CLOTS AND ANTICOAGULATION IN PREGNANCY: WHAT THE INTERNIST NEEDS TO KNOW

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OBSTETRICAL INTERNAL MEDICINE

ASSOCIATE CLINICAL PROFESSOR, UNIVERSITY OF ALBERTA
OBJECTIVES

• Develop an approach to diagnosis and initial management of VTE in pregnancy

• Decrease anxiety and palpitations when called for peripartum anticoagulation management

• Develop an awareness of patients requiring antepartum VTE prophylaxis
DISCLOSURES

• I have no conflicts to declare

• All low molecular weight heparin use in pregnancy is technically “off label”
PARTICIPATION

• Text GILLIANRAMSA622 TO 37607
• OR
• RESPOND VIA THE WEBSITE:
  • PollEv.com/gillianramsa622
<table>
<thead>
<tr>
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<th>What is your clinical background?</th>
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<tr>
<td>A</td>
<td>General internist</td>
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<td>B</td>
<td>Internal medicine resident</td>
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<tr>
<td>C</td>
<td>Obstetric internist</td>
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<td>D</td>
<td>Allied Health professional</td>
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<td>E</td>
<td>Other</td>
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WHY SHOULD I CARE?

• Absolute incidence 1-2/1000 pregnancies
WHY SHOULD I CARE?

• Although low absolute incidence (1-2/1000 pregnancies), it is 5 x higher than age-matched women who are not pregnant

• VTE is a leading cause of maternal mortality in Canada

• Risk begins in first trimester and gradually increases into the third trimester (~50% of antenatal VTE)

• The first 2 weeks postpartum is associated with the highest risk and then slowly declines

WHY SHOULD I CARE?

• Up to 42% have post-thrombotic syndrome

• 16-35% have deep vein insufficiency years after the event

DIFFICULTIES IN DIAGNOSING VTE IN PREGNANCY

- Symptoms of DVT/PE
  - Lower extremity swelling
  - Pelvic/lower abdominal pain
  - Dyspnea
  - Tachycardia

- Common symptoms of pregnancy
  - Lower extremity swelling
  - Pelvic/lower abdominal pain
  - Dyspnea
  - Tachycardia/palpitations
CLINICAL PREDICTION

• Wells, modified Wells rule and revised Geneva score have not been validated in pregnancy

• LEFt clinical prediction tool is only pregnancy-specific validated prediction tool
  • Symptoms in left leg
  • Calf circumference difference >2 cm
  • First trimester presentation
  • **But** it only helps in the first trimester and has not been applied prospectively in clinical trials

CASE 1

• 28yo G1P0 presenting at 25 weeks gestation with severe left inguinal pain and swelling
• Describes left lower back/hip pain and an inability to get comfortable
• Mild swelling noted to her left leg compared to the right
• No travel history, no family history VTE, no OCP use in past, no surgeries, no smoke, normal BMI
CLINICAL PRESENTATION

• DVT more common in the left leg (85%) than the right during pregnancy
• More commonly proximal - 72% in iliofemoral veins vs 9% in non-pregnant patient
  • Gravid uterus compresses right iliac artery against left iliac vein causing decreased venous return or “May-Thurner syndrome”

FIGURE 1. VIRCHOW’S TRIAD IN PREGNANCY. (FROM BOURJEILY G, PAIDAS M, KHALIL H, ROSENE-MONTELLA K, RODGER M. PULMONARY EMBOLISM IN PREGNANCY. LANCET. 2010;375(9713):500–512.)
CLINICAL PRESENTATION

• Discomfort (80-95%)

• Edema in the lower extremity

• Isolated lower abdominal/pelvic pain (if isolated iliac vein thrombosis)

• Pulmonary embolism in pregnancy –many symptoms common to pregnancy →
  Dyspnea, tachycardia, leg edema
  • Accounts for only 20-30% of pregnancy associated VTE but has case fatality rate of 2.4%

DIAGNOSIS OF DVT IN PREGNANCY

• Doppler ultrasound
  • repeat within 7 days if first one negative

• If high clinical suspicion of iliac thrombosis or doppler ultrasound unable to visualize iliac veins consider MRI

CASE 1

- Doppler ultrasound: L iliofemoral DVT
WHAT WOULD YOUR INITIAL MANAGEMENT BE FOR THIS PATIENT

- A) Enoxaparin 1mg/kg sc bid
- B) Enoxaparin 1.5mg/kg sc once daily
- C) LMWH bridging to warfarin
- D) Direct oral anticoagulant

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<table>
<thead>
<tr>
<th>Option</th>
<th>Dose</th>
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<tbody>
<tr>
<td>A)</td>
<td>Enoxaparin 1mg/kg sc bid</td>
</tr>
<tr>
<td>B)</td>
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CASE 1

• LMWH once daily or twice daily depending on the agent chosen
  • For Enoxaparin many will start with bid for the first month at least

• Vitamin K antagonists, oral Xa inhibitors, and oral direct thrombin inhibitors are not recommended
IS TWICE DAILY DOSING BETTER THAN ONCE DAILY DOSING?

