

# Thrombophilia in Pregnancy

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# Learning Objectives

- Define thrombophilia and identify those that are most common
- Review incidence, inheritance and prevalence of thrombophilias
- Outline three principle mechanisms that hold clot formation in check
- Know effects of pregnancy on hemostasis
- Discuss screening, diagnosis and management of inherited and acquired thrombophilias

# Let's Define the Terms

- What is a Thrombophilia?
  - A group of common inherited and acquired coagulopathies or predispositions to clotting.
- So, what?
  - Thrombophilias can cause some women to form potentially life-threatening blood clots. They also may put women at risk for adverse pregnancy outcomes.
- What is an adverse pregnancy outcome?
  - Fetal loss in the late-first, second, and third trimesters, severe intrauterine growth restriction (IUGR), placental abruption, and severe and early-onset preeclampsia

# What's the difference?

## ➤ Inherited

- Antithrombin III Deficiency
- Factor V Leiden Mutation
- Prothrombin (G20210A) Mutation
- Mutations in Plasminogen activator inhibitor-1 gene
- Variant of methylenetetrahydrofolate reductase (MTHFR) which causes Hyperhomocysteinemia
- Protein C Deficiency
- Protein S Deficiency

## ➤ Acquired

- Antiphospholipid Antibody Syndrome

# Incidence

- Thrombophilias are associated with approximately 66% of deep venous thromboses (DVT) in women on birth control pills (Katz, 2002)
- Up to 50% of women with a thrombosis in pregnancy have a congenital or acquired thrombophilia (ACOG 234, 2000)
- Women with a thrombophilia have 8-fold increased risk of maternal VTE (Lockwood, 2003)
- Thromboembolic disease is the greatest single cause of maternal death in developed countries

# Prevalence

- General Population (ACOG 234, 2000):
  - Factor V Leiden Mutation 5-9%
    - African American 1%
    - Caucasian 6-11%
  - Prothrombin G20210A mutation 2-4%
  - Antithrombin III Deficiency 0.02-0.2%
  - Protein C Deficiency 0.2-0.5%
  - Protein S Deficiency 0.8%
  - Hyperhomocysteinemia 1-11%
  - Antiphospholipid Antibody Syndrome <1%Katz, 2002

# Inheritance

THROMBOPHILIA	MODE OF INHERITANCE
AT III Deficiency	Autosomal Dominant (AD)
Factor V Leiden Mutation	AD
Prothrombin Mutation	AD
Protein C Deficiency	AD
Protein S Deficiency	AD
Plasminogen Activator Inhibitor	Autosomal Recessive (AR)
Mild Hyperhomocysteinemia due to MTHFR mutation	AR

# Hemostasis

- Blood clot formation is held in check by three principle physiologic mechanisms:
  - Inhibition of thrombin
  - Inactivation of factor V
  - Breakdown of fibrin
- Thrombophilias may arise from defects in any of these mechanisms

