Basics of FXIII Deficiency

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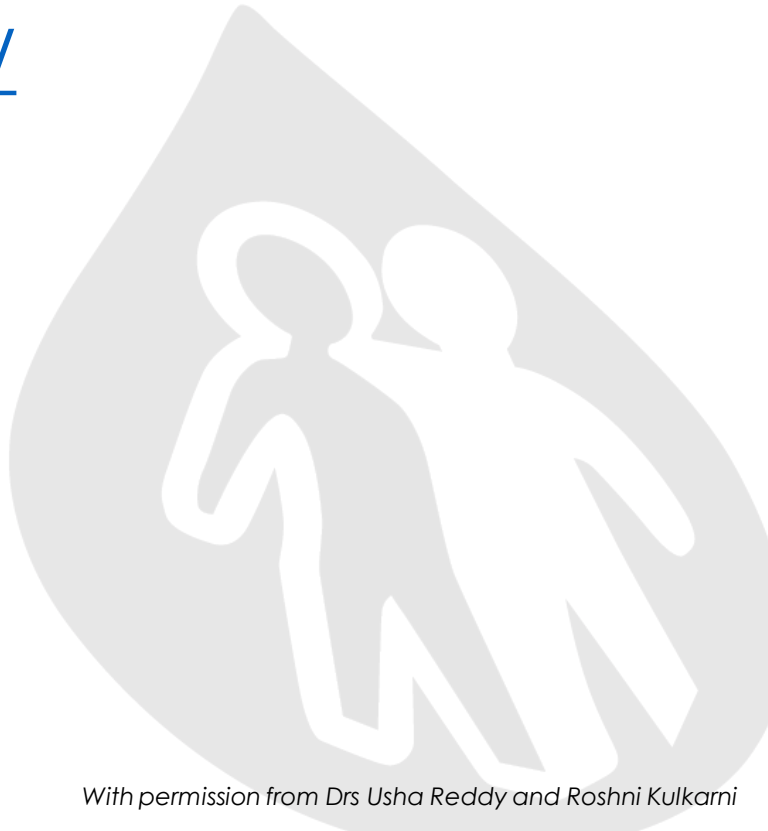
Disclosures

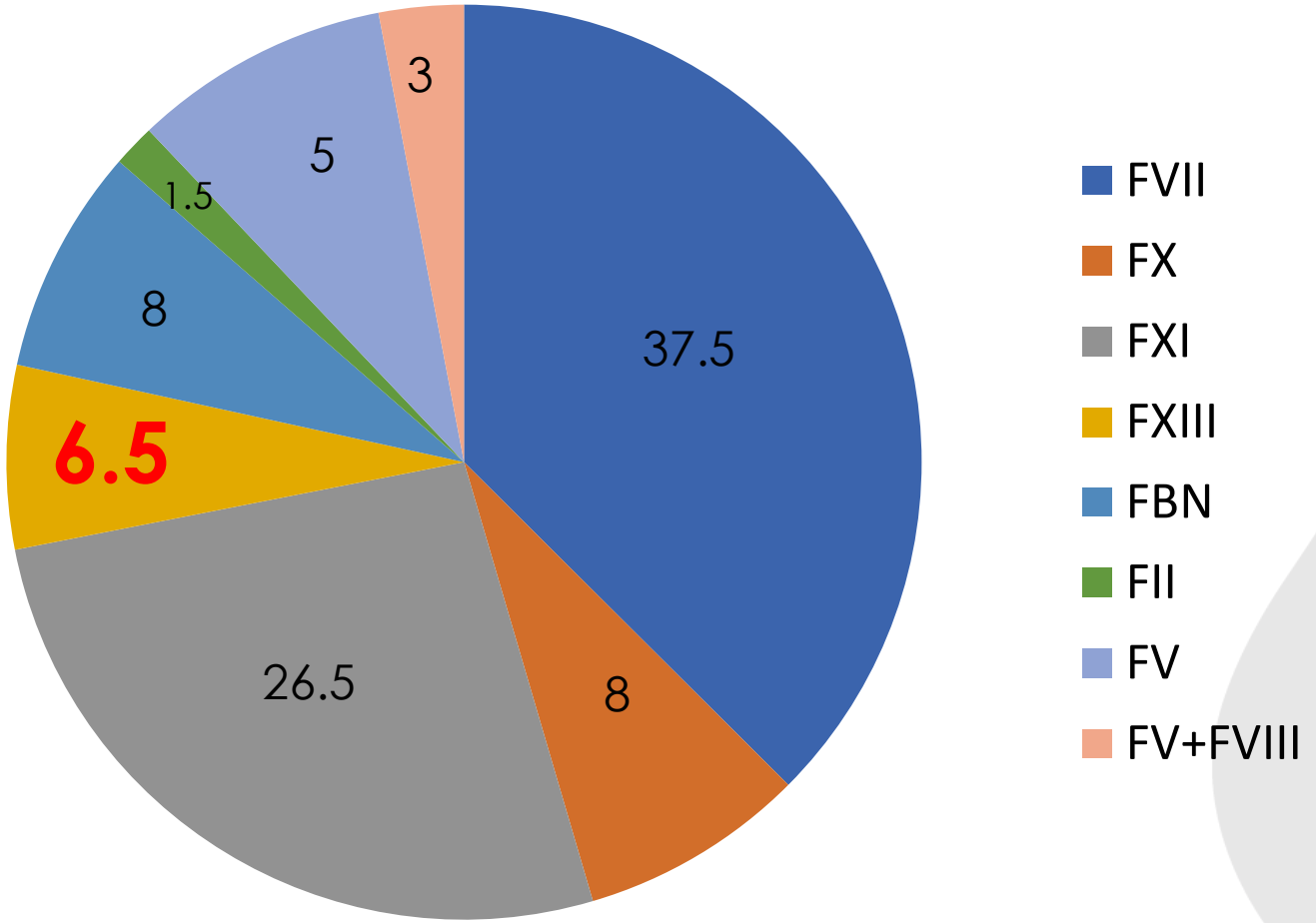
- Research Support: Bayer Pharmaceuticals Inc. for Joint disease Research
- Advisory Board: Novonordisk, Takeda, Bio Products Laboratory