• A) Yes

• B) No

• C) I wish I knew

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Is twice daily dosing better than once daily dosing?

A) Yes

B) No

C) I wish we knew
DOSING FREQUENCY

• Once daily and twice daily dosing appear to have similar efficacy and safety
• But
• We have more clinical experience with bid dosing for initial management and then stepping down to once daily dosing
  • Increased GFR in pregnancy means increased clearance of LMWH
• We know target anti-Xa level with BID dosing should be 0.6-1 U/mL
CASE 2

• 27 year old G3P2 presenting at 7 weeks gestation with gradually increasing dyspnea occurring both at rest and on exertion

• No leg swelling/erythema/pain

• No cough, infectious symptoms, orthopnea or PND

• Mild back pain

• PMHx: DVT at 30 weeks in G1 and at 32 weeks gestation in her second pregnancy (different country), Asthma

• Meds: prenatal vitamin, Ventolin prn
CASE 2

• Tried Ventolin with no improvement in symptoms

• On examination:
  • HR 112, BP 106/64, RR 24, SpO2 98% RA
  • Chest clear, no wheeze
  • CVS normal
  • Abdo unremarkable
  • Legs: equal symmetry, no erythema/edema

• CXR is normal
CASE 2

• Given her presentation and past history you would like to rule out a pulmonary embolism

• But you worry about radiation to the fetus

• What test would you order?
FIRST LINE INVESTIGATION FOR PULMONARY EMBOLISM IN PREGNANCY

• A) CT pulmonary angiogram
• B) v/q scan (or perfusion scan alone)
• C) no test is safe in pregnancy
• D) Bilateral doppler ultrasound

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## Radiation to Fetus

<table>
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<tr>
<th>Investigation</th>
<th>Radiation to fetus (mGy)</th>
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<tr>
<td>CXR (with abdominal shield)</td>
<td>&lt;0.1</td>
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<td>VQ scan</td>
<td>0.1-0.3</td>
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<tr>
<td>Perfusion scan</td>
<td>0.1-0.25 (depending on gestational age)</td>
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<tr>
<td>CTPE</td>
<td>0.1</td>
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<tr>
<td>10 hour flight</td>
<td>0.05</td>
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<tr>
<th>Fetal radiation</th>
<th>Increased risk cancer (%) (child, adult)</th>
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<tr>
<td>1mGy</td>
<td>0.002, 0.006</td>
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<tr>
<td>10</td>
<td>0.02, 0.06</td>
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<tr>
<td>50</td>
<td>0.1, 0.3</td>
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<td>500</td>
<td>1, 3</td>
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INITIAL INVESTIGATIONS

• If suspect PE and there are symptoms of DVT → US

• If normal CXR → VQ: high negative predictive value
  • Ventilation component often omitted, limiting radiation dose to fetus

• If abnormal CXR or indeterminant VQ → CT PE protocol
  • Similar predictive value and rates of indeterminant study as VQ
  • More often non-diagnostic than in non-pregnant pt
  • CT has 20mGy of radiation to breast tissue (20-100 x more than VQ), use of bismuth breast shields decreases exposure by 40%
CASE 2

• Her Perfusion scan is positive for bilateral segmental pulmonary emboli

• She is started on Enoxaparin 1mg/kg sc bid

• Does she have to stay on therapeutic anticoagulation for the whole pregnancy?
WHICH OF THE FOLLOWING IS NOT AN IDEAL OPTION FOR MANAGEMENT?

• A) Continue bid therapeutic LMWH until delivery
• B) Switch to once daily therapeutic LMWH after 1 month and continue until delivery
• C) step down to 75% LMWH at 3 months and then continue until delivery
• D) switch to warfarin until 36 weeks gestation

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Which of the following is not an ideal option for management?

A) Continue bid therapeutic LMWH until delivery

B) Switch to once daily therapeutic LMWH after 1 month and continue until delivery

C) Step down to 75% LMWH at 3 months and then continue until delivery

D) switch to Warfarin until 36 weeks gestation
DURATION OF ANTICOAGULATION

• Continue therapeutic anticoagulation for a minimum of 3 months

• May then consider stepping down to intermediate dose (75% therapeutic) for the duration of pregnancy

• Continue anticoagulation (prophylactic or intermediate dose) for 6 weeks post partum
CASE 2

• Given that her clot was very early in pregnancy and she had concerns about peripartum hemorrhage, we opted to step down to high proph dose (75% of therapeutic) at 31 weeks (after 3 month of therapeutic anticoagulation)

• Post partum she went onto prophylactic dose for 6 weeks

• She did well with no further events
COMMONLY ASKED QUESTIONS
DO YOU NEED TO MONITOR ANTI-XA LEVELS?

