Using an anti-Xa level nomogram to adjust intravenous unfractionated heparin infusion for arrhythmia in pregnancy

W. Sia, E. Toor, N. Wahab, J. Windram, R. Khurana

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UNIVERSITY OF ALBERTA

Hospital Venous Thromboembolism Standard Continuous IV UFH Anticoagulation Protocol and Nomogram (using aPTT levels)

- CBC, INR, PTT before heparin loading dose.
- Loading Dose: _____ (loading dose = 80 units/kg, maximum 5000 units)
- Heparin _____ units IV given in 50 mL NS over 30 minutes or given undiluted by IV push.
- Initial infusion: _____ (initial rate = 18 units/kg/hour up to 1300 units/hour)
- Initial rate at _____ units/hours = _____ mL/hour
- ** Heparin Concentration 25,000 units in 250 mL D5W (100 units/mL)**
- Draw PTT 6 hours after heparin loading dose.
- Adjust heparin dose and repeat PTT according to the table below.

IV UFH Anticoagulation Protocol and Nomogram using aPTT levels

PTT (in seconds)	Heparin Bolus dose (units)	Hold infusion (minutes)	Infusion Rate Change	Repeat PTT
Less than 50	5000	0	Increase by 2 mL (200 units)/hour	6 hours
50-74	0	0	Increase by 1 mL(100 units)/hour	6 hours
75-105	0	0	No change	Next am
106-135	0	60	Decrease by 1 mL(100 units)/hour	6 hours
Greater than 135	0	60	Decrease by 2 mL (200 units)/hour	6 hours

Problems with aPTT to monitor unfractionated heparin

- Issues:
  - Poor correlation with blood heparin concentration, varying response to aPTT reagents, aPTT's responsiveness to other acute-phase reactants or other factors independent of heparin*
  - Subtherapeutic aPTT despite high doses of heparin**
- ACCP 2012 …*reasonable to use anti-Xa levels in patients with VTE who require large doses of heparin****

*Smith M and Wheeler K, Am J Health-Syst Pharm 2010;67:371-4.
**Levine M et al, Arch Intern Med 1994; 154:49-56
***Chest 2012;141(2):24S-43S

