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# Reproductive Health and Rare Bleeding Disorders

**Suchitra Acharya, MD**

*Hemostasis and Thrombosis Center,  
Northwell Health*

**Danielle Nance, MD**

*Banner MD Anderson Cancer Center*



# Disclosures

## **Danielle Nance, MD**

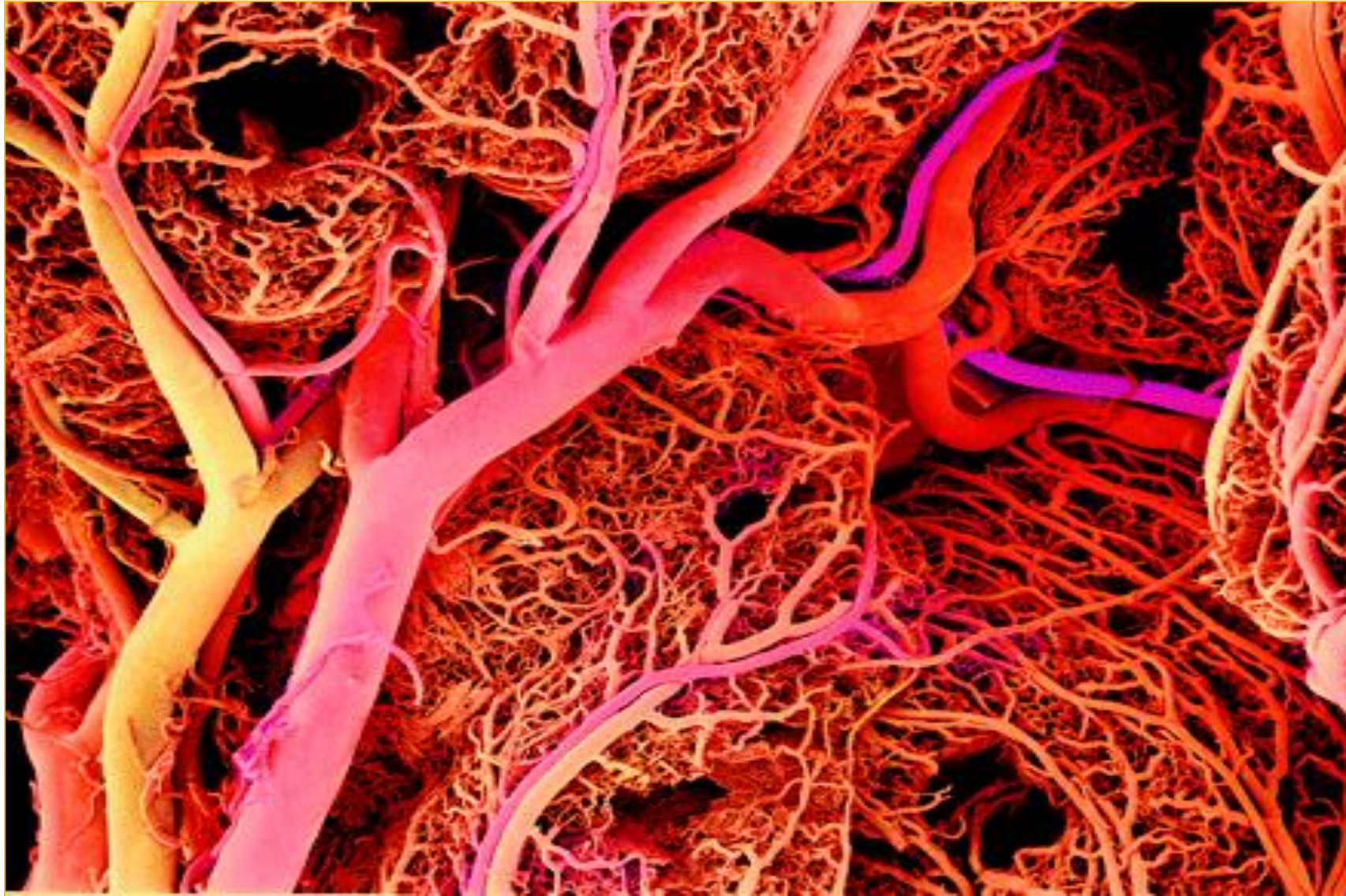
- Ad boards for Anlylam, Aptevo, Bayer, Bioverativ, Genentech, Octapharma, Shire. Speaker fees from Octapharma, Bioverativ. Grant funding from Bayer.

## **Suchitra S. Acharya, MD:**

- Ad Boards: Novonordisk, Takeda, Bio Products Laboratory
- Research Support: Bayer Pharmaceuticals Inc. for Joint disease Research



