

Management of Thromboembolic Disease in Pregnancy

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TED in Pregnancy Cause for Concern

- Incidence of thromboembolic disease (TED) is approx 4-6-fold higher in pregnant women compared to age-matched non-pregnant women
- TED is the leading cause of maternal mortality in developed countries
 - Approx 11% of maternal deaths in the U.S.
- Women with thrombophilias also at risk for placental complications such as pregnancy loss, preeclampsia, placental abruption, and intrauterine growth restriction

Thrombophilias and Risk

Thrombophilia	Odds Ratio
FVL, heterozygous	8.3
FVL, homozygous	34
Prothrombin gene mutation, heterozygous	6.8
Prothrombin gene mutation, homozygous	26
Antithrombin deficiency	4.7
Protein C deficiency	4.8
Protein S deficiency	3.2

Gris J, et al. *Curr Opin Hematol.* 2006; 13:376-381

Talking Points

- Using 2008 guidelines, describe criteria for recommending venous thromboembolism (VTE) prophylaxis for pregnant patients
- Design a monitoring plan for pregnant patients on antithrombotic treatment
- Develop an antithrombotic regimen for the transition from antepartum to postpartum period

Prophylaxis

- CH is a 33 yo female with PMH significant for Left DVT (involving iliac v., CFV, SFV, & popl v.) in Aug 2003. Risk factors in 2003 = s/p Lt leg cellulitis and hx of Mircette® use. Treatment included Enoxaparin followed by Warfarin
- Jan 2008 – positive pregnancy test & placed on UFH 5000 units SQ q12h during 1st trimester, increased to 7500 units SQ q12h at the beginning of 2nd trimester
- May 20, 2008 – c/o Lt calf pain – venous doppler revealed no evidence of DVT

Prophylaxis Were the Guidelines Followed?

2004
 “3.1.1. In patients w/ a single episode of VTE associated w/ a transient RF that is no longer present, we recommend clinical surveillance & postpartum anticoagulants. (Grade 1C). If the previous event is pregnancy- or estrogen-related or there are additional RF, we suggest antenatal anticoagulant prophylaxis (Grade 2C)”

2008
 “7.2.1. For pregnant women w/ a single episode of VTE associated w/ a transient RF that is no longer present & no thrombophilia, we recommend clinical surveillance antepartum & anticoagulant prophylaxis postpartum (Grade 1C)
 7.2.2 If the transient RF associated w/ a previous VTE event is pregnancy or estrogen related, we suggest antepartum surveillance or prophylaxis (prophylactic or intermediate-dose LMWH/UFH) plus postpartum prophylaxis, rather than routine care (Grade 2C)”

Bates SM et al *Chest* Sept 2004; 126(3): 627S-644S. Bates SM et al *Chest.* June 2008; 133(6): 844S-886S.

Definitions: 2008 ACCP Guidelines

	PROPHYLACTIC	INTERMEDIATE	ADJUSTED DOSE
UFH	5,000 units SQ q12h	SQ q12h adj to target an antiXa level of 0.1 - 0.3 U/mL	SQ q12h adj. to target a mid-interval aPTT into therapeutic range
LMWH	Dalteparin 5,000 units SQ q24h OR Tinzaparin 4,500 units SQ q24h OR Enoxaparin 40 mg SQ q24h (although at extremes of body weight modification of dose may be required)	Dalteparin 5000 units SQ q12h OR Enoxaparin 40 mg SQ q12h	Dalteparin 200 U/kg SQ q24h or 100 U/kg q12h OR Tinzaparin 175 U/kg q24h OR Enoxaparin 1 mg/kg q12h
SURVEILLANCE - Refers to clinical vigilance and appropriate objective investigation of women with symptoms suspicious of DVT or PE.			

Troubleshooting

- 26 yo female with hx of recurrent pregnancy loss, now at 15 wk gestation and on UFH 10,000 units SQ q12h and ASA 81mg qd
- c/o severe cutaneous reactions
- MFM asks for suggestions to ameliorate SXS

Troubleshooting

- Conservative measures for mild reactions
 - Site rotation
 - Avoid massaging injection site
 - Warm compresses
 - Topical remedies
- ? alternative UFH
- ? LMWH
- ? fondaparinux
- ? warfarin

Treatment

- CH is a 33 yo female with PMH significant for Left DVT in Aug 2003. RF in 2003 = s/p Lt leg cellulitis and hx of Mircette® use. Enox/warf
 - Jan 2008 – positive pregnancy test & placed on UFH 5000 units SQ q12h during 1st trimester, increased to 7500 units SQ q12h at the beginning of 2nd trimester
 - May 20, 2008 – c/o Lt calf pain – venous doppler revealed no evidence of DVT
- June 4, 2008 – at 26 wk gestation, venous doppler: + DVT involving popl. v, GSV, SFV, & common iliac v.
- What treatment is recommended?