aPTT response in pregnancy is blunted

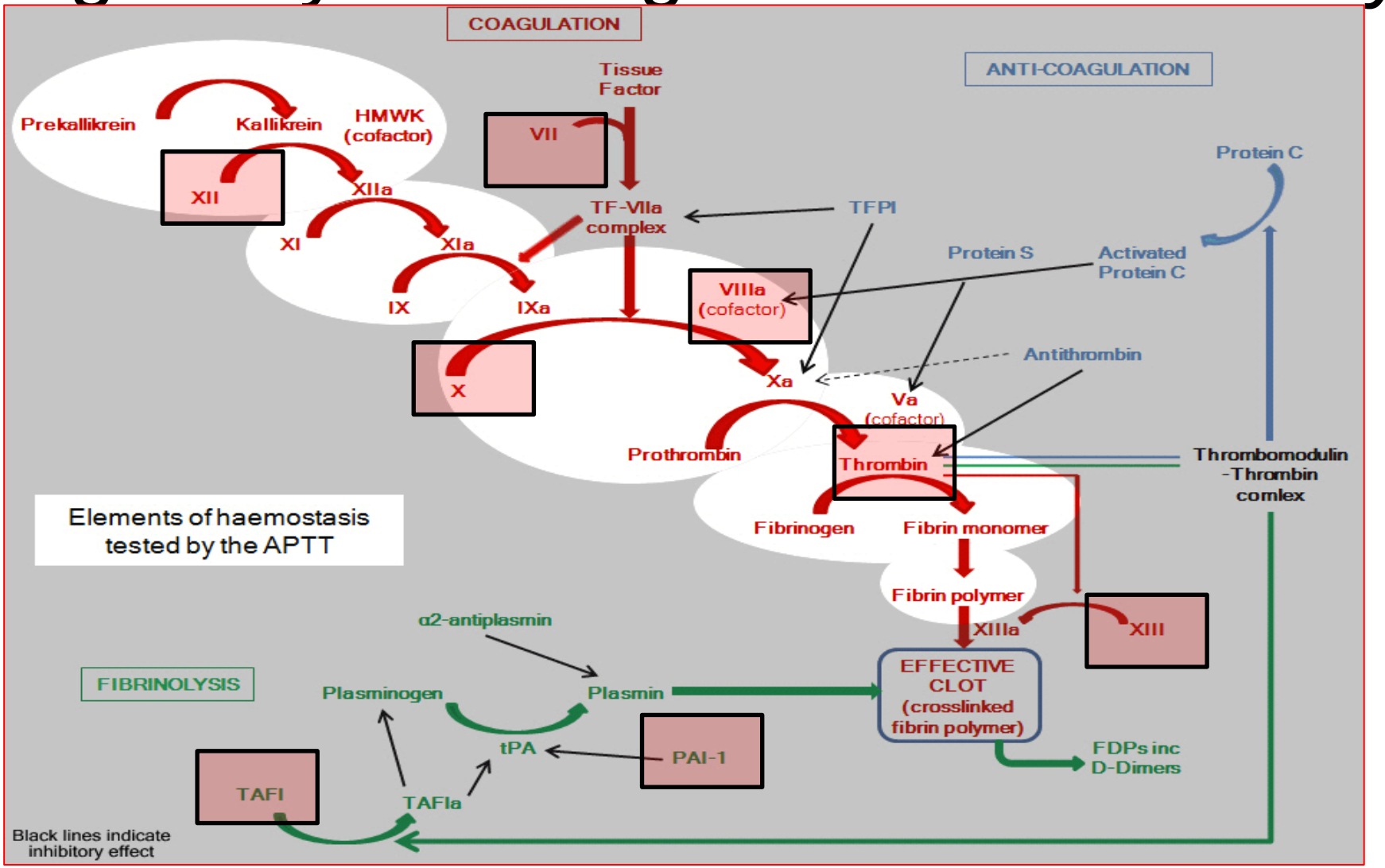
Coagulation factors change in pregnancy

- Fibrinogen, factors II, VII, VIII, X, XII, XIII – increase 20-200 %
- Thrombin activatable fibrinolytic inhibitor (TAFI), PAI-1, PAI-2 - increase

Result in aPTT

- aPTT has an attenuated response to heparin in pregnancy, therefore leading to the risk of incorrect heparin dosage

Coagulation Factor changes in pregnancy affecting the aPTT Pathway



http://www.practical-haemostasis.com

Re-write Heparin Infusion Nomogram using anti-Xa level in Pregnancy

- Concern, e.g. for the same blood sample, aPTT can be lower than therapeutic range whereas anti-Xa level is at target

Using anti-Xa level to adjust iv unfractionated heparin in pregnancy

- CBC, INR, PTT, anti-Xa level before heparin loading dose.
- Loading dose: Consider heparin 5000 units (U) IV given in 50 mL NS over 30 minutes or given undiluted by IV push. (80 U/kg, maximum 5000 units)
- Initial infusion: 18 U/kg/h up to a maximum of 1300 U/h. Heparin concentration 25,000 U in 250 mL D5W (100 U/mL).
- Anti-Xa level 6 hours after heparin loading dose or heparin infusion.
- Adjust heparin dose and repeat anti-Xa level according to the table below.
- Stop IV heparin 6 hours prior to predicted time of delivery.