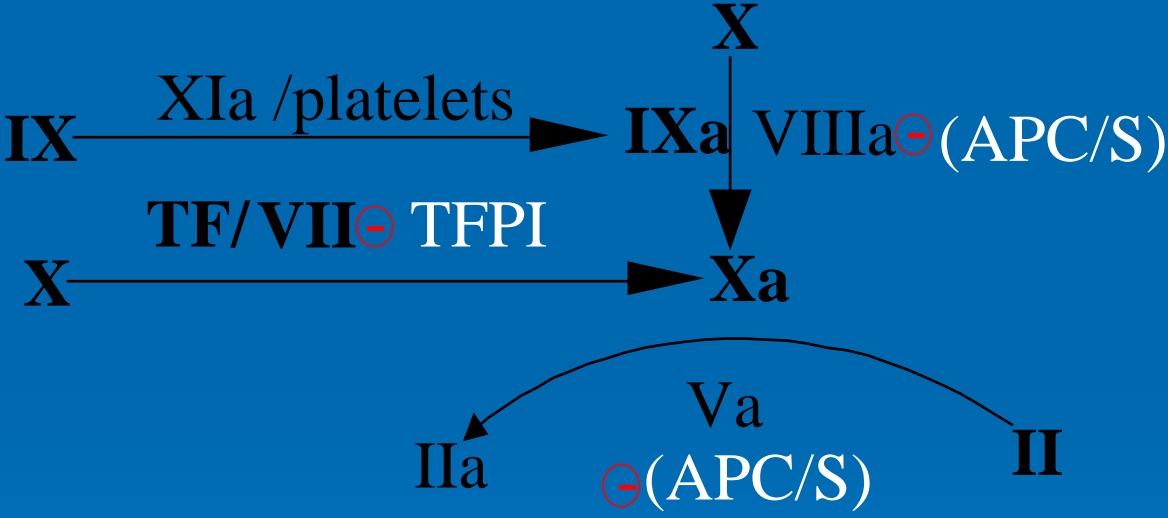
# Inhibition of thrombin

- Antithrombin III (AT-III) is the most potent anticoagulant mechanism
- AT-III is a protein that inhibits thrombin formation, as well as, activated factors X and VII
- Hereditary deficiencies of AT-III affect about one in 5,000 people
- Homozygous AT-III deficiency is not compatible with life
- Woman who is heterozygous for AT-III deficiency will have close to a 100% chance of developing a venous thrombosis sometime in her life.

# Inactivation of factor V

- Most thrombophilias involve abnormalities in this second mechanism of anticoagulation
- When protein C (PC) is exposed to damaged endothelium, it is activated and binds with protein S (PS) to form the activated protein C (APC) complex
- APC then binds to factor V, inactivating it, and thus, inhibiting the conversion of prothrombin to thrombin by factor X
- Deficiencies of PC and PS occur in one in 200
- Homozygous individuals for PC or PS deficiency usually die as newborns

# Inactivation of factor V



# Inactivation of factor V

- Factor V Leiden is a mutation that leads to resistance in binding with the APC complex
- Since factor V is required for conversion of prothrombin to thrombin, if it cannot be turned off, production of thrombin becomes continual and extensive
- Factor V Leiden alone may be responsible for at least 40% of DVTs in pregnancy
- Homozygosity for factor V Leiden incurs an almost 100% risk of DVT during lifetime