http://reddymed.com/hdbc/



With permission from Drs Usha Reddy and Roshni Kulkarni

Prevalence of FXIII Deficiency (%)



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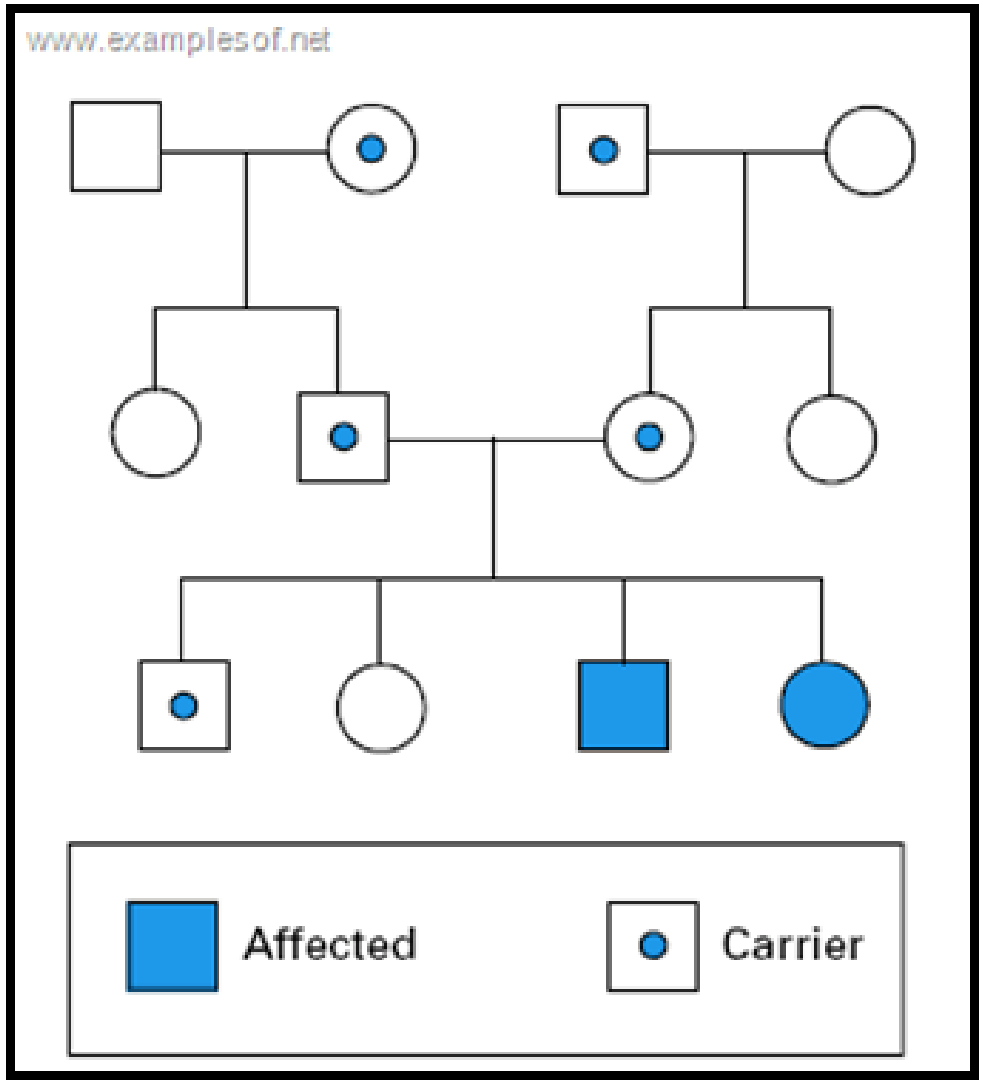
WFH: http://www.wfh.org/ ; EN-RBD: http://www.rbd.eu/