Treatment

What do the Guidelines offer?

2004

"2.1 In women w/ acute VTE, we recommend either adjusted-dose LMWH throughout pregnancy or IV UFH (bolus followed by infusion to maintain the aPTT in the therapeutic range) for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy. Anticoagulants should be administered for at least 6 weeks postpartum (Grade 1C+)"

"2.2 In women receiving adjusted-dose LMWH or UFH therapy, we recommend discontinuing the heparin 24 hrs prior to elective induction of labor (Grade 1C)"

2008

"6.1.1 For pregnant women with acute VTE, we recommend initial therapy with either adjusted-dose SQ LMWH or adjusted-dose UFH (IV bolus followed by a continuous infusion to maintain the aPTT within the therapeutic range or SQ therapy adjusted to maintain the aPTT 6 hr after injection into the therapeutic range) for at least 5 days. (Grade 1A)"

"6.1.2 For pregnant women with acute VTE, after initial therapy, we recommend that SQ LMWH or UFH should be continued throughout pregnancy (Grade 1B)"

Bates SM et al Chest Sept 2004; 126(3): 627S-644S. Bates SM et al Chest. June 2008; 133(6): 844S-886S.

Treatment

What do the Guidelines offer?

2004

"2.1 In women w/ acute VTE, we recommend either adjusted-dose LMWH throughout pregnancy or IV UFH (bolus followed by infusion to maintain the aPTT in the therapeutic range) for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy. Anticoagulants should be administered for at least 6 weeks postpartum (Grade 1C+)"

"2.2 In women receiving adjusted-dose LMWH or UFH therapy, we recommend discontinuing the heparin 24 hrs prior to elective induction of labor (Grade 1C)"

2008

"6.1.3 For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 6 months. (Grade 2C)"

"6.1.4 For pregnant women receiving adjusted-dose LMWH or UFH therapy, we recommend discontinuation of the heparin at least 24 hr prior to elective induction of labor (Grade 1C)"

Bates SM et al Chest Sept 2004; 126(3): 627S-644S. Bates SM et al Chest. June 2008; 133(6): 844S-886S.

Not your typical patient..

- 17yo W♀ @ 36 wks gestation dx'd with Lt DVT
 - Involving CFV, SFV, popl. v. and PTV
- LMWH or IV UFH or SC UFH?

ACCP: "Women with a very high risk for recurrent VTE (e.g. proximal DVT or PE within 4 weeks of delivery can be switched to therapeutic IV UFH, which is discontinued 4-6 hours prior to the expected time of delivery... Alternatively a temporary IVCF can be inserted and removed postpartum."

- started on IV UFH per VTE protocol
- Current UFH rate = 16ml/hr or 1600 units/hr
- Current PTT = 62.7 sec (txic PTT range = 51-80 sec)
- plans for d/c home...

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Subcutaneous UFH Therapy

- used clinically in pregnancy
- Dosed q 12 - 8 hrs
 - decrease interval if dose >10,000 units (1cc)
- Dose must account for SC bioavailability
 - 24 hr IV dose + 10-30%
- aPTT drawn MID-INTERVAL

- Continuous infusion pump

Therapeutic Subcutaneous UFH

Subcutaneous Heparin Compared with Continuous Intravenous Heparin Administration in the Initial Treatment of Deep Vein Thrombosis: A Meta-analysis. *Annals of Internal Medicine*. 1992;116:279-284

Comparison of Fixed-Dose Weight-Adjusted Unfractionated Heparin and Low-Molecular-Weight Heparin for Acute Treatment of Venous Thromboembolism (FIDO) *JAMA*. 2006;296:935-942.