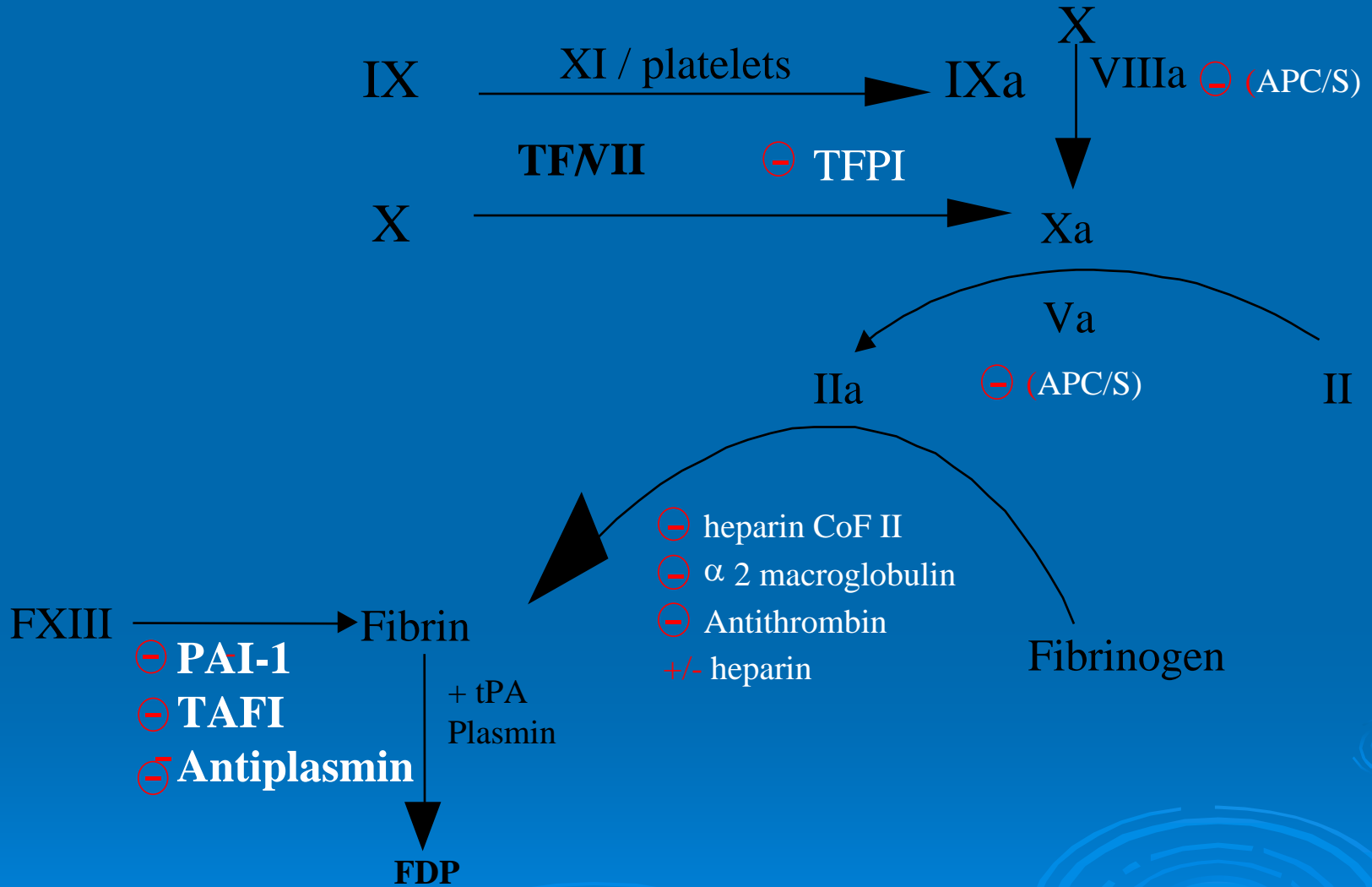
# Inactivation of factor V

- The second most common thrombophilia is the G20210A mutation in the prothrombin protein
- This leads to excessive accumulation of prothrombin in the serum
- The greater the amount of prothrombin, the greater the conversion into thrombin
- Homozygous individuals have a very high risk of developing a DVT in their lifetime

# Breakdown of Fibrin

- Fibrinolysis, the third principle antithrombotic system, maintains the balance between clot formation and breakdown
- Fibrin clots are broken down primarily by plasmin
- The plasmin precursor, plasminogen, can be activated by tissue type plasminogen activator (tPA) which is inhibited by type 1 plasminogen activator inhibitor (PAI-1)
- Mutations in the promoter region of the PAI-1 gene impair plasmin generation-and that results in increased fibrin

# Anticoagulant Pathway



# Other Thrombophilias

- Two other thrombophilias increase the risk of clotting in women: antiphospholipid syndrome and hyperhomocysteinemia
- These both induce thrombosis and disease by disrupting the endothelium of small blood vessel walls, setting the stage for activation of clotting cascade

# Hyperhomocysteinemia

- A thrombophilia in which increased amounts of the essential amino acid homocysteine build up in the plasma
- Elevated levels have a toxic effect on the endothelium, leading to clot formation
- A mutation in methylenetetrahydrofolate reductase (MTHFR) may cause mild to moderate hyperhomocysteinemia
- Estrogen decreases homocysteine levels in serum, so this disease rarely causes DVT in pregnancy, but it may postpartum