Autosomal Recessive Inheritance(AR)



Prevalence of FXIII Deficiency

Defect	Iran	Italy	UK
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%)
FVII	300 (6.6%)	58 (1.3%)	62 (1.3 %)
FV + FVIII	80 (1.7%)	29 (0.7%)	18 (0.3%)
FVIII	**3000 (65.4%)**	**3428 (79.9%)**	**3554 (77.2%)**
FIX	**900 (19.6%)**	**626 (15.0%)**	**762 (16.1%)**
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

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Mannucci PM , Blood 2004

Rate of Consanguinity

1- 40-70%

2 - 50%

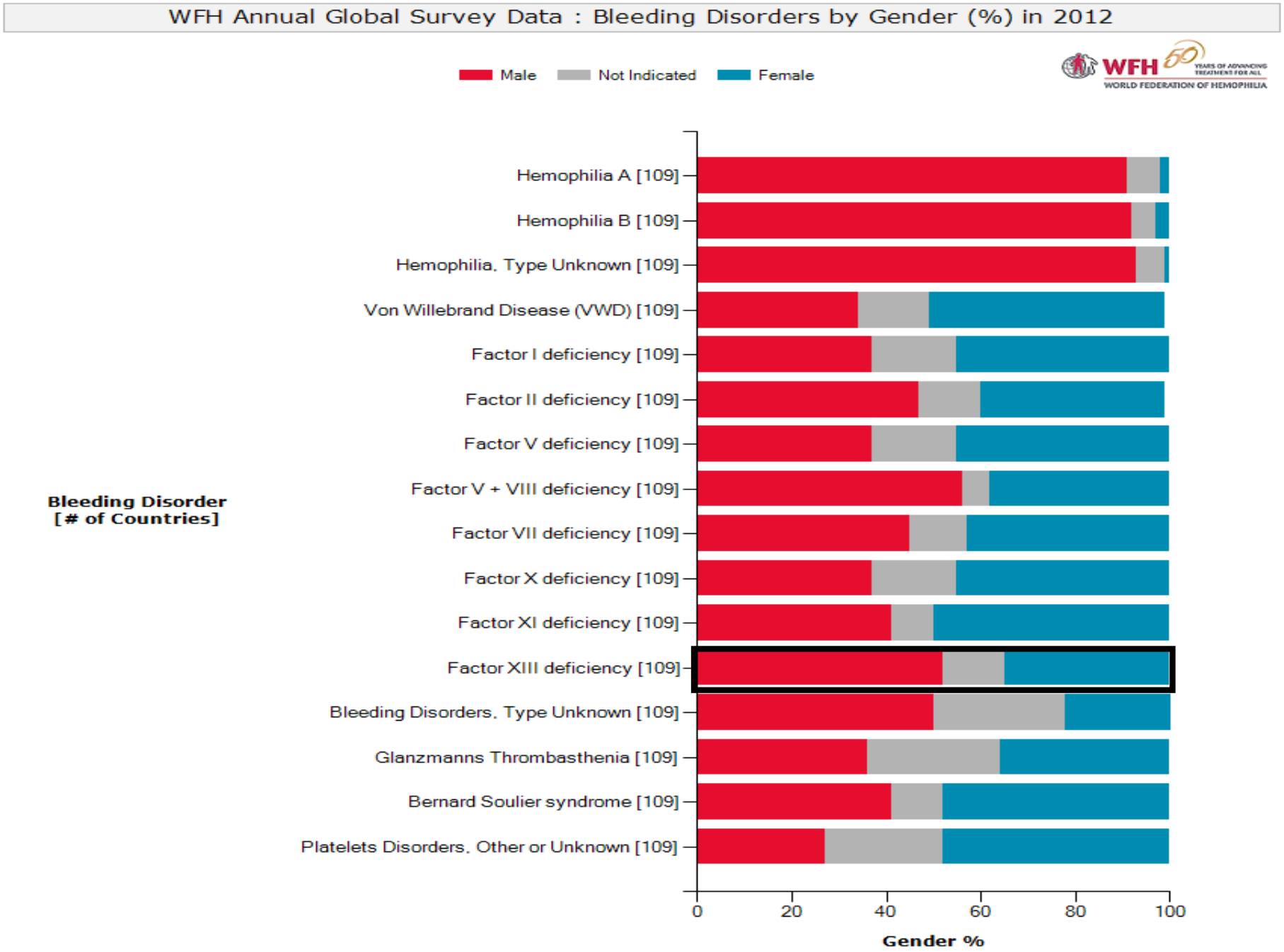
3 - 85%

4 - 49%

5 - 40%

6 - 60%

RBDs – 3-7 -fold higher in the Middle East and SE Asia than the western world

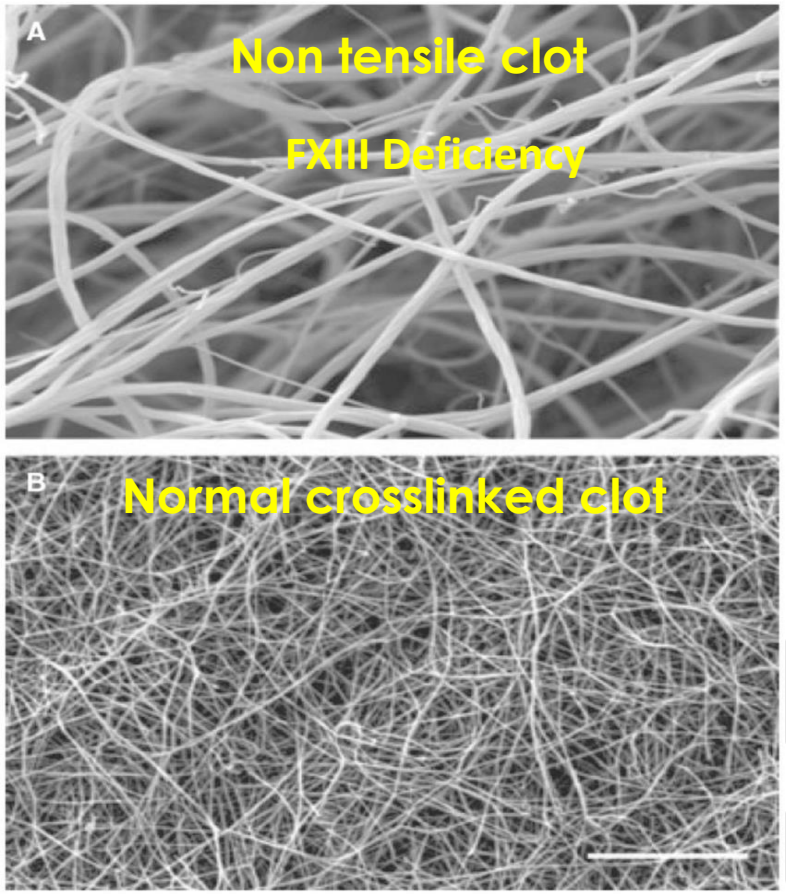

WFH Annual Global Survey Data : Bleeding Disorders by Gender (%) in 2012
Male
Not Indicated
Female
WFH
