

Pregnancy Associated Thrombosis

Keith E Swanson
North Dakota Academy of Family Physicians
Family Medicine Update
Big Sky, MT
January 21, 2015

Disclosures

- I am the furthest thing from an obstetrician
- I tend to favor the Chest Guidelines
 - Substantial disagreement amongst various scientific societies
- No financial conflicts of interest
- We will focus on Thrombosis rather than “adverse pregnancy outcomes”
 - Controversial
 - See the first disclosure!

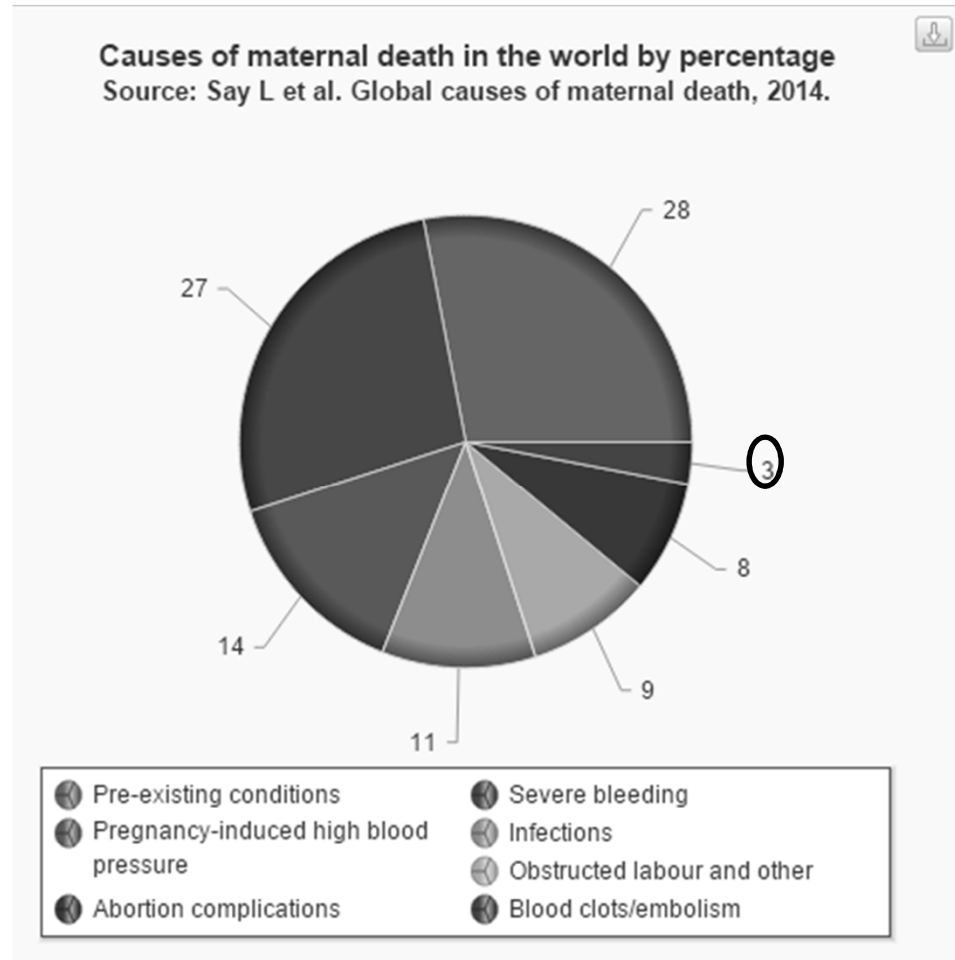
Objectives

- Epidemiologic characteristics of Pregnancy associated VTE
- Pearls in risk counseling
- Diagnostic do's and don'ts
- OCPs and VTE
- When is chemical prophylaxis warranted
 - ABC's of chemical prophylaxis
- Acute management of VTE in the pregnant patient.

Quiz

- Which of these complications of pregnancy results in more maternal deaths?
 - A. Bleeding
 - B. Clotting
 - C. Neither