# Hyperhomocysteinemia

- It may be associated with recurrent embryonic loss, as well as, fetal loss
- It is both embryotoxic and mutagenic
- As many as 50% of open neural tube defects may be associated with the MTHFR mutation
- Cardiac malformations may also be associated with elevated homocysteine levels

# Hyperhomocysteinemia

- It is exacerbated by deficiencies in vitamin B<sub>12</sub> and folic acid
- Diagnosed by measuring fasting homocysteine levels
- Classified by the fasting homocysteine level:
  - Severe (greater than 100 micromol/L)
  - Moderate (25-100 micromol/L)
  - Mild (16-24 micromol/L)

# Antiphospholipid Syndrome

- Autoimmune condition characterized by the presence of, at least, one clinical feature **AND** the presence of specific circulating antiphospholipid antibodies
- The most specific clinical features are thrombotic events, autoimmune thrombocytopenia, and fetal loss:
  - One or more unexplained deaths  $\geq$  10 weeks
  - One or more premature births  $\leq$  34 weeks (not PTL)
  - Three or more spontaneous abortions  $<$  10 weeks

# Pregnancy-Associated changes in Coagulation

- Increase in clotting factors
  - 20-200% increase in levels of fibrinogen and factors II, VII, X, VIII, and XII and PAI-1
- Decrease in anticoagulant and fibrinolytic activity
  - Protein S levels decrease by 40% (second trimester 30%, third trimester 24% lower limit of normal)
  - APC resistance decreases
- Thus, the net effect of these pregnancy-induced changes is to exacerbate the clinical effects of thrombophilias

# Screening

- Two step screen
  1. History
  2. Hematologic Assessment
- Only if the historical screen is positive, should a hematologic assessment be done.

Katz, 2002

# History

- \* Personal history of a thrombosis
- \* Family history of DVT or PE
- \* Personal history of abruption, severe IUGR, severe or early preeclampsia < 32 wks
- \* Personal history of:
  - Three pregnancy losses <10 wks
  - Two losses > 10 wks
  - Unexplained loss > 20 wks
- \* Personal history of thrombosis
- \* Family history of thrombosis, controversial
- \* Women with first-degree relative with AT-III deficiency or homozygous factor V Leiden or prothrombin G20210A
- \* Test patients with history of thrombosis, recurrent fetal loss, early or severe preeclampsia or severe unexplained IUGR for antiphospholipid antibodies

(Katz, 2002)

(ACOG 19, 2000)

# Hematologic Assessment

- Lupus anticoagulant and anticardiolipin antibodies
- Factor V Leiden mutation
- Prothrombin G20210A mutation
- AT-III antigen activity levels
- Fasting homocysteine levels or MTHFR mutation (no longer recommended-PB 124)
- Protein C antigen activity levels
- Protein S antigen activity levels (free and total)
- PAI-1 activity levels (not recommended PB 124)

\*\*Testing for AT-III, PC, and PS in the setting of extensive clotting, warfarin use or heparin administration may result in falsely low values.

# Why Treat with Heparin?

- Uteroplacental thrombosis is a common feature in pregnancies complicated by IUGR, severe preeclampsia, abruption, and fetal loss
- Prophylaxis with heparin has been suggested to prevent their recurrence
- Rationale for this approach is that maternal heparin administration will decrease vascular injury and thrombin generation, thereby reducing thrombosis in the uteroplacental circulation

# Why use LMWH?

- Reduces risk of 3 complications caused by unfractionated heparin:
  - Bleeding
  - Osteoporosis (mean bone loss of 5% w/ Heparin)
  - Thrombocytopenia
- Two types of thrombocytopenia
  - More common type that is benign, reversible, nonimmune and occurs within the first few days of therapy and typically resolves by 5 days
  - Less common, more severe type that is immune mediated called heparin induced thrombocytopenia (HIT)
    - Occurs in 5-14 days of treatment in as many as 3% of patients
    - May result in widespread thrombosis