WORLD FEDERATION OF HEMOPHILIA
Bleeding Disorder
[# of Countries]
Hemophilia A [109]
Hemophilia B [109]
Hemophilia, Type Unknown [109]
Von Willebrand Disease (VWD) [109]
Factor I deficiency [109]
Factor II deficiency [109]
Factor V deficiency [109]
Factor V + VIII deficiency [109]
Factor VII deficiency [109]
Factor X deficiency [109]
Factor XI deficiency [109]
Factor XIII deficiency [109]
Bleeding Disorders, Type Unknown [109]
Glanzmanns Thrombasthenia [109]
Bernard Soulier syndrome [109]
Platelets Disorders, Other or Unknown [109]
0
20
40
60
80
100
Gender %

FXIII aka Fibrin Stabilising Factor

- FXIIIa cross-links fibrin into strong clot

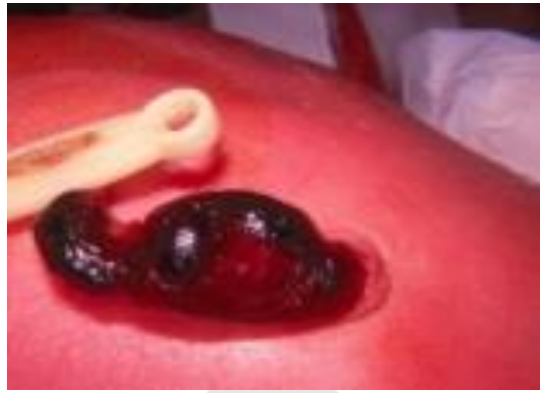
  Important for

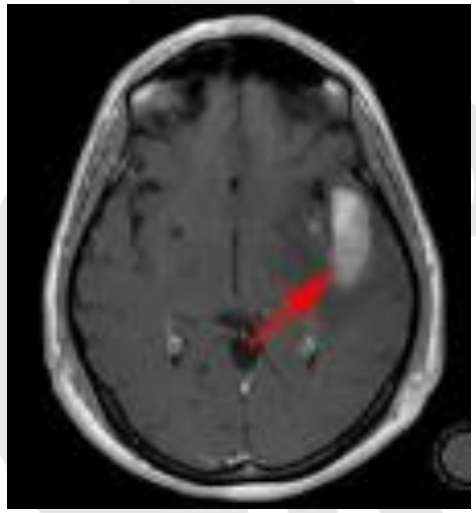
  - Resistance to clot breakdown
  - Wound healing
  - Maintaining pregnancy