VTE in pregnancy

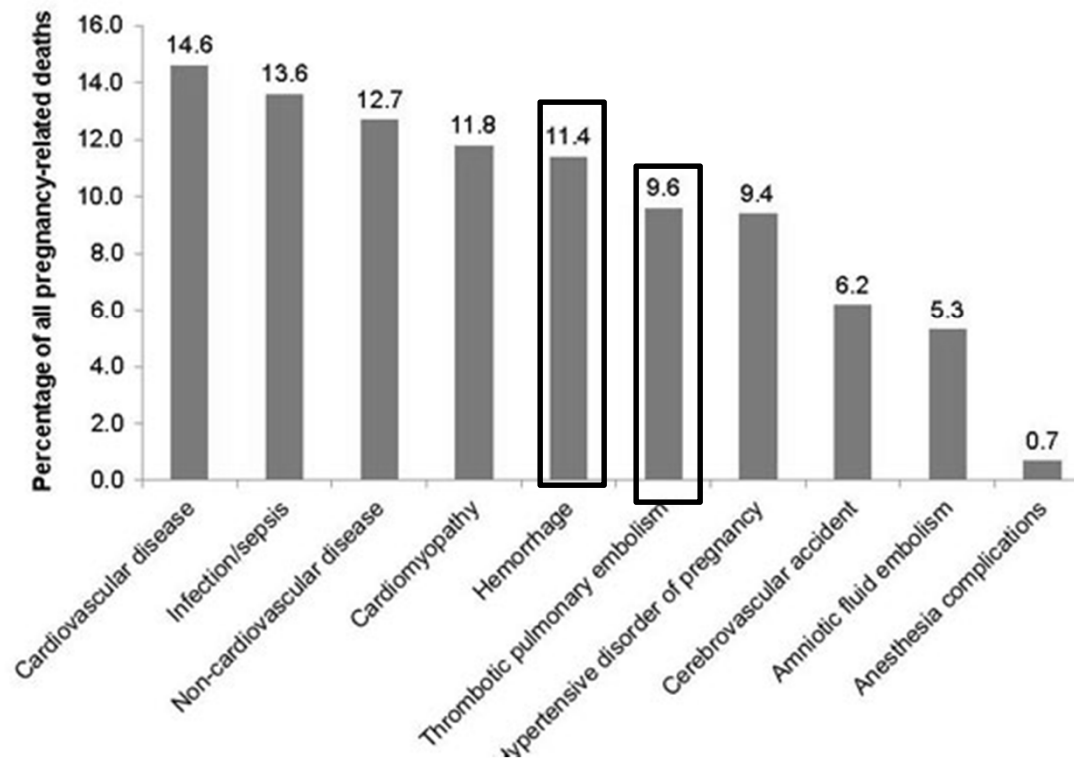


The Big Picture!

Source: WHO

Maternal Death in the USA

Causes of pregnancy-related death in the United States: 2006-2010



Source: CDC

Paucity of Data

- Very few high quality studies
 - VTE risk factors
 - risks/benefits of antithrombotic therapy
- CHEST Guidelines (2012)
 - Most recommendations → low/moderate quality
 - “In the absence of direct evidence from randomized trials of reasonable quality, indirect evidence from randomized trials in non-pregnant pt. considered applicable to the present population”