IV to SC conversion of UFH

- UFH IV 1600 units/hr
- Approximately 38,000 – 39,000 units/24hr
 - Account for change in F
- Q8hr dosing regimen needed
 - Pt preference determined (7a,3p,11p)
- UFH 15,000 units SQ q8hr
 - First dose given 1 hr before d/c IV infusion of UFH (1600)
 - 20,000 unit/cc vials secured w/ local pharmacy
- PTT ordered @ 1100 STAT

D/C Home Planning

- PTT = 58.9 sec (11/18/08)
- Cont UFH 15,000 units SQ @ 7a,3p,11p
- Calcium carb 500mg po qd & titrate to TID w/ meals
- PTT STAT on 11/20/08 & prn

- 11/20 PTT = 90 sec (@ 1030)
 - Slightly supratherapeutic – no change yet
- 11/24 PTT = 91 sec
 - Slightly supratherapeutic – decr 14,000 units q8hr
- 12/1 PTT = 100 sec
 - Supratherapeutic – decr 13,000 units q8hr & cont until notified by OB for possible induction
- 12/7 – pt admitted
 - Delivered healthy baby boy, no complications
 - Postpartum: UFH 10,000 units q8hr & warfarin was begun

Troubleshooting

An ob-gyn resident calls with the following:

In clinic, a pregnant woman, wt = 206#, with a history of left arm DVT 2 months earlier and placed on enoxaparin 100mg SQ q12h. An antiXa level was drawn and reported as 0.37 units/ml. What should the resident do for this patient?

Therapeutic range = 0.6 – 1.0 units/ml (ACCP)

Draw 4 hr s/p q12h dose, 6 hr s/p q24h dose

Postpartum Anticoagulation

KS, 27yo in 2006, hx of PE, 1st pregnancy
UFH antepartum

How is anticoagulation resumed in the postpartum period?

For lactating women:

UFH, LMWH, warfarin, danaparoid, lepirudin
are recommended options

Pentasaccharides (fondaparinux) are not

Postpartum Anticoagulation

VISIT DATE	INR GOAL	INR	TOTAL WEEKLY DOSE (MG)
01/15/2006	2.5	2	42.5 (5mg qd except 7.5mg q MWF)
01/18/2006	2.5	1.9	42.5
01/24/2006	2.5	1.5	50 (10mg x 1, incr 7.5mg x 5d/wk, 5mg q MF)
01/31/2006	2.5	1.7	55 (10mg x 1, incr 7.5mg qd)
02/07/2006	2.5	1.4	60 (10mg x 1, incr 7.5mg x 5d/wk, 10mg q MF)
02/21/2006	2.5	1.5	65 (incr 10mg x 5d/wk, 7.5mg q MF)
03/07/2006	2.5	1.5	75 (incr 10mg x 5d/wk, 12.5mg q MF)
03/21/2006	2.5	1.5	77.5 (incr 10mg x 4d/wk, 12.5mg q MWF)
04/04/2006	2.5	2.24	77.5 (d/c 4/11/06)
06/19/2008	2.5	1.62	77.5 (on 10mg qd ppt; resume 10mg x 4d/wk, 12.5mg qMWF)
06/24/2008	2.5	2.15	77.5
07/08/2008	2.5	2.51	77.5
08/04/2008	2.5	1.56	82.5 (15mg x 1, 10mg x 4d/wk, 12.5mg qMWF)
08/14/2008	2.5	1.56	85 (incr 10mg x 4d/wk, 15mg q MWF til d/c)

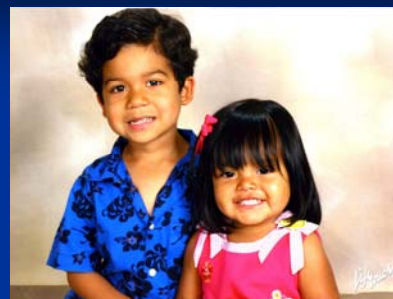
Special Considerations

- Treatment decisions impact the health of the baby in addition to that of the mother
- Many women prefer to view their pregnancy as 'normal' & a healthy part of the life cycle, not as a medical condition
- Education can help women find the balance between avoiding 'medicalizing' their pregnancy and avoiding risk to the fetus.
- Most women place a high value on avoiding risk to the fetus and a low value on avoiding the cost and inconvenience of antithrombotic therapy

Bates SM et al Chest. June 2008; 133(6): 844S-886S.

Conclusions & Practical Points

- Most recent guidelines provide greater specification of assessing the VTE risk of pregnant patients as well as the options for prophylaxis and treatment
 - Therapeutic choices for gestation week 36 and beyond remain challenging
- LMWH have become favored over UFH for prophylaxis and treatment of VTE
 - antiXa levels must be timed appropriately



? QUESTIONS ?