Clinical Manifestations of FXIII Deficiency

- Rare and severe 1 : 3 million
- Common with consanguinity
- Lifelong bleeding tendency , may present at birth
- Persistent umbilical cord bleeding
- Severe bleeding tendency
- Spontaneous bleeding into the brain
- Bleeding into the skin and lining areas
- Joint and muscle bleeds- rare





Bleeding Pattern in FXIII Deficiency

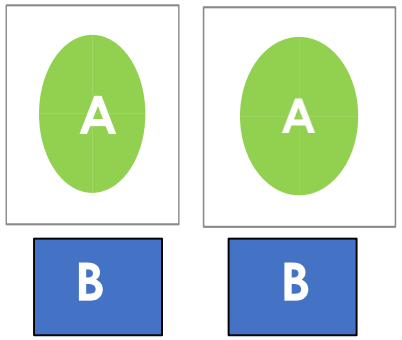
- Trauma and surgery-related
- Delayed bleeding after trauma / surgery
- Impaired wound healing in ≈30%
- Inadequate scar formation
- Recurrent , spontaneous miscarriages

FXIII PROTEIN

FXIII circulates as a tetramer (A_2B_2)

- **2 A subunits (active)**
- **2 B subunits (carrier)**

Subunit A
- ✓Active
- ✓Synthesized in
  - Megakaryocytes
  - Placenta



Subunit B
- ✓Carrier for A
- ✓No enzymatic activity
- ✓Synthesized : Liver

FXIII Subtypes

Type	Deficiency	Frequency and Severity
1	Combined (A & B) subunits	• Very rare
3	Subunit B	• Rare • Less severe
2	Subunit A	• Most common • Severe bleeding

FXIII Deficiency: Laboratory Diagnosis

Screening tests (CBC,PT, aPTT, fibrinogen, thrombin time) = NORMAL

Berichrom assay	**FXIII activity**
ELISA	**FXIII subunit A and subunit B antigen**
Urea clot lysis	**Poor sensitivity ; it is normal above levels > 2-3 %**

Proposal of classification based on International project on RBDs

FXIII (activity levels)

- <30% may bleed
- 15% is good therapeutic target – less likely for spontaneous bleeding
- <5% associated with 90% bleeding risk

Coagulant factor	Coagulant activity		
	Severe	**Moderate**	**Mild**
Fibrinogen	undetectable	0.1-1g/L	> 1g/L
FII	undetectable	< 10%	> 10%
FV	undetectable	< 10 %	>10%
FV +FVIII	< 20%	20-40%	> 40%
FVII	<10%	10-20%	> 20%
FX	< 10%	10-40%	> 40%
FXIII	undetectable	< 30%	> 30%

Peyvandi et al, 2012

Treatment Strategies for FXIII Deficiency

Replacement therapy

- severity of deficiency
- bleeding phenotype
- half life of factor
- minimum hemostatic level
- type of bleed
- replaced until healing is complete

Prophylaxis

- intracranial / recurrent hemarthroses
- pregnancy
- pre-dental, surgery

Antifibrinolytic agents

- aminocaproic acid; tranexamic acid

Treatment: FXIII-Containing Products

FXIII-Containing Products	Issues
• FXIII concentrates ▪ Corifact (plasma-derived for subunit A and B deficiency) since 2011 ▪ Tretten (recombinant for subunit A deficiency only) since 2013	• Virally inactivated / recombinant • Smaller volume
• Fresh Frozen Plasma (FFP) • Cryoprecipitate	• Not virally inactivated • large volume (1 U/mL), allergic reactions

Plasma – derived FXIII concentrate dosing

Adjust dose = + /- 5 u/kg for troughs : 5 – 20 %

FXIII Activity Trough Level (%)	Dosage Change
One trough level of <5%	Increase by 5 IU per kg
Trough level of 5% to 20%	No change
Two trough levels of >20%	Decrease by 5 IU per kg
One trough level of >25%	Decrease by 5 IU per kg

Time since last dose	Dose
Within 7 days	Additional dose may not be needed
8 - 21 days	Additional, partial, or full dose may be needed based on FXIII trough level
21 - 28 days	Full prophylactic dose

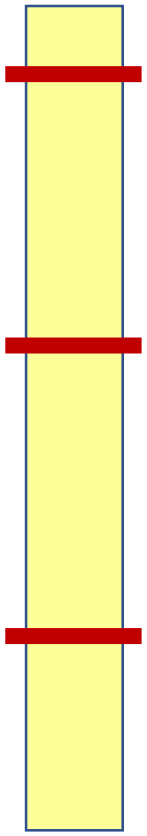
Long-term Prophylaxis for FXIII Deficiency

- Prophylaxis essential and works!
- FXIII–long half-life: 11-14 days ; low levels adequate to prevent severe bleeding
- Regimens vary
  - Factor XIII concentrate: every 4-6 wks – PREFERRED TREATMENT
  - FFP: 15-20 mL/kg every 4-6 wks