# Hemostasis: 100K Miles of Vessels





# Hemostasis = Healing



Vessel injury



Ruptured epithelium

Vessel spasm



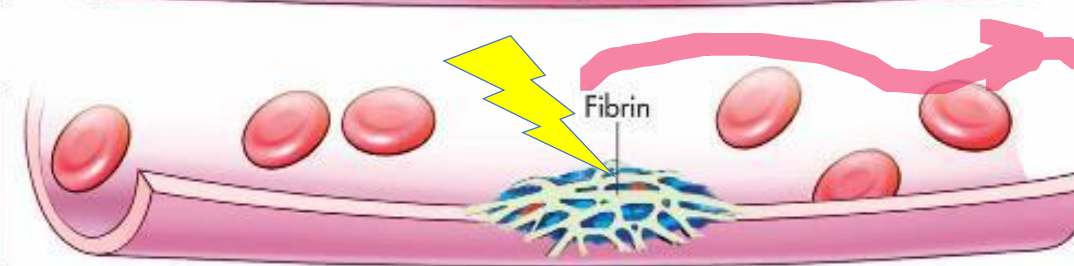
Spasm

Platelets adhere to injury site and aggregate to form plug



Platelets

Formation of insoluble fibrin strands and coagulation



Fibrin

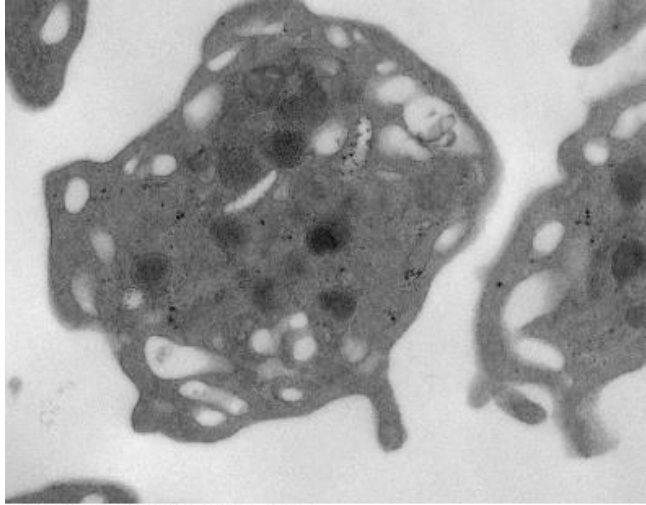
Collagen provides the anchor

VWF is the tether

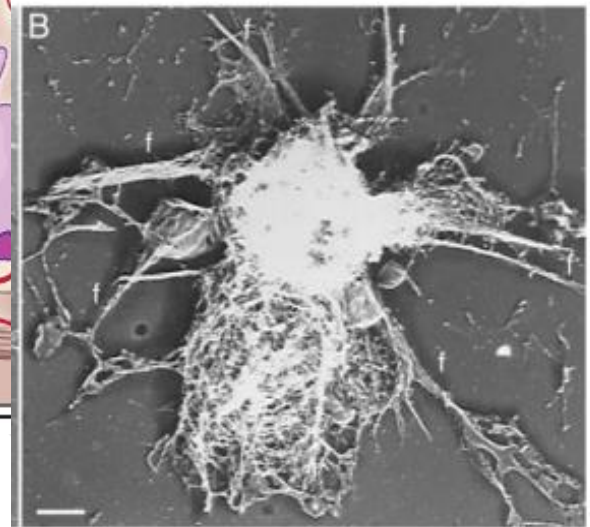
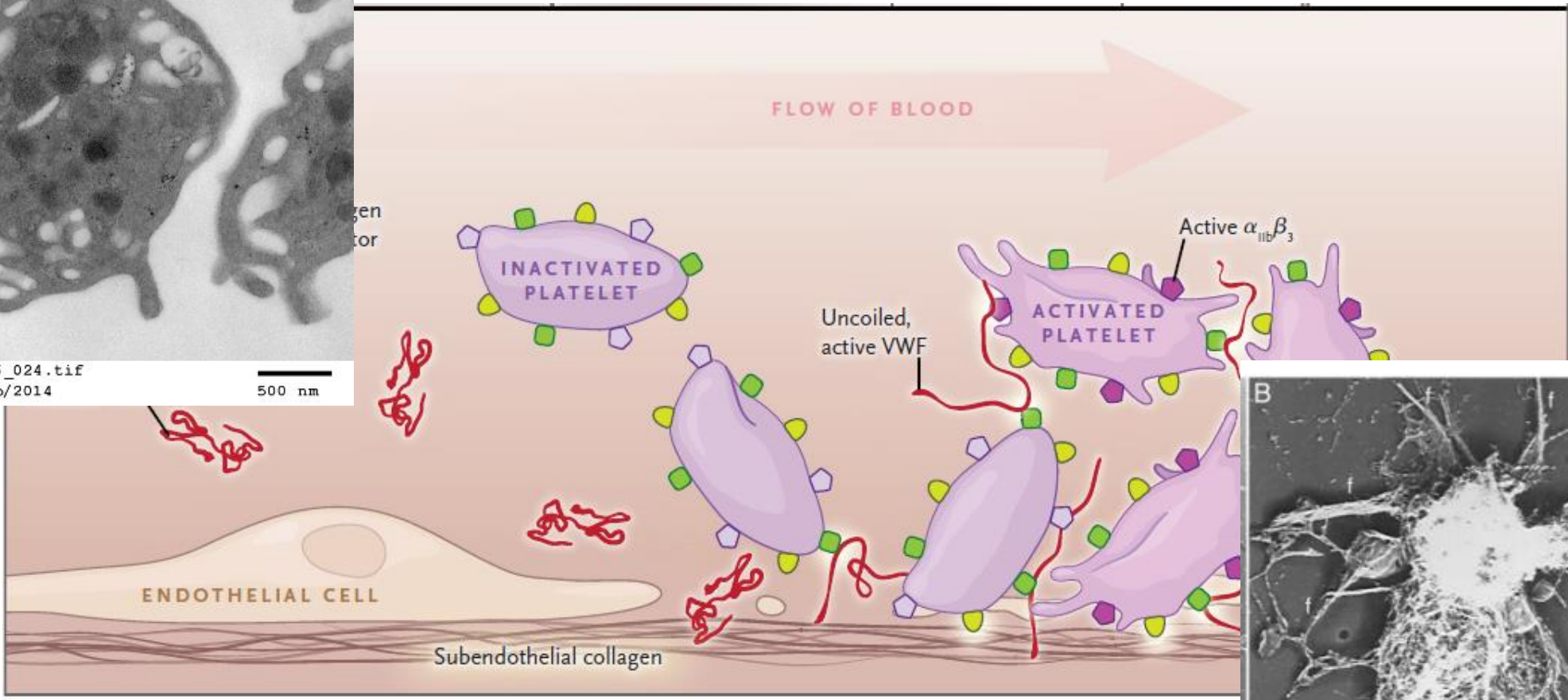
Platelets are the surface



