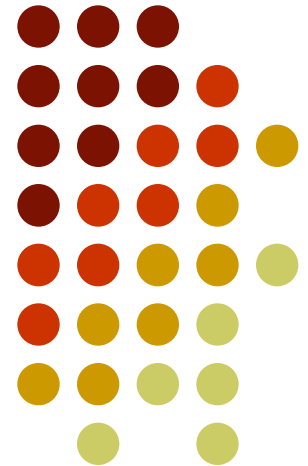


# Thrombophilias in Pregnancy

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September 19, 2009



# Why Thrombophilias?



- Our patient population
- Pregnancy Complications
- Evolving area
- Controversy/confusion regarding management

# 'Kathy'



- 32 yo G1 P0 woman at 9 weeks known to be heterozygous for FVL
- Family doctor wants advice re:
  - Risks
  - Management in pregnancy/PP

# 'Jill'



- 36 yo G1P1 woman with an IUFD at term
  - Preconceptual counseling
  - Any further testing
  - Management in future pregnancy

# 'Kelly'



- 29 yo G2P1 woman at 6 weeks
- PObHx of severe preeclampsia->delivery at 22 weeks
  - She had “?some blood tests done” which were abN after her last pregnancy
  - By the way she had a DVT 4 weeks PP
  - Family doctor needs help!

# Objectives



- Overview of inherited and acquired thrombophilias
- Maternal/fetal complications
- Indications for testing – who, when
- Management in pregnancy



# Thrombophilias

- Inherited or acquired conditions which increase risk of thromboembolic disease
- Evolving field: new thrombophilias being discovered
- More commonly identified in pregnancy
- Associated with VTE and adverse pregnancy outcomes
- Questions arise re: screening/management

# Thrombophilias



- Inherited thrombophilias present in 8-15% Caucasian populations
- Underlie 50% of episodes of VTE in pregnancy

# Thrombophilias



- Genetic (inherited)
  - abnormalities of procoagulant factors
  - deficiencies of natural anticoagulants
- Acquired

# Inherited Thrombophilias



- Factor V Leiden Mutation (AD)
- Prothrombin gene (G20210A) mutation (AD)
- Antithrombin III deficiency (AD)
- Protein C deficiency (AD)
- Protein S deficiency (AD)
- Plasminogen activator inhibitor deficiency (AR)
- MTHFR C677T Mutation (AR)

# Acquired Thrombophilias



- Antiphospholipid Antibody Syndrome
  - Lupus anticoagulant
  - Anticardiolipin antibody
  
- Nephrotic Syndrome
  - ↓ antithrombin levels

# Hemostasis in Normal Pregnancy



- Net effect of pregnancy changes in hemostasis
  - Hypercoagulable state
- Complex physiologic adaptation
  - expansion maternal/fetal circulations at utero-placental interface
  - control bleeding from placental site at time of separation

# Virchow's Triad



# Virchow's Triad

- **Hypercoagulability**
  - ↑ clotting factors
  - ↓ natural anticoagulants
  - ↑ platelet aggregation





# Virchow's Triad

- **Stasis**
  - ↑ venous distension, ↓ venous tone
  - Compression of IVC from uterus
  - ↓ venous flow in lower extremities



# Virchow's Triad

- **Endothelial damage**
  - Vascular damage at delivery





# Venous Thromboembolism in Pregnancy

- Pregnancy predisposes to VTE in addition to other factors
- Leading cause of maternal morbidity and mortality
- 0.5-3/1000 births
  - All trimesters and PP
- 50% DVT; 50% PE



# Risk Factors for VTE

- Previous VTE
- Age > 35
- Obesity
- Family history
- Prolonged bedrest/immobility
- Caesarean section
- Operative vaginal delivery
- Uterine instrumentation
- Other pelvic surgery
- Malignancy
- **Thrombophilias**





# Factor V Leiden Mutation

- Impairs APC & PS complex inactivation of FVa
- Evolutionary survival advantage by decreasing blood loss, PPH
- Most common inherited thrombophilia
  - 5-9% European population
  - Rare in Asian and African populations
- Not uncommon in carriers of other inherited thrombophilias



# Factor V Leiden Mutation

- Heterozygotes : 5x normal risk of VTE
- Homozygotes: 80x normal risk of VTE



# Factor V Leiden Mutation

- Present in ~ 40% pregnant women with VTE
- Actual risk of VTE in pregnancy
  - asymptomatic heterozygous
    - 0.2%
    - RR=7
  - homozygous
    - 1.5% (17% with Hx VTE)
    - RR=25



## Prothrombin Gene (G20210A) Mutation

- Increased risk of thrombosis/pregnancy complications
- Mutation in promotor of the prothrombin gene
- 2-5% Europeans
- Leads to  $\uparrow$  prothrombin  $\rightarrow$   $\uparrow$  risk VTE