Consider primary prophylaxis for all patients with severe deficiency(< 5%)

Girls and Women with FXIII deficiency

Lifetime



Heavy menstrual bleeding:

- in 30-70% in all RBDs ; 26% in FXIII deficiency

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

Miscarriages:

- FXIII 50-63%

Ovulation associated rupture of corpus luteum

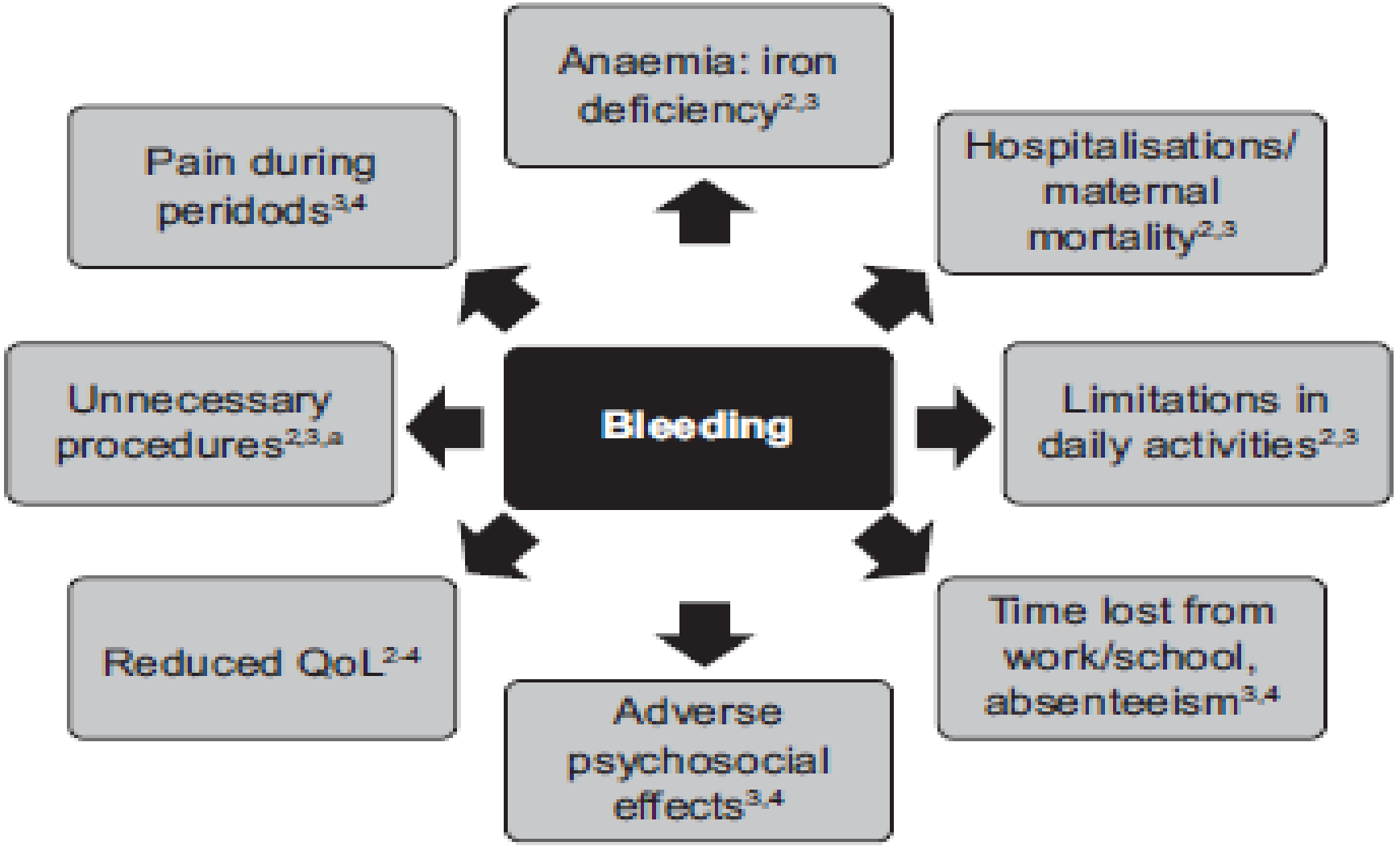
Goodwin 1989, Haverkate 1995, Burrows 2000, Lak 2003, Myers 2007, Mensah 2011

Post partum bleeding:

- FXIII high rates

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

Consequences of Heavy Menstrual Bleeding



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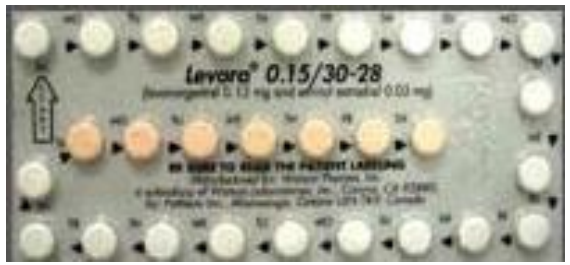
Kulkarni R et al, 2015

Management of heavy menstrual bleeding in FXIII Deficiency

Considering Pregnancy Soon?