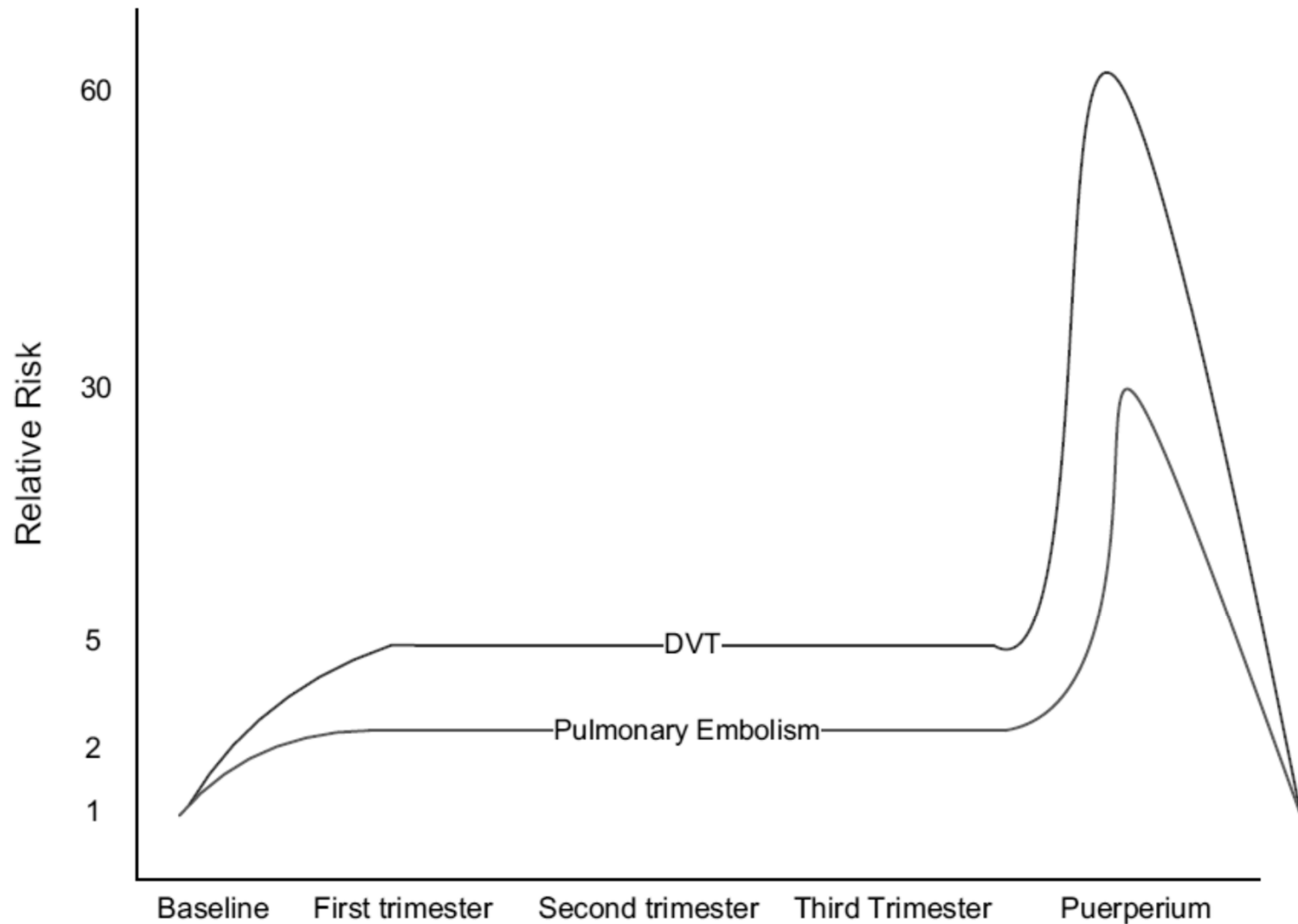
Epidemiology

- Overall incidence: 0.6-1.72/1000 deliveries
 - 5 fold risk over age/gender matched controls
 - 20-60 fold in puerperium
- In women of child bearing potential, pregnancy accounts for 50% of VTE
- 9-10% of pregnancy related death d/t VTE
 - ~ 74 deaths per year in USA
- Relative vs. absolute risk
 - Despite 5x increased risk...
 - Only 0.05-0.2% of all pregnancies effected by VTE
 - Critically important when counseling

Characteristics

- DVT > PE *during* vs. PE > DVT *after*
 - 2/3 DVT occur in the antepartum state
 - Evenly distributed over all three trimesters
 - If post-partum, likely within initial month, and most commonly in 2nd week postpartum
 - > 50% PE occur in post-partum
 - Remember the relative time period of these states
 - PE: 2-fold antepartum vs. almost 30-fold post-partum
 - Left LE >> Right LE
 - 70-80% (some 90%) antepartum DVT (vs. 55% non-pregnancy)
- More likely large, occlusive, proximal
 - 70% ileo-femoral (vs. 9% outside pregnancy)
 - Pelvic much more common → 10-13% vs 1% (DVT in gen pop)
 - Diagnostic challenge → lower ab pain, pelvic girdle pain, back pain
 - As a consequence, more likely to embolize
- High level of unrecognized clinical burden
 - PTS common given high incidence of proximal disease
 - 42% = any degree; 7% with severe (3-16 y of f/u)
 - Reduced QOL has been documented

Relative Risk DVT/PE during pregnancy



Doc, My feet are swollen, I
can't breath, and my heart
is racing!!



“If all you have is a hammer, everything looks like a nail”¹

1. Bernard Baruch

Meet your Hammers...



Dr. Brown

“Welcome to your third trimester!”



Dr. Paulson

“Call 911 and start the heparin bolus!”

Beware, the Similarities..

- High index of suspicion
 - s/s pregnancy very similar to those of VTE!!
 - Leg swelling, Dyspnea, Tachycardia, Tachypnea
 - Pelvic VTE a/w atypical presentations
 - Ab pain, back pain etc.
 - Ultrasound more challenging
- May delay recognition

Patho-mechanisms

- Why this revved up state of hyper coagulability?
- Theory: stop hemorrhage with still birth
 - Developing world....
 - Hemorrhage >> clot
- Hyper-coagulable state + proper uterine contraction *prevents* profuse uterine hemorrhage.
- Side effect: more blood clots...

Rudolf Virchow



Venous stasis

- Compression of pelvic veins by gravid uterus
- Exaggerated compression of left iliac vein by right iliac artery
- Hormone-mediated reduction in venous smooth muscle tone



Altered coagulation

- Increased promoters of coagulation (fibrinogen; factors V, VII and VIII, as well as von Willebrand factor)
- Decreased inhibitors of coagulation (free protein S)
- Decreased fibrinolysis (increased PAI-1, placental synthesis of PAI-2)