# The Platelet Plug

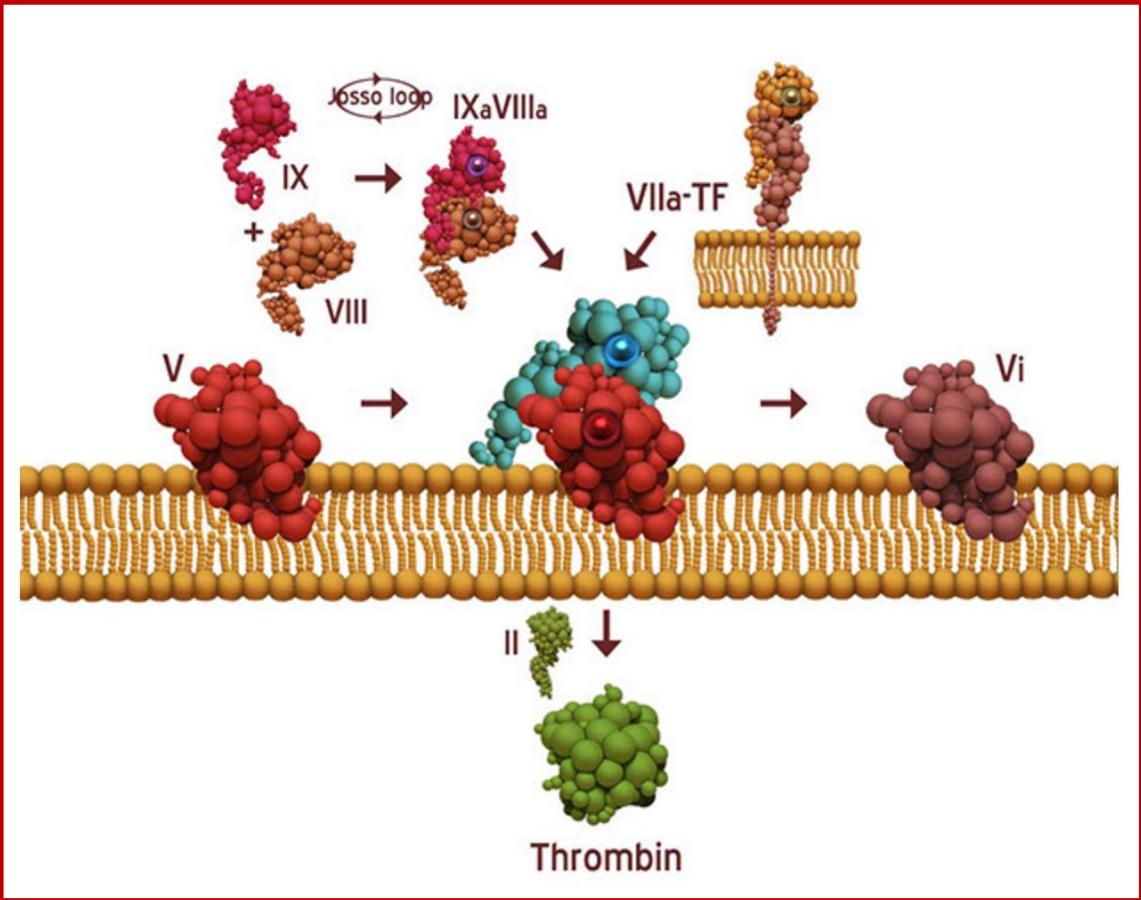


UTAH sample #16\_024.tif  
L6 UTAH Feb/2014  
500 nm

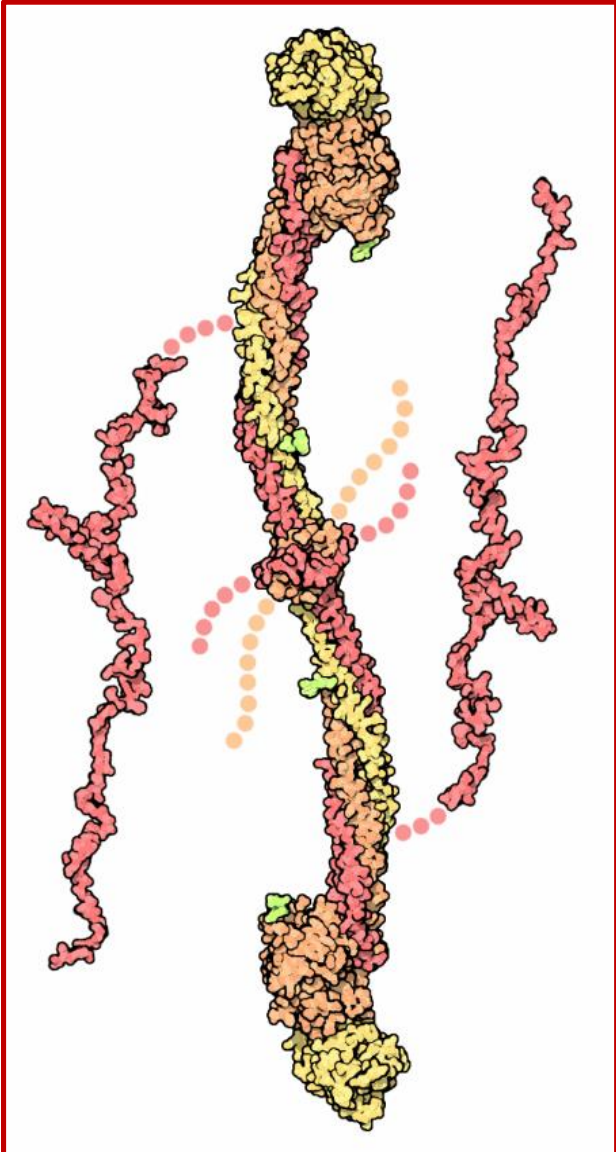


*Am J Physiol Cell Physiol* 285: C797–C805, 2003.

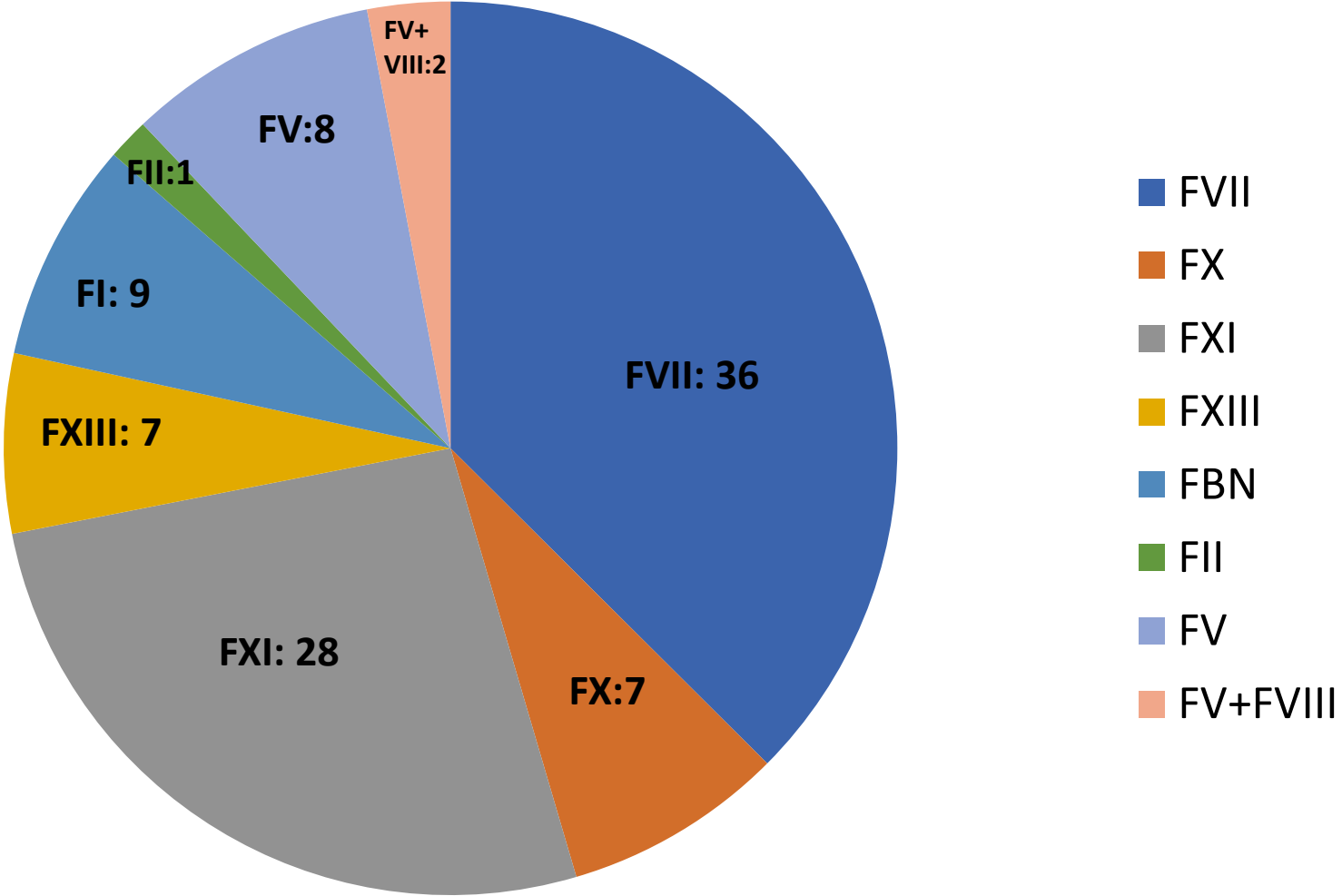
# The Fibrin Net



Multiple sites of feedback loops on the surface of the growing thrombus



# Prevalence of RBDs - Clotting Factor Deficiencies (%)





<b>Defect</b>	<b>Iran</b>	<b>Italy</b>	<b>UK</b>
Fibrinogen	70 (1.5%)	10 (0.2%)	11 (0.2%)
Prothrombin	15 (0.3%)	7 (0.02%)	1 (0.02%)
FV	70 (1.5%)	21 (0.5%)	28 (0.6%)
<b>FVII</b>	<b>300 (6.6%)</b>	<b>58 (1.3%)</b>	<b>62 (1.3%)</b>
FV + FVIII	80 (1.7%)	29 (0.7%)	18 (0.3%)
<b>FVIII</b>	<b>3000 (65.4%)</b>	<b>3428 (79.9%)</b>	<b>3554 (77.2%)</b>
<b>FIX</b>	<b>900 (19.6%)</b>	<b>626 (15.0%)</b>	<b>762 (16.1%)</b>
FX	60 (1.3%)	16 (0.4%)	25 (0.5%)
FXI	20 (0.4%)	60 (1.3%)	150 (3.3%)
FXIII	80 (1.7%)	31 (0.7%)	26 (0.5%)