# Treatment with Unfractionated Heparin

## ➤ Therapeutic:

≥ 10,000 U twice a day to three times per day to achieve

## ➤ Prophylaxis:

- 5,000-7,500 Units Q 12 hrs first trimester
- 7,500-10,000 Units Q 12 hrs second trimester
- 10,000 units Q 12 hrs third trimester
  - OR-
- 15,000-20,000 units daily in divided doses

# Treatment with Low-Molecular-Weight Heparin (LMWH)

## ➤ Therapeutic:

- Dalteparin 5,000-10,000 units Q 12 hours, or
- Enoxaparin 30-80 mg Q 12 hours
- To achieve antifactor Xa level 0.6-1.2  $\mu$ /mL 4 hours after dose

## ➤ Prophylaxis:

- Dalteparin 5,000 units once or twice daily, or
- Enoxaparin 40 mg once or twice daily

# Are Some Inherited Thrombophilias worse than Others?

## ➤ Highly thrombogenic thrombophilias:

- AT-III Deficiency
- Homozygote (or double heterozygote) Factor V Leiden mutation
- Homozygote Prothrombin (G20210A) Mutation

## ➤ Less Thrombogenic Thrombophilias:

- Heterozygote Factor V Leiden Mutation
- Heterozygote Prothrombin (G20210A) Mutation
- Mutations in PAI-1 gene
- Hyperhomocysteinemia
- Protein C Deficiency
- Protein S Deficiency

# How to Manage Inherited Thrombophilia

- Highly Thrombogenic Thrombophilias
  - Therapeutic heparin or LMWH
  - Treat antepartum until onset of labor to maintain antifactor Xa level 0.6 – 1.2  $\mu\text{mL}$  4 hours after dose
  - If using LMWH, discontinue 12-24 hours prior to epidural or switch to Heparin at 36-37 wks
  - Restart LMWH or heparin 6-12 hours after delivery
    - Must continue heparin for at least 4 days when initiate coumadin, and until INR therapeutic for 48 hours
  - Continue anticoagulation until 6 weeks postpartum and until 3-6 months postpartum if history of VTE

# How to Manage Inherited Thrombophilia

- ACOG Practice Bulletin 124, Sept. 2011
- Indications for Screening
  - Personal H/O VTE associated with nonrecurrent risk factors
  - First Degree relative H/O thrombophilia or VTE under 50 not associated with risk factors
  - Insufficient evidence for screening for a history of recurrent fetal loss, abruption, IUGR, preeclampsia.

# How to Manage Inherited Thrombophilia

- ACOG Practice Bulletin 124, Sept. 2011
- Individualize management
  - CD
  - Prolonged immobility
  - Obesity
  - FMH thrombophilia or VTE

# How to Manage Inherited Thrombophilia

- ACOG Practice Bulletin 124, Sept. 2011
- Intrapartum Management
  - Compression devices until ambulatory
  - D/C 24-36 hours before IOL or CD
  - > 4 hours after heparin no increased risk for hemorrhage
  - > 12 hours after prophylactic and > 24 hours after therapeutic dose LMWH regional anesthesia is considered safe
  - Protamine sulfate can be used if rapid reversal is necessary

# How to Manage Inherited Thrombophilia

- ACOG Practice Bulletin 124, Sept. 2011
- Postpartum
  - Doses of UFH or LMWH should be equal to or greater than antepartum therapy
  - 4-6 hours after SVD
  - 6-12 hours after CD
  - Warfarin 5 mg daily X 2 then INR based, continue UFH or LMWH 5 days and until INR therapeutic (2-3).
  - All are compatible with breastfeeding-Level B

# How to Manage Inherited Thrombophilia

- ACOG Practice Bulletin 124, Sept. 2011
- Postpartum
  - FVL, Prothrombin Gene Mutation avoid estrogen containing contraception