Using Anti-Xa Level for Adjusting Intravenous Unfractionated Heparin Infusion

Anti-Xa level (U/mL)	Heparin bolus dose (U)	Hold infusion (minutes)	Infusion rate change	Repeat anti-Xa level
<0.20	5000	0	Increase by 2 mL (200 U)/h	6 hours
0.20-0.34	0	0	Increase by 1 mL (100 U)/h	6 hours
0.35-0.7	0	0	No change	Next am
0.71-0.85	0	60	Decrease by 1 mL (100 U)/h	6 hours
>0.85	0	60	Decrease by 2 mL (200 U)/h	6 hours

Using Anti-Xa Level for Adjusting Intravenous Unfractionated Heparin Infusion in Peripartum Thromboembolic Disease, by E. Tse, R. Khurana, G. Clarke and W. Sia. Submitted.

Case

- G2P0 patient with complex congenital cardiac disease:
  - repaired cleft mitral valve for mitral stenosis and regurgitation
  - coronary artery bypass surgery for anomalous LAD
  - previous myocardial infarction
  - history of paroxysmal atrial fibrillation with ischemic stroke
- On lifelong anticoagulation.

Case...peri-delivery plan

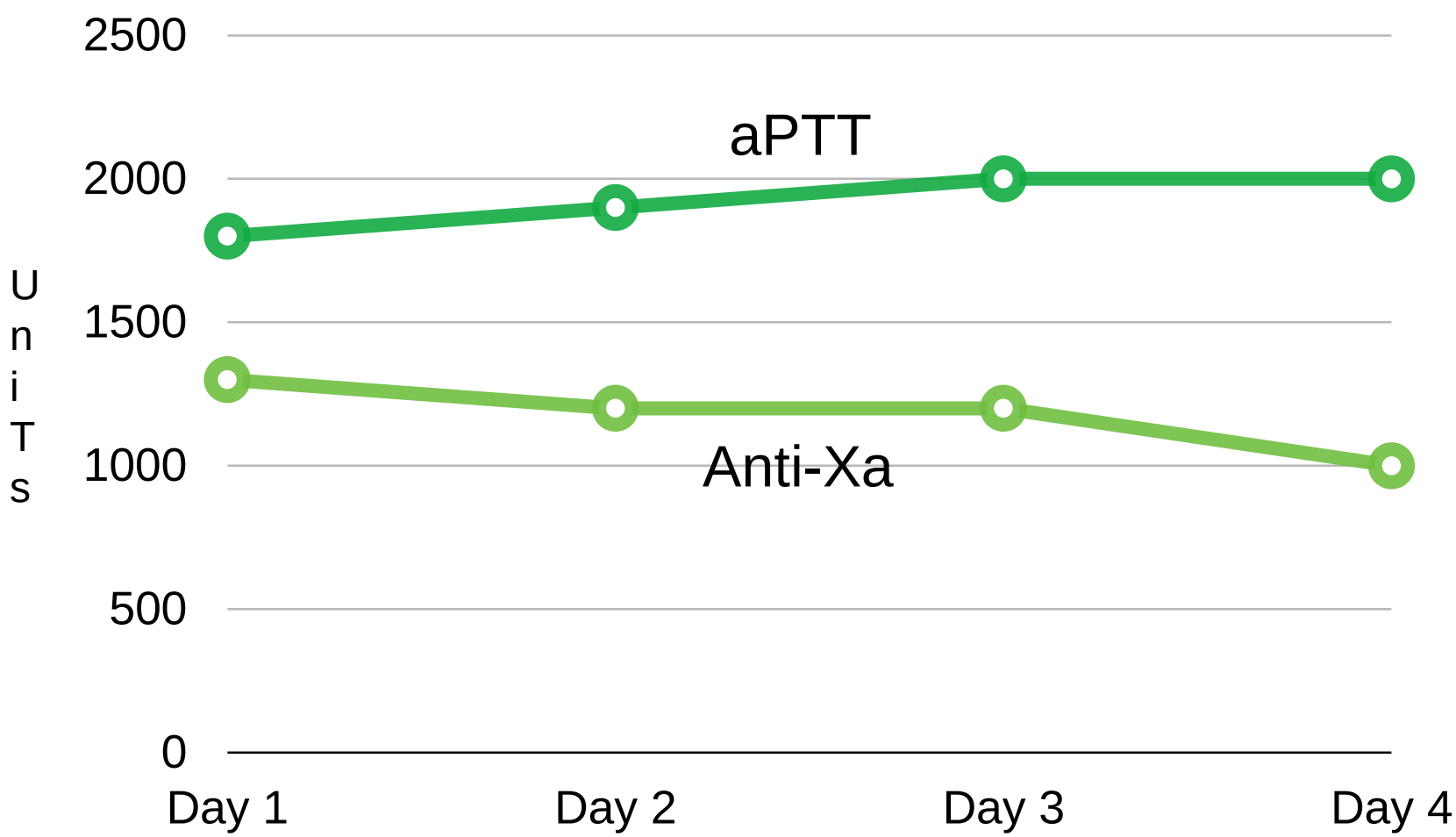
- In her second trimester, recurrent episodes of rapid atrial fibrillation requiring electrical and chemical cardioversion
- Due to her high thromboembolic risk, and anticipating a potentially a long labor in a nulliparous woman, IV UFH was used to bridge before her planned induction of labor.