**3 - 5 fold higher prevalence in Iran**

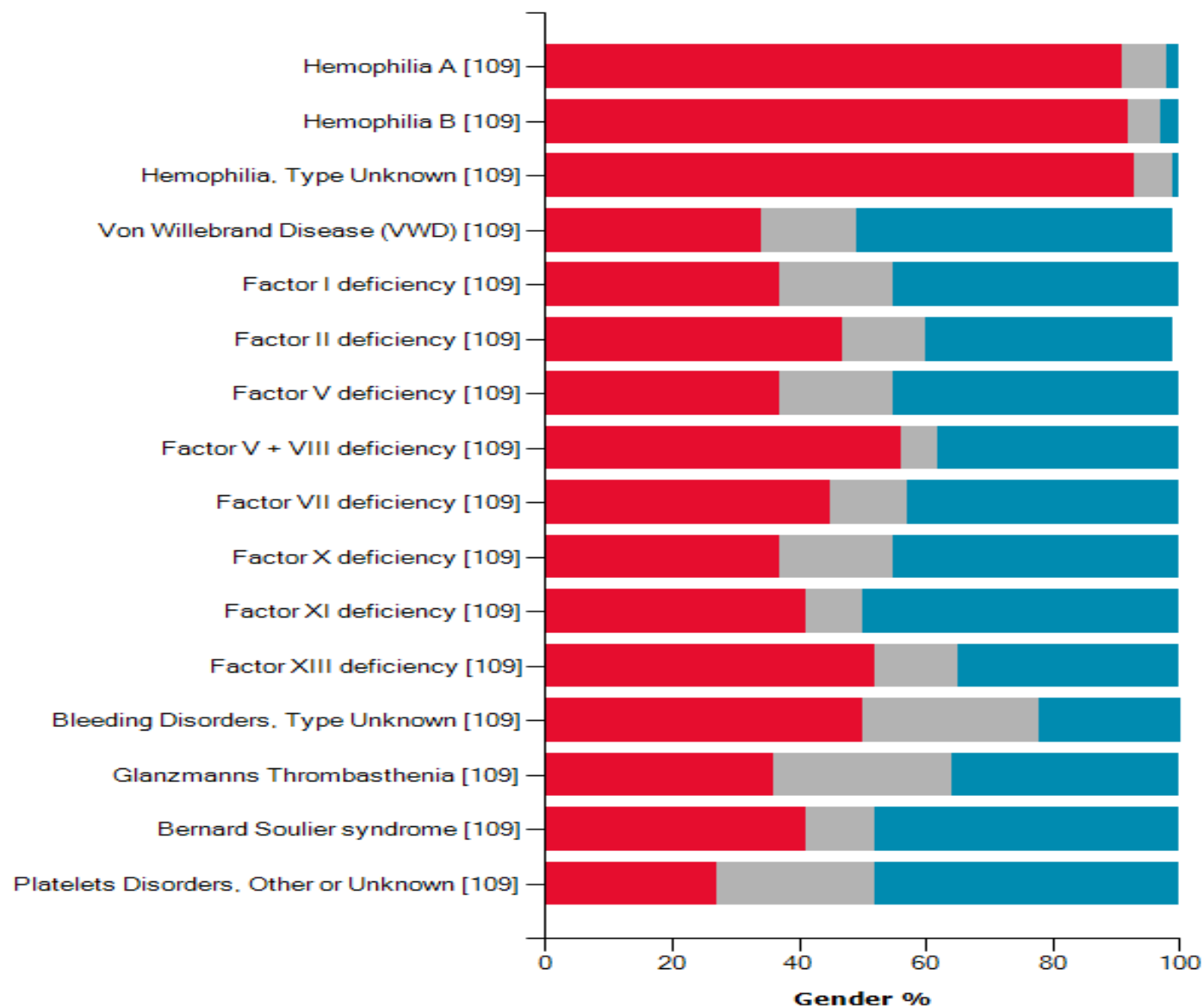


WFH Annual Global Survey Data : Bleeding Disorders by Gender (%) in 2012



Male Not Indicated Female

**Bleeding Disorder  
[# of Countries]**



# Rate of Consanguinity

1 - 40-70%

2 - 50%

3 - 85%

4 - 49%

5 - 40%

6 - 60%

RBDs – 3-7 -fold higher in the Middle East and SE Asia than developed countries



# Issues Related to RBDs

## Provider

- Recognition
- Lack of numbers at treatment centers
- Heterogeneity of symptoms
- Lab to make diagnosis
- Optimal therapy
- Access to therapy



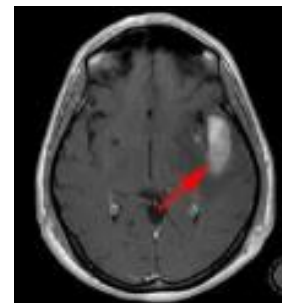
## Affected Individual/Family

- Diagnosis: Finding physician with knowledge of RBDs
- Therapy: Access , cost
- Consequences of inadequate diagnosis & therapy
- Stigma
- Fear
- Isolation

# Clinical Symptoms

## Highly variable bleeding tendency

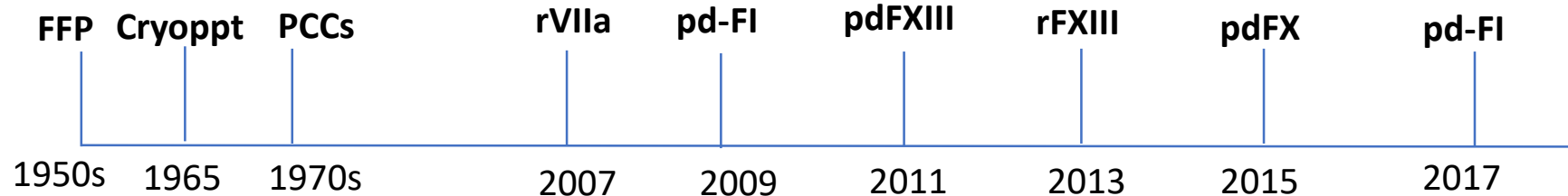
- Most common symptoms
  - Skin and lining area bleeding
  - Heavy menses and prolonged bleeding at labor and delivery
  - Excessive bleeding with invasive procedures including circumcision
- Frequently in fibrinogen(FI), FVII, FX and FXIII deficiencies
  - CNS bleeding, umbilical cord bleeding, joint bleeds and soft tissue haematomas: GI bleeding: Mainly in FX deficiency
- Frequent in afibrinogenemia and FXIII deficiency
  - Spontaneous abortion





