acquired Hemophilia

- Autoimmune disorder occurring most frequently post-partum
- Sudden onset of hematomas at puncture sites; bleeding may be life threatening



Diagnosis of “Hemophilias”

- aPTT may be normal in carriers of factor VIII or IX deficiency (need to measure specific levels)
- aPTT prolonged in classic factor VIII, IX, XI deficiency; PT is normal
- aPTT does not correct in acquired hemophilia (inhibitor); factor VIII usually low
- PT prolonged in factor VII deficiency 

Treatment of the “Hemophilias”

- Factor VIII carrier status similar to vWD (OCP, DDAVP, antifibrinolytic agents, recombinant factor VIII)
- Factor IX carrier status (recombinant IX)
- Factor XI (FFP)
- Factor VII (Novoseven, recombinant VIIa)
- Acquired hemophilia (rVIIa, immunosuppressants)



Recombinant VIIa

- Activates the extrinsic pathway independent of TF, VIII, IX
- Activates platelets directly
- Initially used in inhibitor patients and factor VII deficiency
- Reported efficacy in ITP, thrombasthenias, uremia, liver disease



Immune Thrombocytopenic Purpura (ITP)

- In the age range of 15-40 yrs incidence in women predominates (2.6:1)
- Often insidious onset
- Severe menorrhagia (often with other associated bleeding symptoms)
- May affect infant as well since IgG Ab crosses placenta



Diagnosis and Treatment of ITP

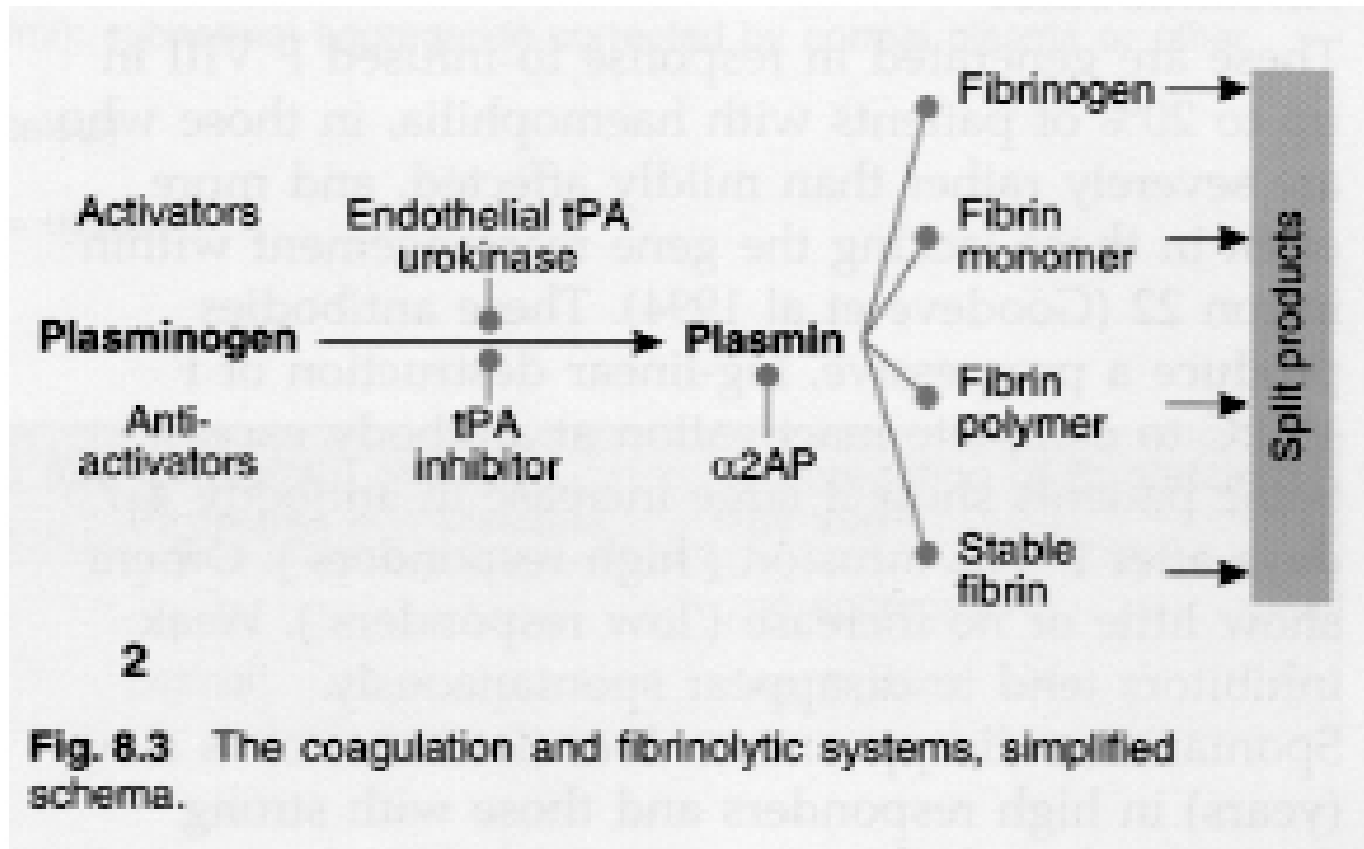
- Low platelet count
- May be associated with underlying immune disorder
- IVIG or Win Rho (Rh+ patients)
- Steroids
- Splenectomy