Paired aPTT and antiXa levels

Day/ Time	aPTT (seconds, therapeutic 75-105)	Anti-Xa level (therapeutic 0.35-0.7)	Rate of heparin infusion (U/h)	Action based on aPTT nomogram	Action based on Anti-Xa nomogram
Day 1 @ 10:30 h	32	0.46	N/A	Bolus 5000 units, then start infusion rate at 1300 U/h	Start IV UFH infusion at 1300 U/h
Day 1 @ 1810h	65	0.74	1300	Infusion rate increased by 100 U/h, aPTT level repeated in 6h	Infusion held for 60 min, then infusion rate decreased by 100 U/h, anti-Xa level repeated in 6h
Day 2 @ 0235 h	67	0.63	1200	Infusion rate increased by 100 U/h, aPTT repeated in 6h	No change
Day 2 @ 0750h	78	0.76	1200	No change, aPTT repeated next morning	Infusion held for 60 min, then infusion rate decreased by 100 U/h, anti-Xa level repeated in 6h

*Last dose of the enoxaparin was at 2000 h the day prior to induction

Heparin Dose required to maintain therapeutic level



Case….delivery

- Patient went into active labor, hence heparin infusion was stopped.
- aPTT was obtained 4 hours after and was at 36 and anti-Xa level 0.27. Epidural was given for normal aPTT,
- Patient delivered vaginally
- No postpartum hemorrhage

Case…..postpartum

- Postpartum, she was given LMWH prophylaxis about 12 hours postpartum, then increased to therapeutic LMWH 12 hours after
- Usually we bridge to warfarin about 1 week postpartum (or 2 weeks post c-section)

Conclusion

- Use of anti-Xa level to guide UFH infusion in pregnancy to be feasible and reliable
- While similar nomograms have been published in the non-pregnant literature, none are currently available in pregnancy
- Due to the pitfalls of using aPTT in pregnancy, anti-Xa levels should be considered to be used to guide UFH dosing in pregnancy

Maternal Heart Health Clinic

Edmonton, Alberta, Canada

Obstetric Medicine

- Rshmi Khurana, *Obstetric Internist, University of Alberta*
- Winnie Sia, *Obstetric Internist, University of Alberta*
- Erin Toor, *Obstetric Internist, University of Alberta*
- Debbie Germaine, *Nurse Practitioner*
- Jodi Wilkie, *Pharmacist*
- Anelia Enstrom, *Dietitian*

Cardiology

- Nazneem Wahab, *Cardiologist, CK Hui Heart Institute*
- Jonathan Windram, *Adult Congenital Cardiologist, Mazankowski Heart Institute*

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