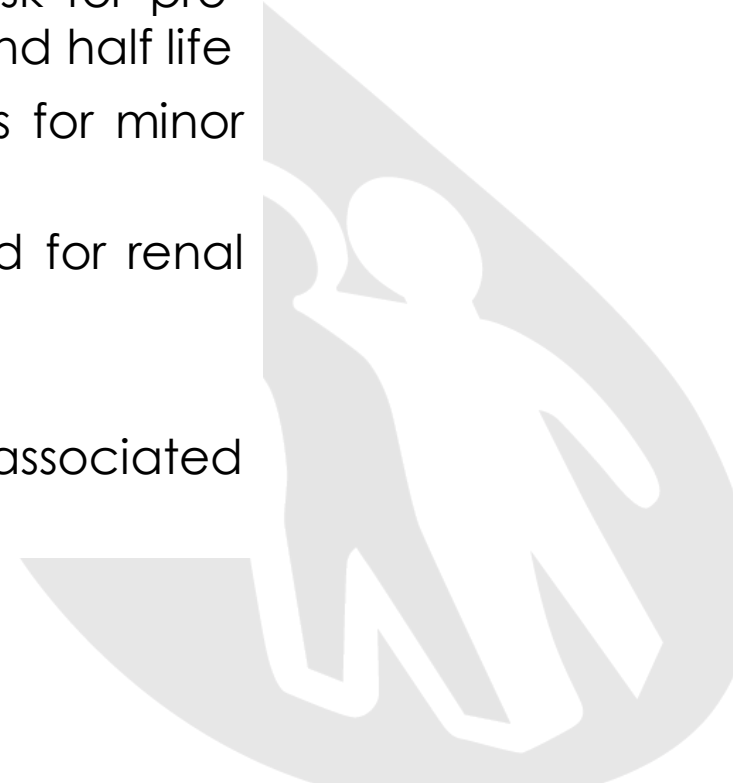
# Summary of Factor Replacement

Deficiency	FFP	Platelet	Cryoppt	Plasma Concentrate	Prothrombin Complex (PCC)	Recombinant Factor
Fibrinogen (FI)	Last choice		# 2 choice	# 1 choice		
Prothrombin (FII)	# 2 choice				# 1 choice	
<b>Factor V</b>	<b>x</b>	<b>x</b>				
Factor VII	Last choice			x (not USA)	#2 choice	# 1 choice
Factor X	Last choice			# 1 choice	# 2 choice	
<b>Factor XI</b>	<b>x</b>			x (not in USA)		
Factor XIII	Last choice		# 2 choice	# 1 choice		# 1 choice



# Caution about replacement products

- **Safety of replacement products and availability and preferably patients to be treated at an HTC**
- **Specific single** recombinant or plasma derived **concentrates** should always **be the first choice**
- Bleeding history and use of Bleeding scores to determine bleeding risk for pre-surgical/ dental prophylaxis; replacement based on hemostatic level and half life
- Adjunctive treatments including local measures/ antifibrinolytic agents for minor bleeds and mucocutaneous bleeding
- Amino caproic acid and Tranexamic acid is relatively contraindicated for renal tract bleeding and in cases with high thrombotic risk
- Pay attention to volume overload with FFP use
- High / repeated doses of PCC, single factor concentrates have been associated with arterial and venous thrombosis

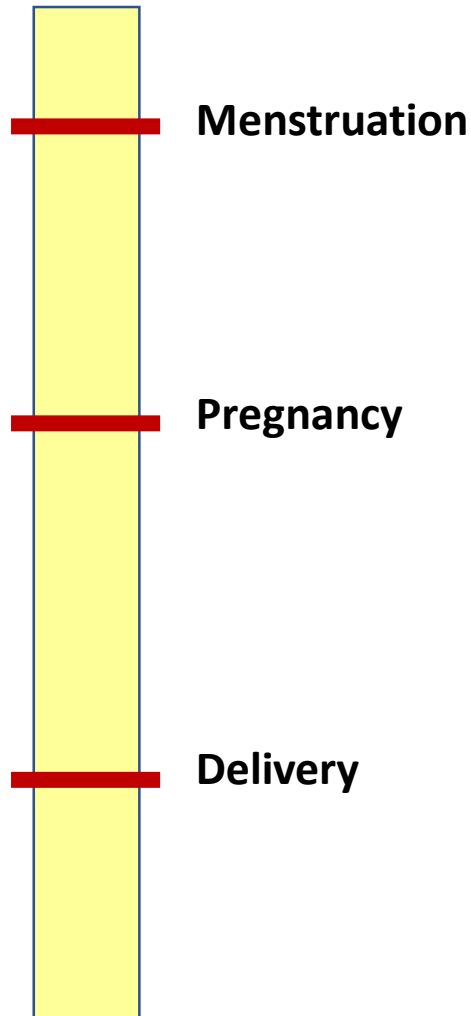


# Role of Prophylaxis ??

- **Prophylaxis need in RBDs related to**
  - Bleeding frequency
  - Severity of spontaneous bleeding
  - Risk of long-term sequelae
- **Types of prophylaxis in RBDs**
  - **Primary prophylaxis:** Before any bleeding occurs recommended in **severe FXIII deficiency** - risk for intracranial hemorrhage
  - **Secondary prophylaxis:** After a bleeding event, to prevent recurrence musculoskeletal bleeding or life-threatening hemorrhage as in FVII, FX, FXIII and in severe cases of Fibrinogen (FI) and FV deficiencies
- Data regarding benefit of prophylaxis in RBDs sparse



# Women with RBDs



## Heavy menstrual bleeding:

- in 30-70% in all RBDs

*Lak 1999, Siboni 2009, James 2010, Khair 2013, Mariani 2013, Shetty 2014, Napolitano 2014*

## Miscarriages:

- Afibrinogenemia 30-50%
- Hypofibrinogenemia 29%
- Dysfibrinogenemia 38%
- FXI 10%
- FXIII 50-63%

*Goodwin 1989, Haverkate 1995, Burrows 2000, Lak 2003, Myers 2007, Mensch 2011*

## Post partum bleeding:

- Hypofibrinogenemia 45%
- FV 76%
- FVII,FX,FXI,FXIII high rates

*Goodwin 1989, Noia 1997, Kadir 1998, Burrows 2000, Kulkarni 2006, Teixeira 2012, Baumann Kreuziger 2013*





# Heavy Menstrual Bleeding (HMB)

	Factor I	Factor II	Factor V	Factor V+VIII	Factor VII	Factor X	Factor XI	Factor XIII
Gender	50%	47%	46%	43%	47%	43%	54%	42%
<b>HMB</b>	Unknown	Unknown	<b>60%</b>	UK	46%	50%	<b>67%</b>	26%

[www.wfh.org/en/data-collection](http://www.wfh.org/en/data-collection)

ovulation associated rupture of corpus luteum – homozygous FVII, FX deficiency; FV – 20%<sup>1</sup>