## Prothrombin Gene (G20210A) Mutation

- Accounts for 17% VTE in pregnancy
- Actual risk of VTE in pregnancy
  - asymptomatic heterozygous
    - 0.5%
    - RR=9.5
  - homozygous
    - 2.8%



# Protein C Deficiency

- Vitamin K dependent protein
- After activation by thrombin, exerts negative control of clotting cascade (profibrinolytic)
- Deficiency results in disruption of normal clot dissolution



# Protein C Deficiency

- 0.5% of Caucasians
- Present in 10-12% of VTE in pregnancy
- Lifetime risk VTE 50%
- Actual risk of VTE in pregnancy
  - 2%
  - RR=13

# Protein S Deficiency



- Vitamin K dependent protein
- Necessary cofactor for anticoagulant function of APC
- Levels decrease in pregnancy by 40%, thus affecting testing in pregnancy
- There are gestational age ranges of N

# Protein S Deficiency



- .03-1.3% of Caucasians
- Present in 10-13% of VTE in pregnancy
- Actual risk of VTE in pregnancy
  - 7%

# Antithrombin

- Natural anticoagulant
- Most severe of inherited thrombophilias
- 0.02% in Caucasians
- Generally present with recurrent VTE
- 70-90% lifetime risk VTE
- Homozygous state not compatible with life





# Antithrombin Deficiency

- Present in 1-3% of VTE in pregnancy
- Actual risk of VTE in pregnancy
  - asymptomatic heterozygous
    - 8-10%
    - RR=120
- Lifelong anticoagulation if +VTE



## Hyperhomocysteinemia & MTHFR Mutation

- Homocysteine is naturally occurring amino acid
- High levels ? implicated in VTE
- Most common etiology is homozygosity of the MTHFR gene
- Often associated with low serum folate
- 5-15 % of Canadians have 1 mutation



# Hyperhomocysteinemia

- Deficiencies of Vit. B6, B12 & FOLATE can lead to elevated levels
- Supplementation can often reduce levels to N
  - not shown to decrease risk of thrombosis or
  - other complications except NTD
- ? No increased risk in pregnancy for VTE



# Antiphospholipid Antibodies

- Diverse group antibodies –most common
  - Lupus anticoagulant (LAC)
  - Anticardiolipin antibody (ACA)
- LAC is misnomer... it is not specific to SLE
- LAC & ACA have procoagulant activity
- Increased risk of venous and arterial thrombosis
- Risk VTE in pregnancy 15%
- Recurrent thrombosis common ~60%

# Antiphospholipid Syndrome



- Diagnosis requires 2 elements:
  - 1. Correct clinical setting
    - Unexplained thromboembolic event
    - Adverse pregnancy outcome
    - Autoimmune thrombocytopenia
  - 2. At least one confirmatory test
    - LAC +/- ACA



# Estimated Risk of VTE in Pregnancy

●	Disorder	Risk
1.	AT deficiency	8-10%
2.	APLAS	15%
3.	PC deficiency	2%
4.	PS deficiency	7%
5.	FVL	0.2% (ht) 1.5% (hz)
6.	PGM	0.5% (ht) 2.8% (hz)
7.	FVL/PGM	4%
8.	Hyperhomocysteine	no recognized increase



# Thrombophilias and Pregnancy Complications

- Thrombophilias may predispose to adverse pregnancy outcomes
- Mechanism
  - impaired placental development & function due to compromised vascular support system
  - result of prothrombotic state



# Thrombophilias and Pregnancy Complications

- Adverse outcomes
  - Recurrent loss
  - Severe preeclampsia/HELLP
  - Unexplained stillbirth
  - IUGR
  - Placental Abruption



# Thrombophilias and Pregnancy Complications

- Adverse outcomes
- Studies small, controversial, populations heterogeneous
- Influenced by confounders



# Fetal Loss

- Meta-analysis and prospective cohort studies
- Fetal loss higher in women + thrombophilia (30% vs 23%:OR=1.4)
- Recurrent Loss
  - FVL: OR=7.8
  - PGM: OR=2.6
  - 1+ thrombophilias: OR=1.7
- IUFD
  - FVL: OR=3.3
  - PGM: OR=2.3
  - Protein S: OR=7.4
  - AT: OR=5.2
  - 1+ thrombophilias: OR = 14.3

- Kist 2008, Preston 2006, Rogue 2004, Smith 2007



# Preeclampsia

- Increased risk of PE
    - Thrombotic effects on placenta
    - Additional medical disorders in patients
  - Association
    - FVL: OR=2.2
    - Protein S: OR=12.7
    - Protein C: OR=21.5
    - MTHFR: OR=2.6
- Lin 2005, Morrison 2002, Kocher 2007