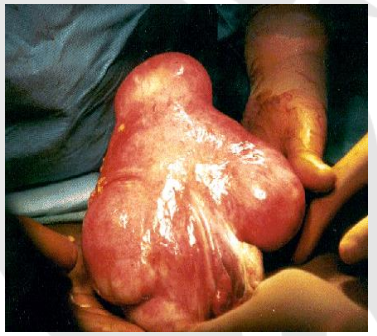
NO

Hormonal Control
- Levonorgestrel IUD
- COCs
- Progestins

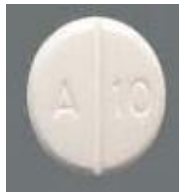


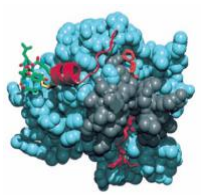
Completed Reproduction?

Hysterectomy Endometrial Ablation



YES





Hemostatic Agents
- Factor concentrate
- Tranexamic acid
- Aminocaproic acid

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Courtesy: Robert Sidonio and Peter Kouides, MD

Recommendations for Pregnancy in Women with FXIII Deficiency

- **Requires multidisciplinary team approach:** hematologist with lab support for monitoring, obstetrician –gynecologist, anesthesiologist, primary care physician
- **Careful monitoring of all pregnant women with FXIII deficiency preferably** at a Bleeding Disorder Center (HTC); replacement therapy starting in the **first trimester** based on bleeding history
- **Epidural Anesthesia Use**: No specific guidelines for epidural anesthesia in RBDs. If using regional block, maintain factor levels > 50% for duration of catheter placement and 12-24 hrs post removal
- **Vaginal vs C-section**: choose delivery that is safe for mother and child
- **Potential risk of bleeding during delivery:** PPH to be considered strongly and discussed
- **Women at risk for late PPH (2 weeks post) :** check CBC before discharge – counsel about excessive bleeding, and follow up
- **Identification** of carrier status

FXIII Deficiency and Pregnancy

- Without FXIII replacement, very high risk of miscarriage
  - **FXIII concentrate preferred to FFP or cryoprecipitate soon after conception**

- FXIII plasma level >10% required **to prevent obstetrical bleeding**

  - Early gestation:
  - After 6 months:
  - At onset of labor:

Management of The Suspected Newborn with FXIII Deficiency

- **Avoid forceps, vacuum**, fetal scalp monitoring in a suspected newborn
- C-section to avoid intracranial hemorrhage
- **Cord blood testing** for factor level if feasible
- **Screening head ultrasound** to rule out an intracranial bleed
- Intracranial bleeding can be delayed up to 4-5 days- education of mother to report signs of vomiting, lethargy, seizures
- Vitamin K ,hepatitis B vaccine at birth; in general **avoid intramuscular injections, give them subcutaneous, AVOID heel sticks**
- Risk of inhibitor development and early factor exposure unknown – **avoid elective procedures in newborns**
- Referral to a Bleeding Disorder Center or Hemophilia Treatment Center

Thank you!