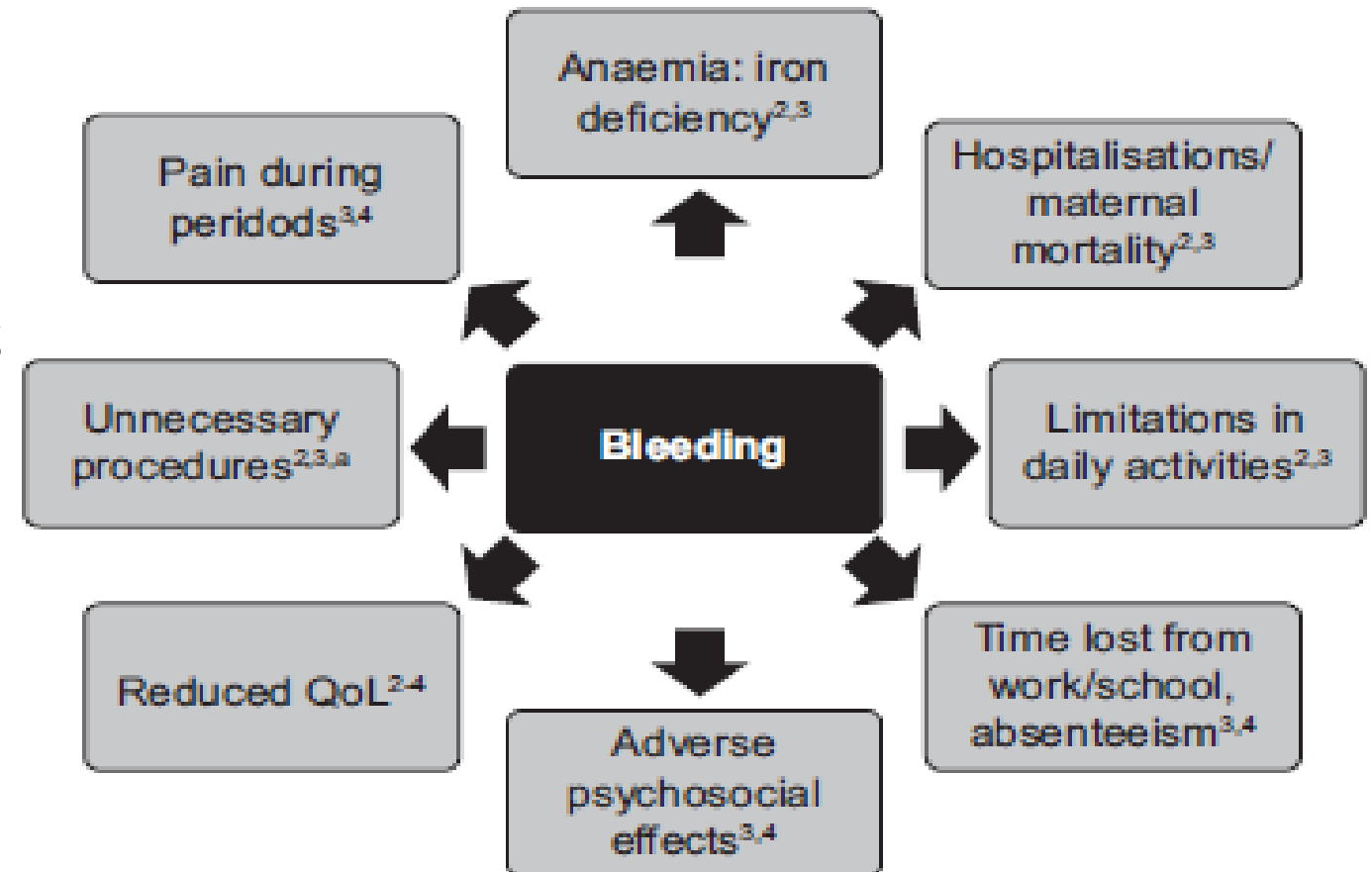
hemoperitoneum: Afibrinogenemia<sup>2</sup>

endometriosis, hyperplasia, polyps and fibroids<sup>3</sup>



# Other Gyn symptoms

- Heavy menses – pain during and mid cycle
- Peri –menopausal bleeding requiring treatment
- Bleeding into ovarian cysts
- Endometriosis
- Endometrial polyps, fibroids



# Bleeding Assessment

**Pictorial Blood Loss Assessment Chart (PBAC)**  
**Menstrual chart and scoring system**

Date of start:  day  month  year      Score:

Towel	1	2	3	4	5	6	7	8
Clots/flooding Clots: size								

Tampon	1	2	3	4	5	6	7	8
Clots/flooding Clots: size								

**Scoring System**

**Towels**

- 1 point for each lightly stained towel
- 5 points for each moderately soiled towel
- 20 points if the towel is completely saturated with blood

**Tampons**

- 1 point for each lightly stained tampon
- 5 points for each moderately soiled tampon
- 10 points if the tampon is completely saturated with blood

**Clots**

- 1 point for small clots
- 5 points for large clots

Source: U.K. Haemophilia Society, A Guide For Women Living with von Willebrand 's

## Sisterhood App



e-PBAC , e-BAT

# Management of heavy menstrual bleeding in women with a bleeding disorder

Considering Pregnancy Soon?

NO

**Hormonal Control**

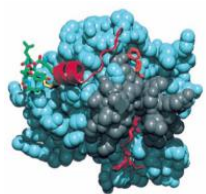
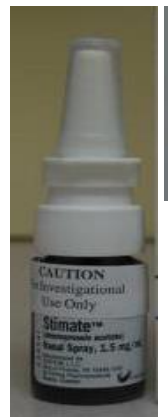
- Levonorgestrel IUD
- COCs
- Progestins



YES

**Hemostatic Agents**

- Tranexamic acid
- Aminocaproic acid
- Factor concentrate?
- DDAVP in HA and VWD
- Platelet transfusions



**Completed Reproduction?**

**Hysterectomy**  
**Endometrial Ablation**





# L.A.R.C (long-acting reversible contraceptives)

- Levonorgestrel Intrauterine Device (LNG)-IUD
  - Reductions in blood loss of up to 80% after 3 months and up to 97% after 1 year
- Etonorgestrel subdermal implant
  - Amenorrhea 30-40% after 1 year
- American Academy of Pediatrics policy statement on contraception for adolescents lists LARC as 1<sup>st</sup> line (2014)



# Debunking Myths about IUD

- The American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the Centers for Disease Control and Prevention (CDC), and the Society of Family Planning support use of LARC by adolescents
- Risk of Pelvic Inflammatory Disease highest in first 20 days after insertion
  - overall absolute risk is 1.6 cases per 1000 woman–years of use
  - May decrease risk of PID with long term use
- If sexually transmitted disease (STI) is diagnosed after the IUD is in place, it may be treated without removing the IUD
- Does **NOT** increase risk of infertility