# IUGR



- Low flow placental circulation + hypercoagulable state -> ideal environment for placental thromboses
- Meta-analysis
  - Small association between thrombophilia and IUGR
    - FVL: OR=1.2
    - PGM: OR=1.1
    - Protein S: OR=10.2
  - Facco 2009, Alfirevic 2005



# Abruption

- Significant dose dependent increase in risk (Rogue 2004)
  - 1 thrombophilia: OR=10.5
  - Multiple thrombophilias: OR=14.9
  - AT: OR=60
- Meta-analysis/cohort studies
  - PGM: OR=29-31
  - MTHFR: OR=2.3-2.6
    - Ray 1999, Alfirevic 2005



# Fetal Thrombophilia

- Genetic risk based upon maternal thrombophilia
- ? Adverse consequences
  - Preterm birth
  - IUGR
  - Perinatal stroke
  - Cerebral palsy
- Gibson 2006, Gibson 2005, Gopel 1999, Schlembach 2003

# Adverse Perinatal Outcomes



- Women with APO more likely to have an abnormal thrombophilia screen
- Dependent upon thrombophilia involved
- Ongoing research,... as is prevention of adverse obstetrical outcomes in women with thrombophilias

# Prevention of Adverse Perinatal Outcomes



- Data derived from observational studies
  - Controversial
- Individualize treatment with multidisciplinary team
- Education re risks
- Increased maternal/fetal surveillance
- ASA 81 mg
- ? Heparin
  - Depends upon thrombophilia and APO



# Screening for Thrombophilias

- Conditions warranting consideration
- Pre-pregnancy
  - Personal history of thrombosis
  - Strong family history
    - VTE in 1<sup>st</sup> degree relative < 50
    - Known thrombophilia
  - Adverse pregnancy outcome
    - fetal loss (recurrent loss/IUFD)
    - severe/recurrent pre-eclampsia
    - IUGR
    - abruption necessitating delivery < 34 wks

Population screening not recommended

# Testing in Pregnancy



- Ideally performed:
  - remote from the thrombotic event
  - while not pregnant, not on hormonal tx
  - not taking anticoagulation
  - if it may modify management
- Molecular screening unaffected by pregnancy
- PS and APC resistance; fall in pregnancy
- Functional tests are modified by pregnancy

# Testing in Pregnancy



Condition	Effect of pregnancy	Test	? Reliable in Pregnancy
Factor VL	↑	Genetic test	yes
PGM	↑	Genetic test	yes
AT-III	↓ / →	s. protein	?
Protein C def	↑ / →	s.protein	?
Protein S def	↓	s.protein	?
MTHFR	↑ / →	Genetic test	yes
LAC	↑	Ab. ELISA	yes
ACA	↑	Ab. ELISA	yes



# Approaches to Management

- **Maternal Risks**

1. VTE
2. Preeclampsia
3. Abruptio

- Pt. advised re:  
sign/ sx. VTE,  
preeclampsia

- **Fetal Risks**

1. Fetal loss
  2. IUGR
  3. Abruptio
- Fetal surveillance
    - NST
    - BPP/Dopplers
    - Growth U/S



# Thromboprophylaxis in Pregnancy

- Who are patients to 'consider' for therapy?
  - Previous VTE
  - Thrombophilia +/- VTE
  - 1+ risk factors for VTE
- If treated, when?
  - Antenatal, Postpartum, Both
- If treated, how?
  - which agent
  - dose
  - monitoring



# Lower Risk Women

- Heterozygous FVL
- Heterozygous PGM
- Protein C or S Deficiency
- Previous VTE outside of pregnancy
- 1+ risk factors, excluding thrombophilia, in addition to pregnancy
  - Obesity, Bedrest, Complex delivery, etc



# Lower Risk Women

- Lacking 'good' evidence (2C)
- General Treatment Guidelines
  - 'Consider' antenatal prophylaxis if ongoing risk/1+risk
    - Personal Hx VTE
  - Postpartum Rx x 6 weeks



# Higher Risk Women

- Acute VTE in current pregnancy/PP
- Long term anticoagulation
- High risk thrombophilia
  - Antiphospholipid Antibody Syndrome
  - Antithrombin Deficiency
  - Homozygotes for FVL mutation
  - Homozygotes for PGM mutation
  - Compound heterozygotes for FVL or PGM
- Thrombophilia + previous VTE/adverse pregnancy outcome
- Multiple risk factors



# Higher Risk Women

- General Treatment Guidelines:
  - Antenatal prophylaxis
    - Higher risk thrombophilia(s)/no previous VTE
  - Antenatal treatment
    - Acute VTE in pregnancy
    - Higher risk thrombophilia + previous VTE/adverse outcome
    - Normally anticoagulated
  - PLUS
  - Postpartum treatment
    - x 6+ weeks
    - 12+ weeks if acute VTE
    - Lifelong if N anticoagulated