# How to Manage Inherited Thrombophilia

- Less Thrombogenic Thrombophilia
- Compound heterozygosity for FVL and Prothrombin G20210A
  - WITH prior VTE or adverse pregnancy outcome,
    - Use prophylactic heparin or LMWH antepartum
    - Postpartum coumadin with history of VTE, affected first degree relative or other risk factor for thrombosis

# How to Manage Inherited Thrombophilia

- Less Thrombogenic Thrombophilia
  - If patient has no history of VTE or adverse pregnancy outcome
    - No antepartum prophylaxis is necessary
    - However, consider postpartum prophylactic anticoagulation if patient has affected first degree relative or other risk factor for thrombosis

# How to Manage Acquired Thrombophilia

- Antiphospholipid Syndrome (APS)
  - Prophylactic heparin or LMWH
  - ASA daily (60-85 mg)
  - Start heparin and ASA after confirmation of live embryo
  - Still 2/3 preeclampsia, 40% risk of IUGR, 25% risk of delivery < 32weeks (Branch, 1992)
  - IVIG – second line of therapy, in addition to heparin and ASA

# What's Different with Hyperhomocysteinemia?

- If hyperhomocysteinemia is the sole coagulation defect, do not initially treat with heparin
- Begin with supplementation of vitamin B<sub>6</sub>, B<sub>12</sub>, and folic acid (4 mg QD)
- Prophylactic heparin should be considered among hyperhomocysteinemic patients whose elevated homocysteine levels are unresponsive to such vitamin therapy

# How to Manage Acquired Thrombophilia

- ACOG Practice Bulletin January 2011
- Antiphospholipid Antibodies
  - Lupus Anticoagulant
  - Anticardiolipin Antibodies (IgG, IgM > 40 or 99<sup>th</sup> percentile)
  - Anti-beta 2 glycoprotein I (IgG, IgM > 99<sup>th</sup> percentile)
  - Two positive tests at least 12 weeks apart
  - Clinical relevance of IgA uncertain

# How to Manage Acquired Thrombophilia

- ACOG Practice Bulletin January 2011
- Indication for testing
  - Vascular thrombosis
  - Pregnancy Morbidity
    - IUFD  $\geq$  or = 10 weeks with normal fetal morphology
    - Delivery  $<$  34 weeks for severe preeclampsia or placental insufficiency
    - Three consecutive unexplained early losses  $<$  10 weeks (R/O anatomic, hormonal and karyotypic etiologies)

# How to Manage Acquired Thrombophilia

- ACOG Practice Bulletin January 2011
- History of Thrombotic Events-Level C
  - Prophylactic heparin through 6 weeks postpartum (may use Coumadin after delivery)
  - Benefit of adding low dose ASA unknown
- No history of Thrombotic Events-Level B
  - Prophylactic heparin and low dose ASA through 6 weeks postpartum
  - Efficacy of prednisone unknown
  - IVIG not recommended

# How to Manage Acquired Thrombophilia

- ACOG Practice Bulletin January 2011
- Antepartum Surveillance-Level C
  - Growth scans/antepartum testing
  - Supported only by expert opinion
- Nonpregnant-Level C
  - Avoid estrogen containing contraceptives
  - Consult IM, Hematology, Rheumatology

# Learning Objectives

- Define thrombophilia and identify those that are most common
- Review incidence, inheritance and prevalence of thrombophilias
- Outline three principle mechanisms that hold clot formation in check
- Know effects of pregnancy on hemostasis
- Discuss screening, diagnosis and management of inherited and acquired thrombophilias

# In Conclusion

- Inherited and acquired thrombophilias together cause more than half of all maternal venous thromboembolism and have been linked to a two- to fivefold increased risk of fetal loss, IUGR, abruption and early-onset, severe preeclampsia
- Much of our management at this time is based on series, case reports and expert opinion