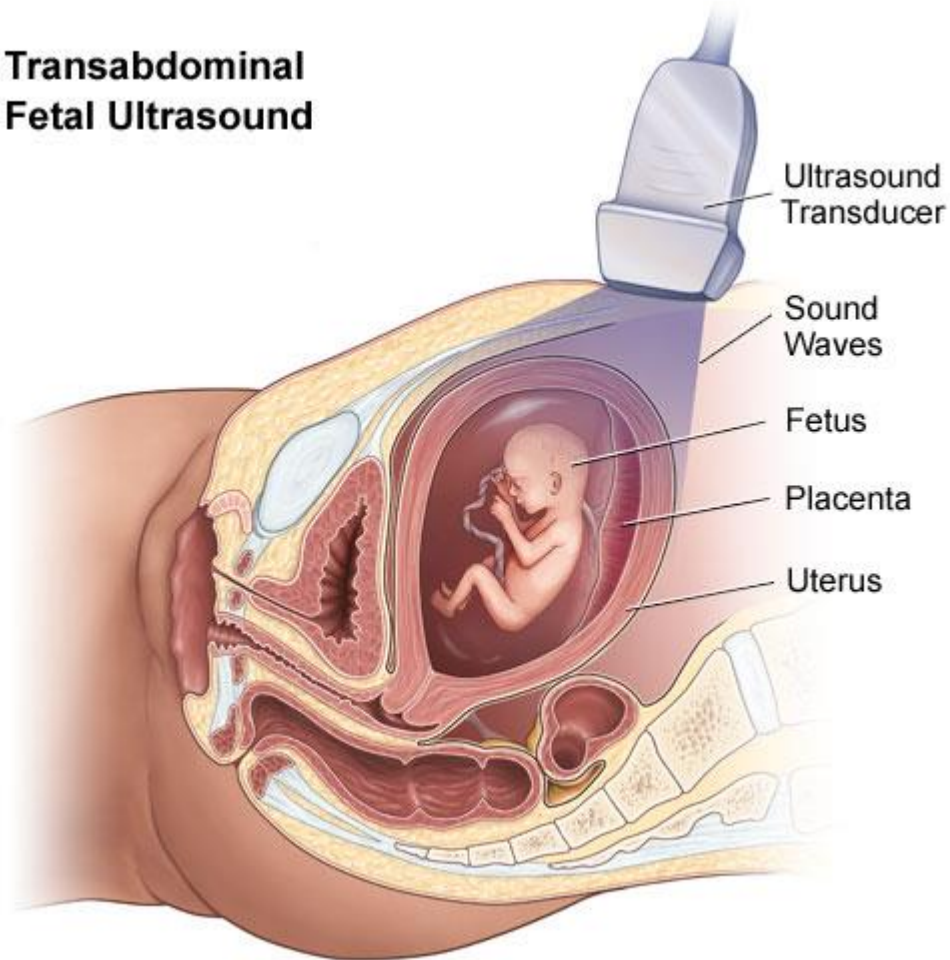
# Reproductive Endocrinology

- Helps a woman or a couple have a healthy pregnancy and baby
- Can be used to help achieve pregnancy
- Helps to ensure a safe delivery
- Both Mother and Fetus are the patient



# Reproductive Endocrinology

## Transabdominal Fetal Ultrasound



## Team members:

- Obstetrician
- Reproductive Endocrinologist
- Genetics Counselor
- Health Behaviors
- Ultrasound technician
- Hematologist
- Lab testing

<https://www.stanfordchildrens.org/en/topic/default?id=fetal-ultrasound-92-P09031>



# What happens?

- Preconception counseling
- History of menses and previous pregnancies
- Family History
- Physical exam
- Preconception testing

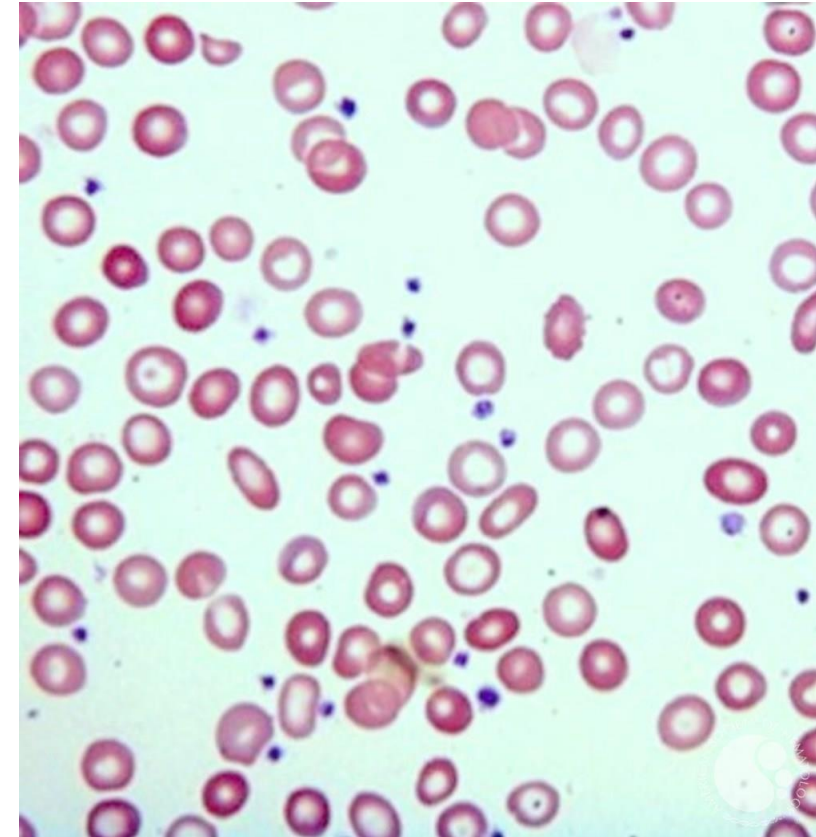




# The Health of the Mother

## Getting Pregnant

- Iron deficiency
- Anemia
- Prolonged uterine bleeding
- Bleeding from ovaries
- Bleeding from intimacy
- Pain with intimacy
- Normal pregnancy stuff



# The Health of the Mother



## Staying Pregnant

- Bleeding from a miscarriage
- Tubal or ectopic pregnancy
- Bleeding during pregnancy
- Early Labor
- Hemorrhage at delivery

# The Health of the Fetus

## During Pregnancy

- Iron deficiency
- Anemia
- Bleeding in the placenta
- Bleeding in the fetus, if the fetus is affected
- Normal pregnancy stuff

## At Delivery

- Early Labor
- Hemorrhage of the mother
- Birth trauma
- Any other complication of pregnancy