Endothelial injury

- Due to venous distension and compression

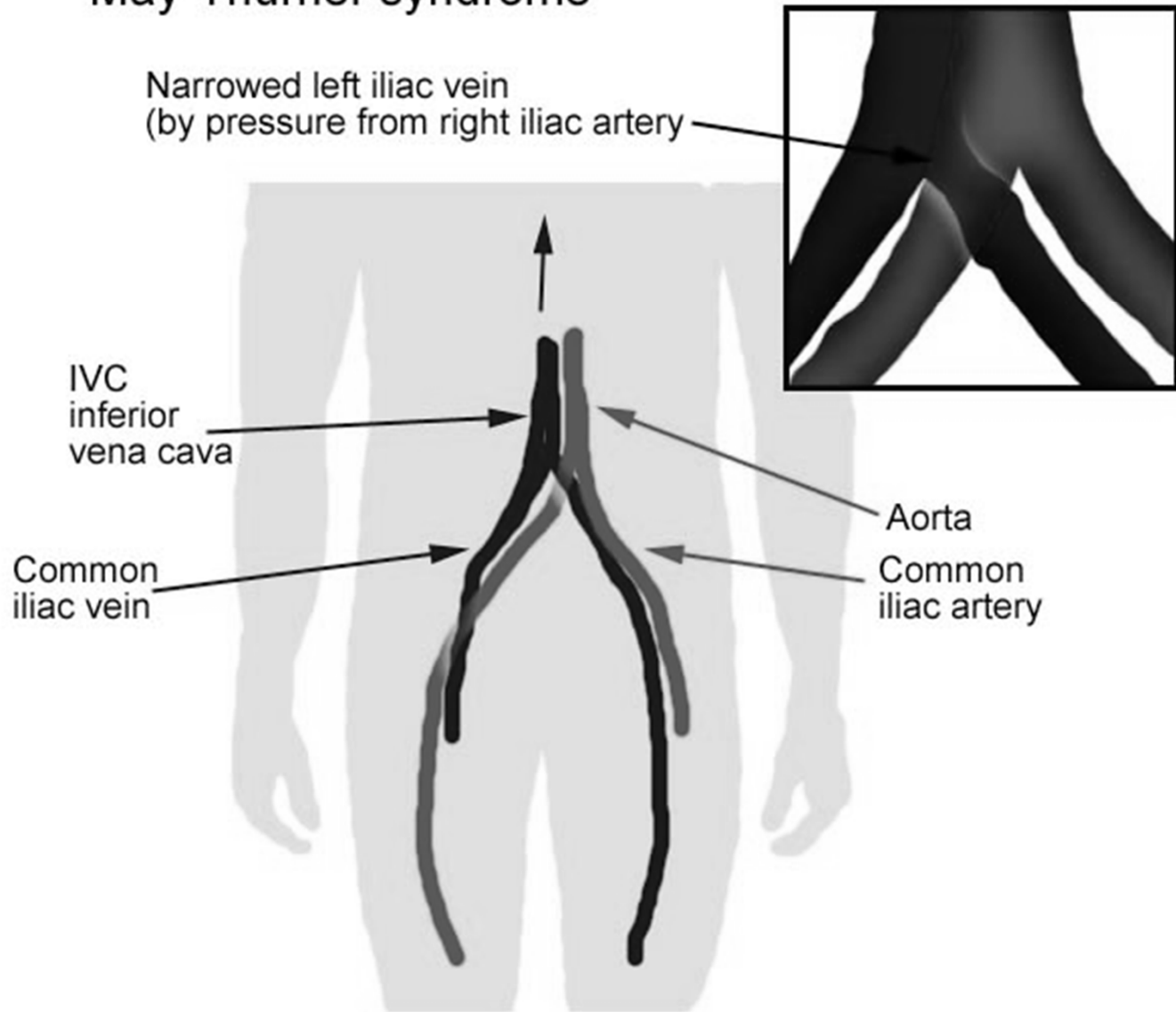
Figure 1. Causes of increased risk of venous thromboembolism in pregnancy. The hemostatic and mechanical changes in pregnancy that contribute to the increased risk of venous thromboembolism are shown.

Data taken from [7,13–15].

Stasis

- Venous flow velocity progressively slows as gestation progresses
 - Left slower than Right
 - Mechanical Compression by Gravid uterus
 - Increased venous capacitance
 - Due to higher circulating estrogen, prostacyclin/NO
 - Essentially half normal venous flow by 25 weeks gestation...
 - *Remains* at this level until 6 weeks post-delivery

May-Thurner syndrome

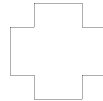


Vascular Trauma

- Endothelial damage
 - Pregnancy induced venous distension
 - Venous compression from normal delivery
 - Surgery and extraction aides
 - Especially C-section
 - Other concomitant pathologic states....
 - Preeclampsia → endothelial activation with subsequent damage
 - Likely d/t cytokine release

Hypercoagulability...

Coagulation activation



Fibrinolytic inhibition

Hypercoagulability...

Increased resistance to APC

- particularly in 2nd/3rd Tri

Anticoagulant factors

Protein S activity decreased

- d/t increased C4b

Coagulation factor XI decreases?

- unclear why this occurs

Coagulation factors increased

VII VIII X XII and VWF

Fibrinogen → 2-fold increase

Fibrin generation increased

Procoagulant factors

Fibrinolysis decreased d/t:

1. decrease tPA activity
2. 5x PAI-1 levels
3. Placental PAI-2 levels
3rd trimester
4. Other complexes

**Pregnancy
+ 8 weeks**

Clinical Risk Factors...

- #1= previous VTE...
 - 15-25% of pregnancy related VTE are recurrent events
- Age > 35, obesity
 - Age > 35 particularly post-partum
- C-section controversial
 - Likely increased with emergency sections
- Essentially, *any* complication of pregnancy/delivery
 - Critical illness, transfusion, infection, preeclampsia
 - Any hospital stay for reasons other than delivery = OR ~17
- Bed rest-→ ante/postpartum
- Puerperium itself → vessel trauma + systemic coag activation
 - More events than during pregnancy
- + FH→ 2-4 x increased risk
- 1+1 = 4...
 - Example: obese + > 1 week immobilization= 62 fold increased risk

Quiz

- Which of the following *inherited* thrombophilias has *NOT* been associated with an increased risk of VTE in pregnancy?
 - A. Heterozygous LfV
 - B. Heterozygous Prothrombin gene mutation
 - 20210A
 - C. Deficiencies in the “natural” anticoagulants
 - Protein C, Protein S, Antithrombin III
 - D. Methylene tetrahydrofolate Reductase Mutations

Table 4. Risk of pregnancy-associated venous thromboembolism(VTE) in thrombophilic women without prior disease.