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Session Evaluation

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

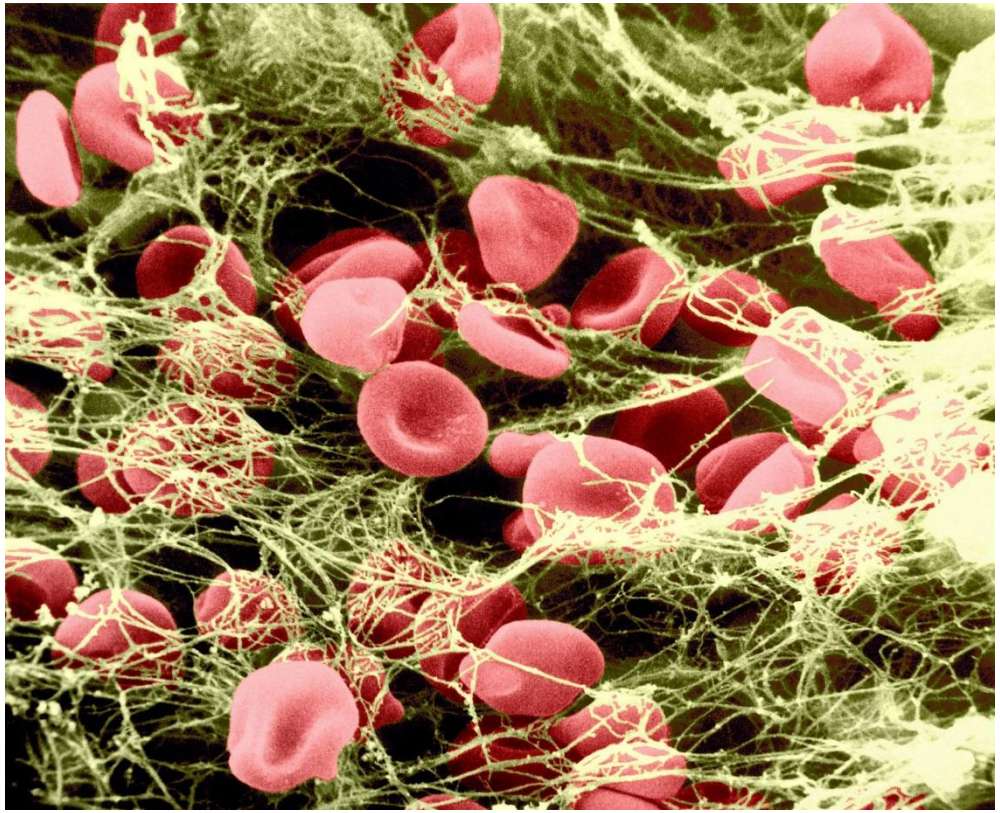
Rate this session

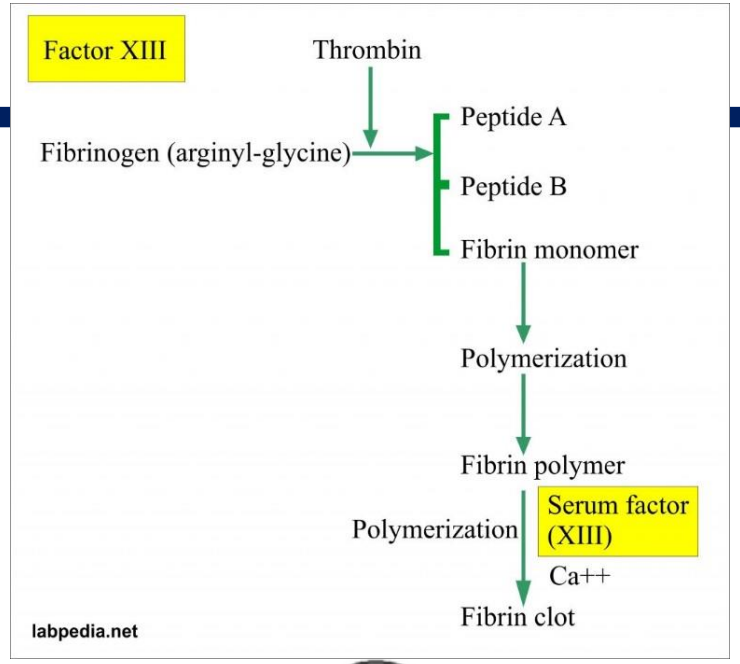
- Meaningful?
- Learned new ideas/skills?
- Will implement new ideas/skills?

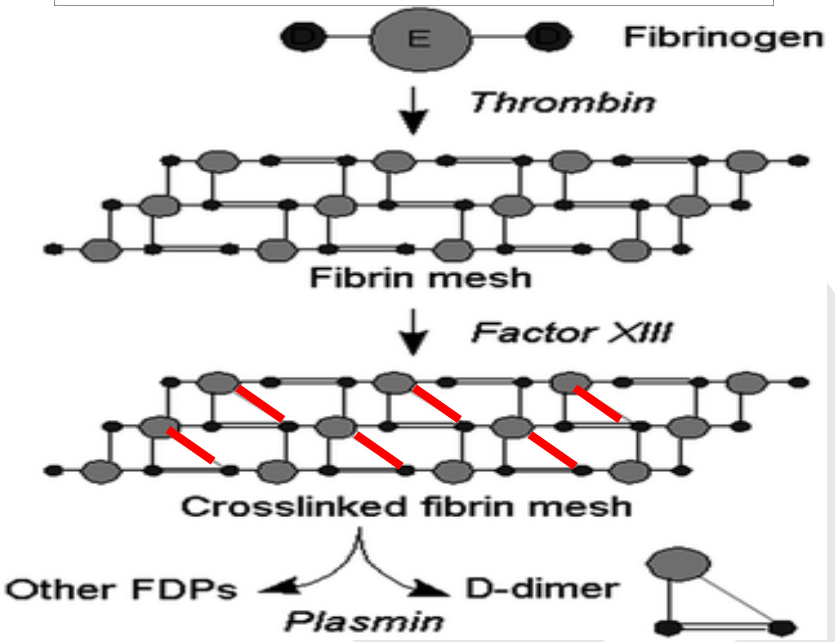
How could this session be improved?

Comments?

FIBRIN STABILIZING FACTOR (FXIII)







Treatment of FXIII Deficiency: General Principles

Replacement of FXIII – Mainstay of treatment

Bleed Treatment and Preventing Bleeding With Surgery	**Prophylaxis**