Miscellaneous Disorders

- Congenital disorders of fibrinogen
 - afibrinogenemia
 - dysfibrinogenemia
- Disorders of fibrinolysis
 - difficult to diagnose and screen for
 - tCLT test
 - potential efficacy of antifibrinolytic agents

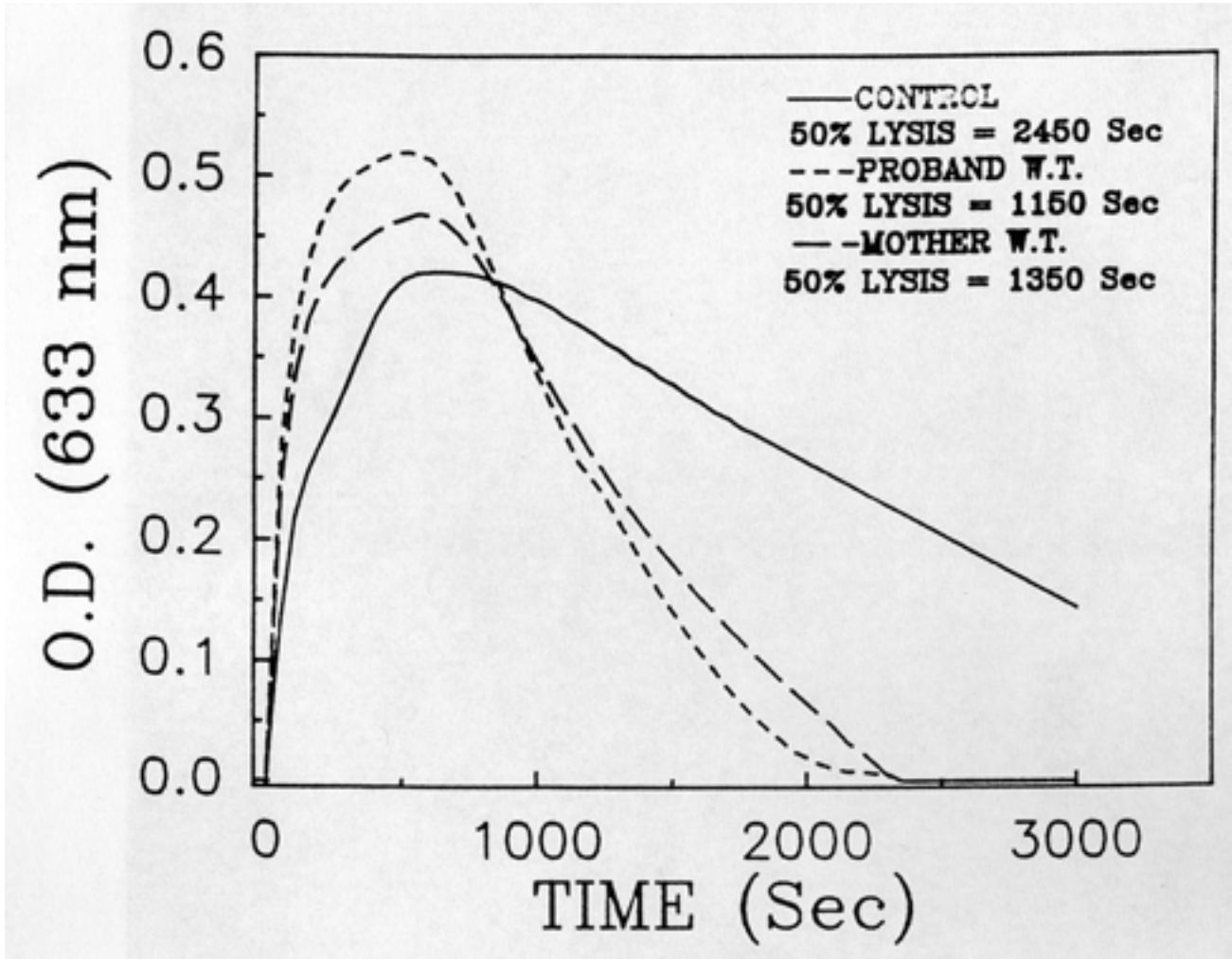




Fibrinolysis; The Forgotten Pathway

- No good screening test
- Clot structure analysis
 - Fibrin fiber size
 - patient PPP mixed with thrombin
 - 4 hour evaluation of fibrin fiber mass via scanning spectrophotometer
 - Tissue plasminogen activator induced clot lysis time
 - patient PPP mixed with thrombin and TPA
 - turbidity development and resolution measured and compared with control







Fibrinolysis: The Forgotten Pathway

- Abnormal screening test requires follow-up with more specific tests to precisely define defect;
- Abnormal fibrinogen (large fiber size)
- Plasminogen
- Alpha-2 antiplasmin
- Plasminogen activator 1 deficiency



Summary

- Menses and pregnancy are challenges to the hemostatic system that are unique to women
- A significant proportion of women with menorrhagia may have an underlying bleeding disorder
- History is critical
- Common things are common (ie vWD)
- Therapy may impact on symptoms and quality of life issues



Return to Main
Menu