• A) Yes, should monitor in all patients
• B) no it is not necessary
• C) It depends

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Do you need to monitor anti-Xa levels?

1) Yes, should monitor in all patients
2) No it is not necessary
3) It depends

When poll is active, respond at PollEv.com/gillianramsa622  📲 Text GILLIANRAMSA622 to 37607 once to join.
ANTI-XA LEVELS

• Monitoring not routinely recommended

• Useful if weight uncertain (pre-pregnancy weight not known or current weight felt to be increased due to water retention)

• Useful at extremes of weight (<50kg or >90kg)

WHAT ABOUT TPA?
REGARDING THE USE OF TPA IN PREGNANCY...

• A) It can be used as it would outside of pregnancy
• B) It crosses the placenta and causes fetal hemorrhage
• C) It can be used in life-threatening PE or limb-threatening DVT
• D) There is not enough data to define safety in pregnancy

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Regarding the use of TPA in pregnancy

A) It can be used as it would outside of pregnancy

B) It crosses the placenta and causes fetal hemorrhage

C) It can be used in life-threatening PE or limb-threatening DVT

D) There is not enough data to define safety in pregnancy
TPA IN PREGNANCY

• Recombinant tPA does not cross the placenta, minimal transplacental transfer of streptokinase

• Guidelines: limit use of thrombolysis to massive life-threatening PE or limb-threatening DVT
THROMBOLYSIS

• Thrombus removal (surgical or pharmaceutical catheter directed) is being studied for iliofemoral DVT
  • Decreased incidence of post-thrombotic syndrome
  • Fetal radiation in First trimester is 175-245 → associated with childhood cancer risk 1.3-2%
  • Second and third trimester can be managed with shielding

• Bottom line: not enough safety data, very much dependent on clinical expertise

CASE 3

• 34 year old G1 currently 34 weeks gestation presenting with tachycardia, palpitations and increased dyspnea

• Diagnosed with right sided pulmonary embolus

• Monitored as inpatient for 24 hours and discharged home on bid LMWH

• What are your recommendations for labour and delivery?
WHAT WOULD YOU RECOMMEND FOR PERIPARTUM ANTICOAGULATION?

• A) Discontinue LMWH 24 hours prior to scheduled delivery
• B) Switch from LMWH to iv UFH on day prior to induction, then hold UFH 6 hours prior to anticipated delivery
• C) Place IVC filter on day prior to induction
• D) It depends on if she is likely to delivery before or after 38 weeks

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What would you recommend for peripartum anticoagulation?

- Discontinue LMWH 24 hours prior to scheduled delivery
- Switch from LWMH to iv UFH on day prior to induction, then hold UFH 6 hours prior to anticipated delivery
- Place IVC filter on day prior to induction
- It depends on if she is likely to deliver before or after 38 weeks
PERIPARTUM MANAGEMENT OF THERAPEUTIC ANTICOAGULATION

• If VTE > 4 weeks prior to delivery:
  • Last dose of LMWH day prior to induction

• If VTE < 4 but >2 weeks prior to delivery
  • Switch from LMWH to iv UFH on day prior to induction (or around 38 weeks and monitor as an inpatient if no induction planned), hold UFH 6 hours prior to anticipated delivery

• If VTE < 2 weeks prior to delivery or high risk clot:
  • Iv UFH or place IVC (if evidence of residual clot on doppler ultrasound)

AFTER DELIVERY

• VTE ≥ 1 month prior to delivery: restart LMWH 4 hours after epidural catheter removed (do not remove epidural catheter until 12 hours after most recent injection of LMWH) at prophylactic dose
  • Therapeutic dose restarted 24 hours after neuraxial anesthesia/delivery

• VTE <1 month prior to delivery: start iv UFH for 24 hours (no bolus) then transition to LMWH
HIGH RISK PATIENT (VTE WITHIN 4 WEEKS OF DELIVERY, HIGH RISK THROMBOPHILIA)

- **4 hours after epidural removal**: Start iv UFH at 500 units/hour
- **24 hours post partum**: LMWH at 75% therapeutic dose sc bid
- **48 hours post partum**: Therapeutic LMWH
LOW RISK VTE: >4 WEEKS PRIOR TO DELIVERY

- 4 hours after epidural removal
  - Prophylactic LMWH

- 24 hours post-partum
  - 75% therapeutic LMWH

- 48 hours post-partum
  - Therapeutic LMWH
CASE 3

• No indication of preterm delivery

• Had last dose of bid LMWH on AM prior to induction and prophylactic dose UFH on evening prior to induction

• On AM of induction had unfavourable cervix with > 12 hours anticipated prior to active labour therefore given UFH 5000 units sc
CASE 3

• Postpartum:
  • 4 hours after epidural removal received Enoxaparin 40mg sc
  • At 28 hours post partum (8 AM) received Enoxaparin 0.75mg/kg sc bid (0800 and 2000)
  • At 52 hours post partum (0800) started Enoxaparin 1.5mg/kg sc once daily
SHE WANTS TO BREAST FEED...
SHE WANTS TO BREAST FEED, WHAT ARE THE SAFE OPTIONS?