# Types of Technology

## Before Pregnancy

- Genetics of the parents
- Gender selection
- Preimplantation genetic diagnosis

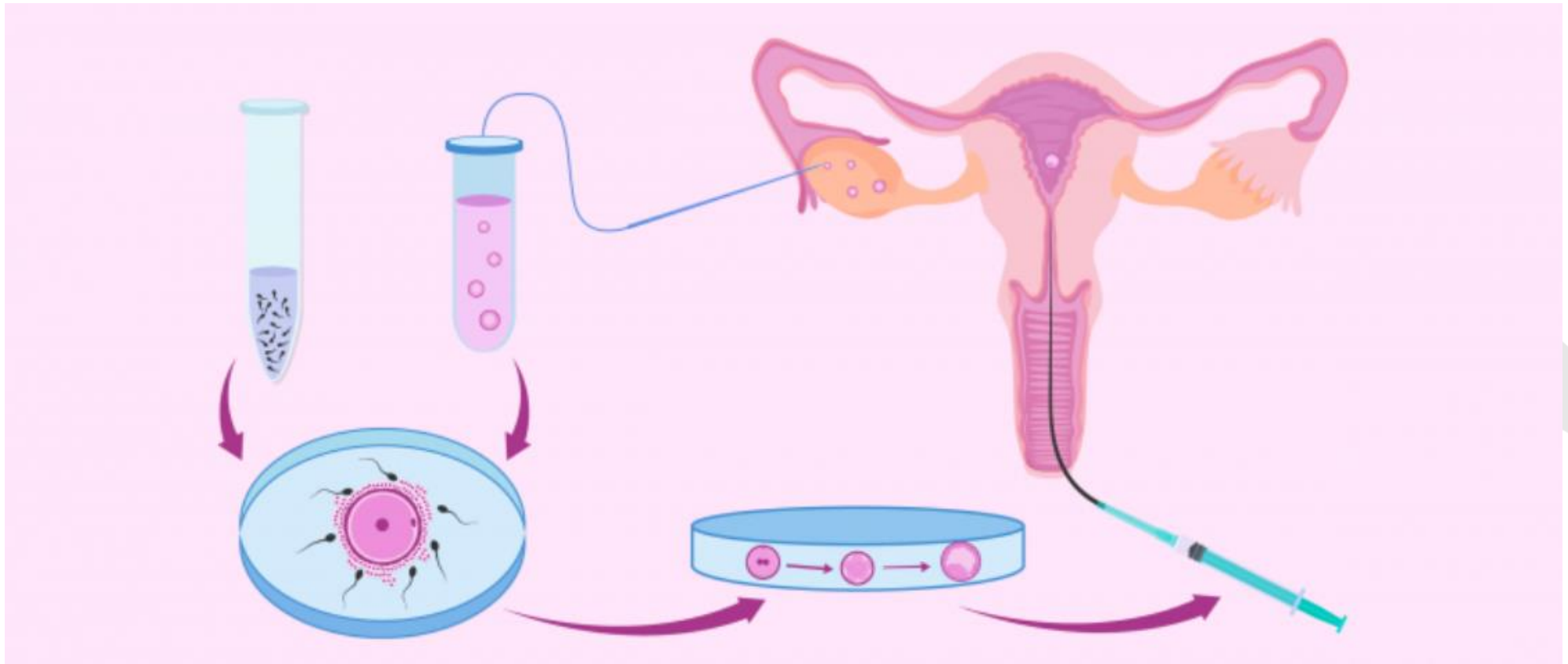
## During Pregnancy

- Chorionic Villus Sampling
- Screening for variants
- Amniocentesis



# Preimplantation Genetic Diagnosis

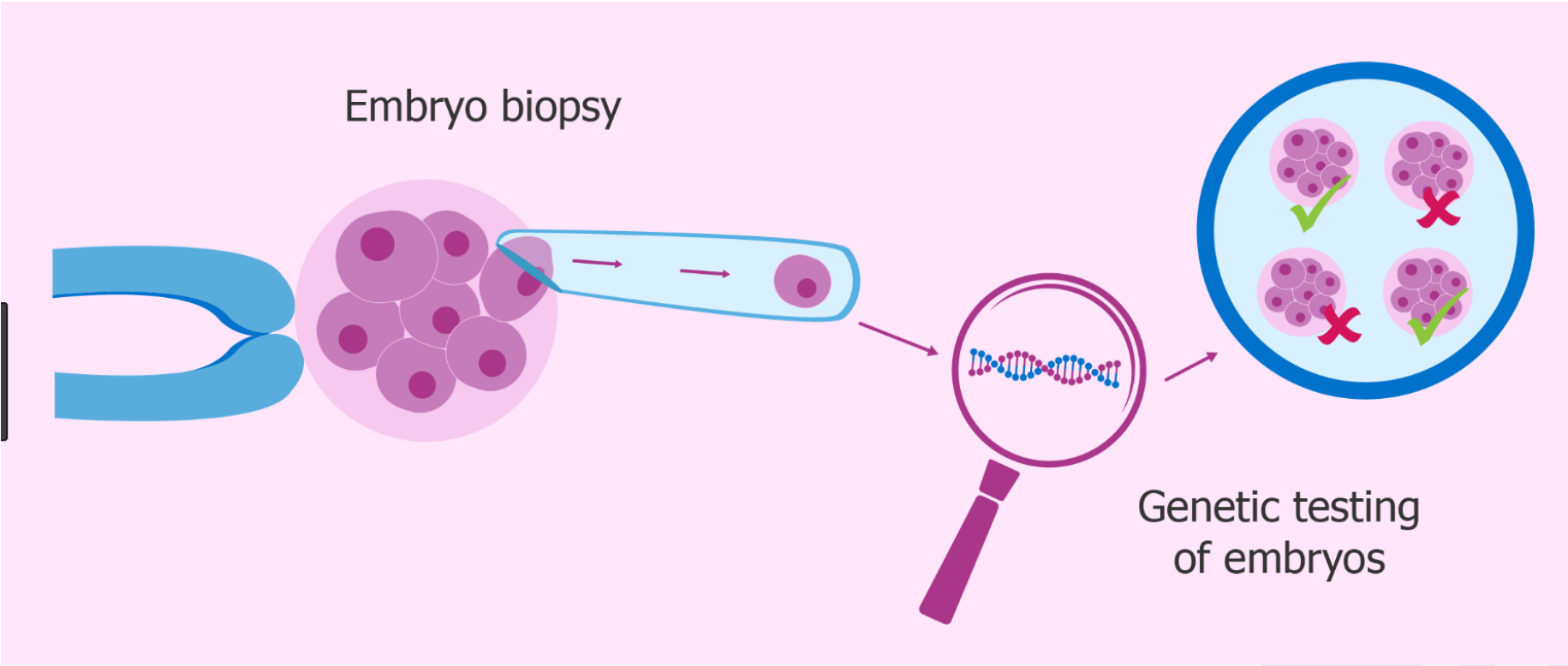
Starts with In Vitro Fertilization...





# Preimplantation Genetic Diagnosis

...Then a cell is tested for the genetic condition



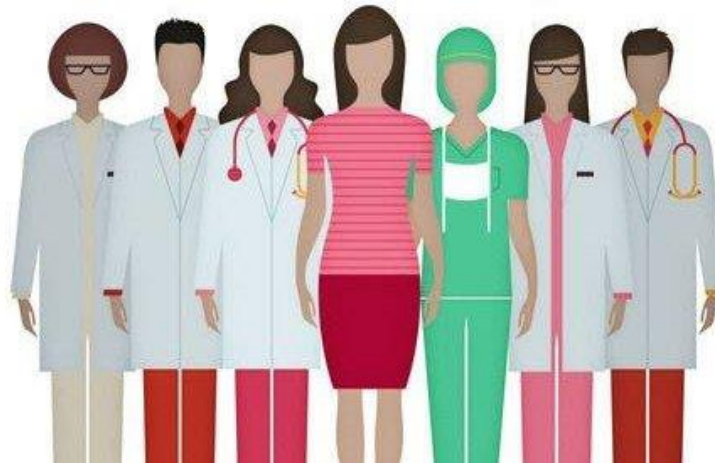
# Hemophilia Treatment Centers (HTCs)



- The Hemophilia Program began in 1982 when the hemophilia community and the federal government devised a plan for the comprehensive care for treatment of persons with bleeding disorders under the auspices of the Maternal Child Health Bureau (MCHB). MCHB established criteria to qualify HTCs as Centers of Excellence. Currently, there are 130 Centers of Excellence (HTCs) nationally that are funded by the MCHB and the CDC.
- The HTCs comprehensive care model is recognized as specialized preventative care.
- Mortality decreased by 40% in patients using a comprehensive HTC.

# Comprehensive Care for Girls and Women at HTC's

- Medical Home
- Diagnosis & Treatment Plans
- 24/7 Triage
- Home Treatment Goals
- **Prevention-focused**
- **Education-focused**
- Collaboration with:
  - Primary Care /Subspecialists
  - Schools/Daycare
  - Service Agencies
- Outcome Monitoring:
  - Data Collection
  - Identify emerging problems



## Multidisciplinary Team:

- Hematologists
  - Pediatric
  - Adult
- Nurses/Nurse Practitioners
- Physical Therapist
- Social Worker
- **Clinic for Girls and Women with Bleeding Disorders**
- Other:
  - Dental professionals
  - Genetic counselors
  - Gynecologist/Obstetrician
  - Research coordinators
  - Liver specialists
  - Nutritionists
  - Data managers
  - Pharmacy

# Hope and Health for All

- Adoption
- Sponsor a child in need
- Volunteer in your community
- Adopt a pet
- Enjoy “bonus kids”



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Help a Child Meet Basic Needs

[Learn More](#)



Help a Student Pay for College

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Help a Child Go to Camp

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Donate or Request Factor

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# Session Evaluation

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**Take a few minutes now to fill out the session evaluation:**

## **Rate this session**

- Meaningful?
- Learned new ideas/skills?
- Will implement new ideas/skills?

**How could this session be improved?**

**Comments?**