Thrombophilia	Personal h/o VTE? 10X RR	Estimated absolute risk of VTE events per 1000 patients*
	Relative Risk of VTE OR (95% CI)	
Factor V Leiden (heterozygous)	8.32 (5.44-12.70)	8/1000
Prothrombin gene variant (heterozygous)	6.80 (2.46-18.77)	6/1000
Factor V Leiden (homozygous)	34.40 (9.86-120.05)	34/1000
Prothrombin gene variant (homozygous)	26.36 (1.24-559.20)	26/1000
Antithrombin deficiency	4.69 (1.30-16.96)	4/1000
Protein C deficiency	4.76 (2.15-10.57)	4/1000
Protein S deficiency	3.19 (1.48-6.88)	3/1000
MTHFR C677T (homozygous)	0.74 (0.22-2.48)	1/1000

Table 1. Risk of Venous Thromboembolism With Different Thrombophilias ↵

	Prevalence in General Population (%)	VTE Risk per Pregnancy (No History) (%)	VTE Risk per Pregnancy (Previous VTE) (%)	Percentage of All VTE
Factor V Leiden heterozygote	1–15	0.5–1.2	10	40
Factor V Leiden homozygote	<1	4	17	2
Prothrombin gene heterozygote	2–5	<0.5	>10	17
Prothrombin gene homozygote	<1	2–4	>17	0.5
Factor V Leiden/prothrombin double heterozygote	0.01	4–5	>20	1–3
Antithrombin III activity (<60%)	0.02	3–7	40	1
Protein C activity (<50%)	0.2–0.4	0.1–0.8	4–17	14
Protein S free antigen (<55%)	0.03–0.13	0.1	0–22	3

Abbreviation: VTE, venous thromboembolism.

General Truths about the thrombophilic pregnant patient

- Inherited thrombophilia is not uncommon:
 - General population 15%
 - Gestational VTE: at least 20%⁸ some say up to 50%!
- Most common: heterozygous LRV and PT gene mutation
 - Together, account for ~ 50% of Thrombophilia-associated VTE in pregnancy
- Wide range of estimated risk
 - AT Type I = ~30% absolute risk vs. Heterozygous FVL = ~1% absolute risk
 - MTHFR = no increased risk (even homozygous!)
- Previous VTE and Family h/o *critical* in estimating individual risk!
 - LRV, -FH, - personal h/o → 5-12/1000 (0.5-1.2% absolute risk)
 - LRV, + FH, - personal h/o → 14/1000 (1.5% absolute risk)
 - LRV, -FH, + personal h/o → 100/1000 (10% absolute risk)
- Deciding *when* to thrombo-prophylax *not* straightforward
 - “Medicalization” of pregnancy
 - Risks to fetus and mother
 - Burden of thromboprophylaxis → painful, (still) expensive, inconvenient
- Threshold to use prophylaxis post-partum lower
 - Shorter length of Rx (6 weeks)
 - Much higher average daily risk
- Given distribution of risk across all three trimesters, Rx throughout

Swanson's Rule of Thumb

- When the risk of thrombosis *exceeds* the risk of significant bleeding (~1.5%), AND patient *fully informed* of Rx burden, then treat.
 - Rx burden: physical and financial
 - Altru Retail Pharmacy → December 31st, 2014
 - Enoxaparin 40 mg sq q daily for 30 days → \$1070.40!!
 - just north of border: → \$360

Quiz

- According to the latest CHEST guidelines, which scenario would call for *antepartum* prophylaxis?
 - A. 24 y/o hf, 1st pregnancy, + hetero LFV, - FH, no previous VTE
 - B. 24 y/o hf, 2nd preg, thrombophilia status unknown, -FH VTE but PE 2 wks. post-partum (1st preg)
 - C. 24 h/o hf, 1st preg, + pro C def, + FH (OCP age 25), no previous VTE
 - D. All of the above

When to Prophylax

- Asymptomatic thrombophilia, - FH VTE
 - no Rx!
 - Exception: homozygous FVL/PT gene mutation
 - post-partum prophylaxis
- Asymptomatic Thrombophilia, + FH VTE
 - Only post-partum prophylaxis (Grade 2C)
 - Exception: homozygous FVL/PT gene mutation
 - Antepartum/postpartum prophylaxis

VERY CONTROVERSIAL!!

When to Prophylax

■ Previous VTE?

- Post-partum Rx recommend for *all*
 - If transient RF → no antepartum Rx!
 - If RF related to previous pregnancy or estrogen → antepartum favored
 - Antepartum clinical vigilance acceptable
- Listen to your patient!

Table 3. Summary of American College of Chest Physicians' recommendations to prevent thrombophilia-related venous thromboembolism.

Prevention of VTE	Recommendation	Strength of recommendation
<i>No prior VTE</i>		
High risk: homozygous factor V Leiden or prothrombin gene mutation		
Positive family history of VTE	Antepartum prophylaxis with prophylactic or intermediate dose LMWH; postpartum prophylaxis for 6 weeks with prophylactic or intermediate-dose LMWH or vitamin K antagonists targeted to an INR of 2.0–3.0	2B (vs no prophylaxis)
No family history of VTE	Antepartum clinical vigilance; postpartum prophylaxis for 6 weeks with prophylactic or intermediate dose LMWH or vitamin K antagonists targeted to an INR of 2.0–3.0	2B (vs routine care)
Lower risk: other thrombophilias		
Positive family history of VTE	Antepartum clinical vigilance; postpartum prophylaxis for 6 weeks with prophylactic or intermediate-dose LMWH or, in women who are not protein C or S deficient, vitamin K antagonists targeted to an INR of 2.0–3.0	2C (vs routine care)
No family history of VTE	Antepartum and postpartum clinical vigilance	2C (vs prophylaxis)
<i>Prior VTE; not receiving long-term anticoagulants</i>		
Moderate-to-high risk		
Single or multiple unprovoked VTE; pregnancy- or estrogen-related VTE	Antepartum prophylaxis with prophylactic or intermediate-dose LMWH	2C (vs clinical vigilance or routine care)
	Postpartum prophylaxis for 6 weeks with prophylactic or intermediate dose LMWH or vitamin K antagonists targeted to an INR of 2.0–3.0	2B (vs no prophylaxis)
Low risk		
Single VTE associated with transient risk factor not related to pregnancy or use of estrogen	Antepartum clinical vigilance	2C (vs prophylaxis)
	Postpartum prophylaxis for 6 weeks with prophylactic or intermediate dose LMWH or vitamin K antagonists targeted to an INR of 2.0–3.0	2B (vs no prophylaxis)

Quiz

- According to the latest CHEST guidelines, which scenario would call for *antepartum* prophylaxis?
 - A. 24 y/o hf, 1st pregnancy, + hetero LFV, - FH, no previous VTE Clinical vigilance only!!
 - B. 24 y/o hf, 2nd preg, thrombophilia status unknown, -FH VTE but PE 2 wks post-partum (1st preg) Antepartum AND postpartum prophylaxis
 - C. 24 h/o hf, 1st preg, + pro C def, + FH, no previous VTE Postpartum prophylaxis
 - D. All of the above

How to “prophylax”

- Heparin products do not cross the placenta and are favored
- Optimal dose unclear
 - No studies comparing one dose to another
- LMWH preferred over UFH (Grade 1B)
 - More predictable
 - Less HITT
 - Less osteoporosis risk

Table 2. Commonly utilized anticoagulant regimens for the prevention of pregnancy complications.

Anticoagulant	Dosing regimen
<i>Low-molecular-weight heparin</i>	
<i>Prophylactic dose</i>	
Dalteparin (Fragmin®, Pfizer Inc., NY, USA)	5000 IU q24h
Enoxaparin (Lovenox® or Clexane®, Sanofi-Aventis, Paris, France)	40 mg q24h
Tinzaparin (Innohep®, Leo Pharma, Copenhagen, Denmark)	4500 IU q24h or 75 U/kg q24h
Nadroparin (Fraxiparine®, GlaxoSmithKline, London, UK)	2850 IU once daily
<i>Intermediate dose</i>	
Dalteparin (Fragmin, Pfizer Inc., NY, USA)	5000 IU q12h or once daily adjusted to anti-Xa of 0.2–0.6 U/ml
Enoxaparin (Lovenox or Clexane, Sanofi-Aventis, Paris, France)	40 mg q12h or once daily adjusted to anti-Xa of 0.2–0.6 U/ml
The choice of anticoagulant and regimen is individualized according to patient risk and preference, drug availability and cost, and availability of laboratory monitoring facilities. Prophylactic doses of low-molecular-weight heparin may require adjustment at extremes of bodyweight. anti-Xa: Anti-factor Xa; q12h: Every 12 h; q24h: Every 24 h.	

Source: Bates, Expert Rev. Hematol. 6(3), 287-300 (2013)

Who should be tested for a thrombophilia?

- Increasingly done
- Benefits remain controversial
 - Do the benefits *justify* potential drawbacks?
 - Negative psychological effects
 - Difficulties with insurability
 - Bleeding risks with primary prophylaxis
 - Additional medical expenses
 - False reassurance from a negative test result
 - Effect of incorporating info into important life decisions
 - Should we have a family?
- Will results affect management?
 - No use when Rx indicated for other risk factors
- Generally, targeted screening more cost effective than universal screening → personal or family h/o.
 - TREAT study

Bottom-line on WHO should be tested...

- Testing MAY be indicated if first degree relative with h/o unprovoked or minimally provoked VTE at young age
 - If positive, may then recommend post-partum prophylaxis
 - In setting of *recurrent* pregnancy loss, screening for APLAs is recommended

Diagnostic Pearls for Acute DVT in Pregnancy

- D dimer and clinical prediction scores NOT validated
 - D-dimer physiologically increased in pregnancy. increases with gestational age
 - Exception: LEFt prediction rule → 100% negative predictive value
- High index of Suspicion/Low threshold for diagnostic study
 - Normal pregnancy causes many similar complaints
 - Atypically presentations not uncommon given higher incidence pelvic involvement
- Do Investigate concerning symptoms, Don't empirically treat
 - Teratogenic risk a/w imaging minimal vs. consequences of misdiagnosis
- Diagnostic studies
 - DUS preferred with excellent sensitivity/specificity
 - If negative → consider repeat in 3 days
 - MRV preferred for pelvic or proximal Iliac vein DVT
 - CXR: although often normal in PE, assists in ruling out other pathology
 - Oligemia, wedge deformity, or pleural effusion may be seen
 - CXR may assist in the decision b/t V/Q vs. CTA
 - Normal CXR= more likely to have diagnostic V/Q scan
 - Abnormal CXR= more likely to have diagnostic CTA
 - ECG: tachycardia, R axis shift

Imaging Modalities/Radiation Concerns

- 50k uGy (5 rads) → max rec exposure in pregnancy
- Fetal ionizing radiation values:
 - V/Q: 110-800 uGy
 - CTA: 10-130 uGy
- Risk of childhood CA:
 - V/Q > CTA
 - 1:280k vs. 1:10 m
 - 35 x RR increase
- Risk of maternal breast CA
 - CTA > V/Q
 - Up to 13% increased lifetime risk
 - Proliferative breast tissue absorbs 35 x more ionizing radiation than baseline

Therapeutic AC in setting of Pregnancy

- Adjusted-dose LMWH safe with low bleeding risk
 - In Acute PE, UFH infusion until stable generally favored
- Keep things simple
 - Dose adjustment not needed
 - Once daily just as good as BID dosing
 - Same dose throughout
- When using UFH...
 - Anticipate higher/more frequent dosing
 - Increased VOD → maternal blood volume increases 40-50%
 - Enhanced renal excretion
 - Increased protein binding

LMHW safety profile

Table 2. Safety of low molecular weight heparin (LMWH) use during pregnancy.*

Complication	Frequency, % (95% CI)
Antenatal bleeding	0.43 (0.22-0.75)
Allergic skin reaction	1.80 (1.34-2.37)
Osteoporotic fracture	0.04 (<0.01-0.20)
Thrombocytopenia (platelets $<100 \times 10^9/L$)	0.11 (0.02-0.32)
Confirmed HIT	0.00 (0.00-0.11)

Data are from Greer and Nelson-Piercy.¹³

*For all indications and all LMWH; $N = 2777$

Warfarin and Pregnancy

- 2 big issues...
 - 1. Teratogenicity
 - 2. Anti-coagulated fetus!
- Teratogenic effects (many)
 - Early phenomenon: 4th-8th wk. when major organs developing
 - Often don't even know pregnant
 - Nasal hypoplasia and stippled epiphyses
 - Likely not as common as once reported
 - ?increased risk of delayed neuropsychiatric issues
 - Higher miscarriage risk
 - Later in pregnancy: fetal bleeding, stillbirth

NOACs and pregnancy related VTE

- Zero Experience!!
- All clinical trials *excluded* pregnancy
- Dabigatran and Rivaroxiban →
“reproductive toxicity” in animal studies
- The specific proteases inhibited may play important roles in fetal development
- CHEST Guidelines:

3.0.4. For pregnant women, we recommend avoiding the use of oral direct thrombin (eg, dabigatran) and anti-Xa (eg, rivaroxaban, apixaban) inhibitors (Grade 1C).

Duration of AC for VTE

- Total Duration of AC: No data...
 - CHEST: “at least 3 months with Rx continued through Puerperium
 - If still pregnant at end of 3 months, unclear to continue at therapeutic levels vs. intermediate dose
 - If high risk for hemorrhage → consider intermediate dose
- LMWH → UFH last 2-4 weeks gestation
 - d/t spinal anesthesia concerns
 - Mitigate risk of epidural/spinal hematoma
 - shorter half-life, reversible
 - Easier to quickly verify clearance (Aptt)
 - Anesthesia Society consensus:
 - No needles within 10-12 h after last LMWH dose
 - Real world: most recommend 24 hours
 - No resumption of prophylactic LMWH sooner than 2 hours
 - Real world: 12 hours
 - Key: onset of labor = no more AC!
 - Optimal: stop all AC 24 hr. prior to onset labor/induction

Peri/Post-partum issues and AC

- IPC until ambulatory
 - Encourage ambulation
 - Treat pain aggressively to allow early ambulation
- Avoid re-initiation too soon...
 - Risk of post-partum hemorrhage may persist for up to 2 weeks
- Warfarin vs. LMWH
 - > 6 weeks: VKA conversion
 - < 6 weeks: stick with LMWH

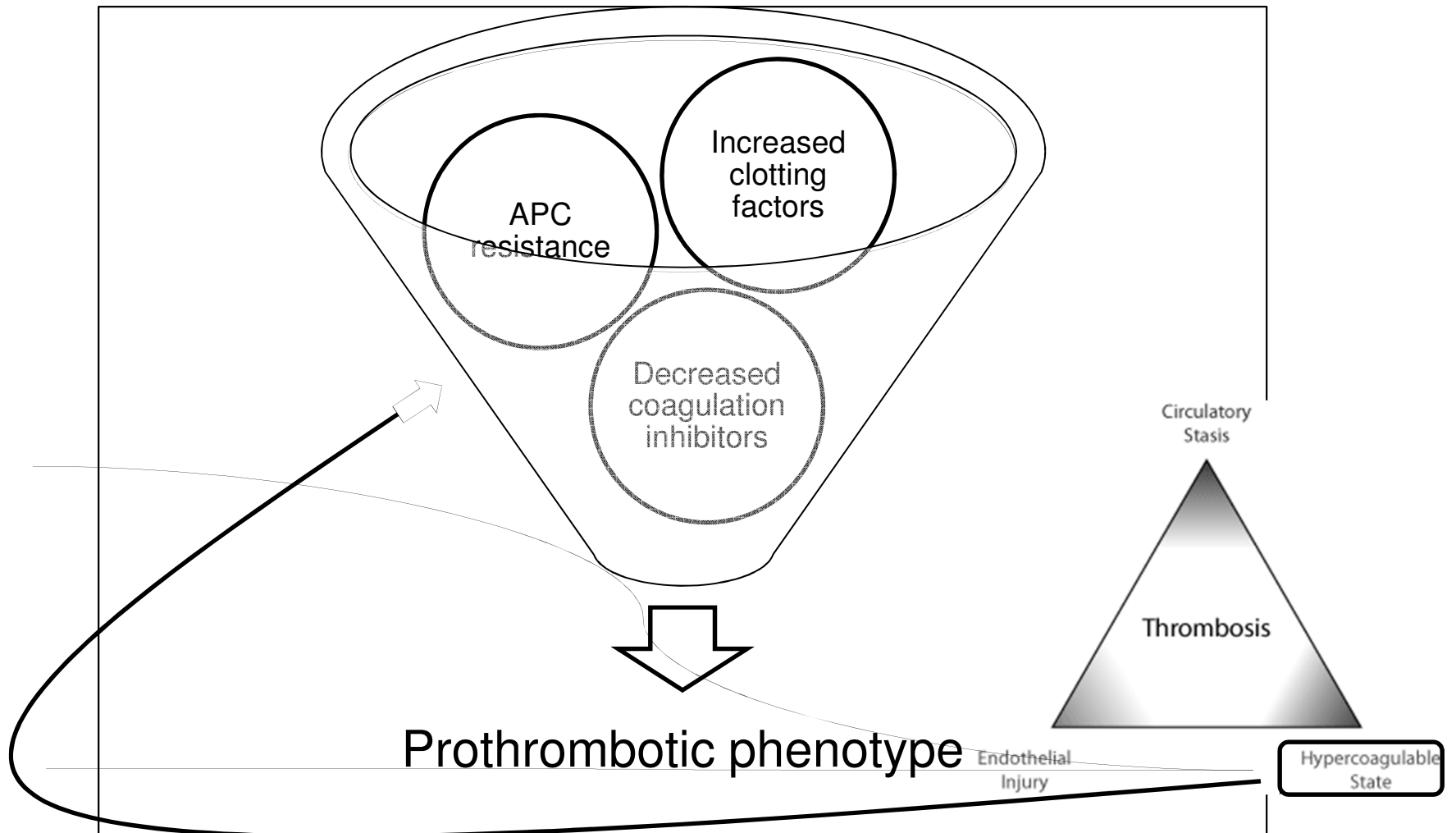


← 3rd generation progestin

2nd generation progestin



OCP Pathomechanisms



OCP+ pregnancy related VTE

- CCF: never again, period (circa 2011)
- CHEST Guidelines: not a word mentioned
- 1950's European population based studies → significant risk of 1st gen OCP
 - Led to substantial decrease in estrogen dose by 70s >50mcg → <30 mcg
- Highest risk: obese, smokers, known inherited thrombophilia
- Generally, a 2-6 fold increased risk with “combined hormonal contraception” (CHC)
 - Increased risk mediated by estrogen dose and type of progestin
 - Second generation progestin safer than newer (3rd gen) progestin
 - HR 1.6-1.8
- Non-oral preparations a/w increased risk
 - Transdermal patch (norgestimate) 7.9 x
 - Vaginal ring (etonogestrel) 6.5 x
- Progestagen only contraception (POC)
 - Selection bias likely → much more likely to have VTE risk factors
 - Danish registry study: conclusion → no increased risk
 - Recent systemic review and meta-analysis all published data → POC NOT a/w increased risk vs. non-users of hormonal contraception
 - Depot forms → conflicting data

HRT

- Likely same risk as OCP BUT...
 - Older, thus *much higher* risk overall vs. OCP
 - 51/100k/yr age 25
 - 207/100k/yr age 60
- Transdermal HRT → less risk
 - Preferred method if really needed in high risk groups
- Known CV effects
 - WHI

Bottom-line...

- Non-hormonal contraception preferred
 - Copper IUD, barrier methods, sterilization
- POC likely safe given recent data
 - Exception: depot preparations
 - Conflicting data
- Second safer than third generation
 - 3rd almost 2 fold increased risk over 2nd

To Summarize...

- VTE “small potatoes” on the world stage
 - Bleeding and infection much more deadly
- VTE much more relevant in “developed” (obese) nations
- We just don’t have a lot of good quality evidence in this area
 - Hence, many opinions
- Pathomechanisms of VTE hit all three of Virchow’s triad
- Acute VTE in Pregnancy can be subtle, more commonly involves the left proximal LE.
- Do not empirically treat without definitively making a diagnosis
 - Imaging related risks to mother/baby pale in comparison to missed dx

To Summarize...

- D dimer is out, clinical prediction tools taken with a “grain of salt”
- Rx Acute VTE with adjusted dose LMWH at least 3 months OR until 6 weeks postpartum recommended
 - Once daily dose, no dose adjustments
- The waters surrounding the question of who should get “prophylaxis” remain murky
 - If anything, *less* emphasis placed on thrombophilia in latest rendition of chest guidelines
 - All with previous VTE *no matter the cause* should get postpartum prophylaxis
 - The intra-societal fights continue!
- Remember, always involve the patient in these decisions!!
- Post pregnancy related VTE contraception should ideally *not* be with estrogen-containing medications
 - If unavoidable, Progestagen-only = safest bet.
 - Older Mustangs are clearly better than newer Mustangs!

Thank-you

Questions?

Suggested Reading

- Chest Guidelines 2012
- Jacobsen et al. VTE a/w Pregnancy and hormonal Rx. *Best Practice and Research Clinical Hematology* 2012 319-332
 - Great section on OCP
- ESHRE Capri Workshop Group. VTE in Women: a specific reproductive health risk. *Human Reproduction Update*. 19(5) 471-482, 2013
- Bates. Preventing thrombophilia-related complications of pregnancy: an update. *Expert Rev. Hematol.* 6(3), 278-300, 2013