# Treatment Options



- Unfractionated heparin
- Low Molecular Weight Heparin





# Warfarin

3 mg  
tablets

28 tablets



# Warfarin



- NOT usually recommended in pregnancy
- Warfarin embryopathy
- High risk period 6-9 weeks GA
- Preconceptional counseling
  - UFH/LMWH with + pregnancy test
  - Heparin pre-pregnancy



# Heparin Therapy - Risks



	UFH	LMWH
Hemorrhage	5%	<1%
Thrombocytopenia	1-3%	<1%
Osteopenia	17%	<1%

# Advantages



## ● Unfractionated

- Long history of use
- Experience
- Does not cross placenta
- Relatively Inexpensive
- Available
- Reversible
- Short half life

## ● LMWH

- Does not cross placenta
- Usually 1x/day
- Weight based dose
- SC injections
- Available
- Safe
- Lower rate of complications (HIT, osteopenia)

# Disadvantages



- **Unfractionated**

- 2x +/-day
- IV initially for therapeutic dose
- Higher rate of complications (ie: HIT, osteopenia)

- **LMWH**

- Expensive
- Long half life
- No reversible agent
- Potential concerns peripartum

# Unfractionated Heparin



- Prophylactic
  - 5000 u sc bid throughout pregnancy
  - OR
  - 5000u sc bid T1
  - 7500u sc bid T2
  - 10000usc bid T3
  - based on higher heparin doses needed to achieve adequate levels as pregnancy advances





# Unfractionated Heparin

- Therapeutic (IV)
  - Heparin Protocol
  - Loading dose: 100u/kg (5000u)
  - Initial infusion: 15-25u/kg/h (min. 1000u/hr)
  - Check PTT in 3-4 hrs
  - Adjust dose to give PTT 2.0-2.5x control
  - Can switch to SC dosing when PTT stable



# Low Molecular Weight Heparin

- Prophylactic
  - Dalteparin (Fragmin) 5000u sc daily
  - Enoxaparin (Lovenox) 40 mg sc daily
- Therapeutic
  - Dalteparin 200u/kg sc q24h
  - Enoxaparin 1 mg/kg sc q8-12h
  - LMWH does not change PTT
  - can follow anti factor Xa activity

# Peripartum Treatment



- Anaesthesia consult
- Change LMWH to UFH at ~ 36 wks
  - await spontaneous labour/planned IOL
  - epidural option
  - shorter  $t_{1/2}$
  - can be reversed by protamine sulfate
- Discontinue LMWH 24 hrs prior to scheduled delivery
  - no reversible agent



# Post Partum Treatment

- Restart UFH or LMWH 6-8 hrs PP if stable
- Continue or switch to warfarin with initial overlap UFH/LMWH until INR at least 2
- Warfarin & heparin safe in breastfeeding

# 'Kathy'



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- Family doctor wants advice re:
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# 'Jill'



- 36 yo G1P1 woman with an IUFD at term
  - Preconceptual counseling
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- 29 yo G2P1 woman at 6 weeks
- PObHx of severe preeclampsia->delivery at 22 weeks
  - She had “?some blood tests done” which were abN after her last pregnancy
  - By the way she had a DVT 4 weeks PP
  - Family doctor needs help!

# Summary



- Pregnancy is a prothrombotic state, with changes in all aspects of Virchow's Triad
- Risk of VTE in pregnancy further increased in those with thrombophilia
- Not all women with thrombophilia will develop VTE or obstetric complications
- Women with adverse pregnancy outcomes more likely to test positive for a thrombophilia and viceversa



# Summary

- VTE is important cause morbidity & mortality & preventative measures are available
- Women with personal or family hx can be tested for thrombophilias
- Thromboprophylaxis is key management strategy for women with previous VTE & thrombophilia
- Thromboprophylaxis or therapeutic anticoagulation key strategy for those with high risk thrombophilias or carriers with strong family hx



# Summary

- Women with a thrombophilia, previous VTE, or risk factor(s) for the same are ideal candidates for **preconceptual** counseling
- Implications for pregnancy and postpartum management
- Multidisciplinary team approach
  - Obstetrics/Maternal Fetal Medicine
  - Hematology
  - Anaesthesia
- Careful antenatal, intrapartum, PP management to optimize outcomes





# IWK Guidelines for PP Prophylaxis

- Increased risk VTE PP
  - 1/7500 births; 1/1870 CS
- Low risk
  - All patients
  - Mobilize
  - TED stockings prn
- Moderate risk/ High risk
  - Above recommendations +
  - Consider heparin
    - Obesity
    - CS in labour
    - Additional risks for VTE
    - Thrombophilia
    - Previous anticoagulation