• A) LMWH
• B) Coumadin
• C) Direct oral anticoagulant
• D) None are compatible with breastfeeding
• E) Both A and B
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OPTIONS FOR BREAST FEEDING

• Compatible with breast feeding:
  • LMWH
  • UFH
  • Warfarin

• Not compatible with breast feeding:
  • Direct oral anticoagulants
WHAT ABOUT VTE PROPHYLAXIS IN PREGNANCY?
CASE 4

• 38yo G1P1, c-section for failure to progress.
• Started OCP 6 weeks post partum
• 9 weeks post partum presented with 2 week history of Rt calf/thigh pain and swelling
• Doppler showed extensive occlusive DVT extending from Rt common femoral vein to ankle
• RFC: treatment of DVT and counselling for future pregnancy (not breastfeeding)
• PMHX: Obesity (BMI 40)
CASE 4

• She was bridged to warfarin x 3 months
• OCP discontinued
• She has questions about future pregnancies
WHAT IS THE MOST APPROPRIATE MANAGEMENT IN A FUTURE PREGNANCY?

• A) Antepartum clinical surveillance, post partum prophylaxis
• B) Antepartum and post partum prophylaxis
• C) Advise against future pregnancy
• D) Therapeutic anticoagulation throughout pregnancy and for 6 weeks post partum
What is the most appropriate management in a future pregnancy?

A) Antepartum clinical surveillance, post partum prophylaxis

B) Antepartum and post partum prophylaxis

C) Advise against future pregnancy

D) Therapeutic anticoagulation throughout pregnancy and for 6 weeks post partum
CASE 4

• Her risk factors for VTE were: OCP, Obesity, recent pregnancy

• I recommended VTE prophylaxis (with weight based dosing) throughout pregnancy as well as post partum
CASE 5

• 31 yo G3 P2

• History of Left leg DVT on OCP, treated for 1 year with repeat doppler negative for DVT

• History of Obesity

• G1 in 2010, was treated with weight based prophylactic LMWH antepartum and for 6 weeks post partum with no events
CASE 5

• G2 in 2011:
  • Irregular menses and was unaware of pregnancy
  • Presented with acute L calf pain
  • Doppler u/s showed subacute DVT, pregnancy testing discovered ~7 week GA pregnancy
  • Treated with therapeutic anticoagulation antepartum and post partum prophylaxis

• Post partum doppler u/s negative, d-dimer normal, FVIII level normal, therefore anticoagulation discontinued (given provoked event)
CASE 5

• In 2012 presented with an idiopathic L leg DVT and was placed on rivaraban
• She is now pregnant, ~5 weeks GA
CASE OF 5

- Her risk factors for VTE in pregnancy:
  - Prior hormone related events x 2
  - Idiopathic event
  - Obesity
WHAT IS THE MOST APPROPRIATE MANAGEMENT

• A) Change to prophylactic weight based LMWH
• B) Change to therapeutic LMWH
• C) Change to warfarin
• D) Continue Rivaroxaban
What is the most appropriate management?

A) Change to prophylactic weight based LMWH

B) Change to therapeutic LMWH

C) Change to warfarin

D) continue Rivaroxaban
CASE 5

• She was immediately switched to therapeutic LMWH and kept on therapeutic dosing throughout the pregnancy and transitioned to warfarin post partum until breastfeeding was complete

• Currently she is on rivaroxaban and has menorrhagia

• NB: EINSTEIN DVT and PE trials (Martinelli I et al. Blood 2016; 127(11): 1417-1425) found no increased risk of VTE with OCP as long as patient on anticoagulation (warfarin or rivaroxaban)
WHO SHOULD RECEIVE VTE PROPHYLAXIS?

- Cochrane review of 16 RCTs, 2592 women: insufficient data to make a firm recommendation
- If prior VTE was associated with a transient risk factor not related to pregnancy or estrogen then risk of recurrence is ~2%
- If prior VTE was unprovoked, pregnancy or estrogen – related the risk increases to ~8%

WHO SHOULD RECEIVE THROMBOPROPHYLAXIS?

• Single VTE, transient non-estrogen related risk factor (no thrombophilia): antepartum clinical surveillance
• All other VTE: antepartum prophylaxis
• All VTE: postpartum prophylaxis x 6 weeks

SOGC GUIDELINES 2014
SUGGESTED RESOURCES:

