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ILLUSTRATED REVIEW

Venous thromboembolism in pregnancy and postpartum: an illustrated review

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Abstract

The topic of this review is venous thromboembolism (VTE) during pregnancy and postpartum. The following topics will be addressed: epidemiology and pathophysiology of VTE in pregnancy and postpartum, diagnostic considerations for VTE in pregnancy, indications for prophylactic and therapeutic anticoagulation in pregnancy and postpartum, choice of anticoagulation in pregnancy and breastfeeding, anticoagulation management during labor and delivery, and anticoagulation considerations for assisted reproductive technology.

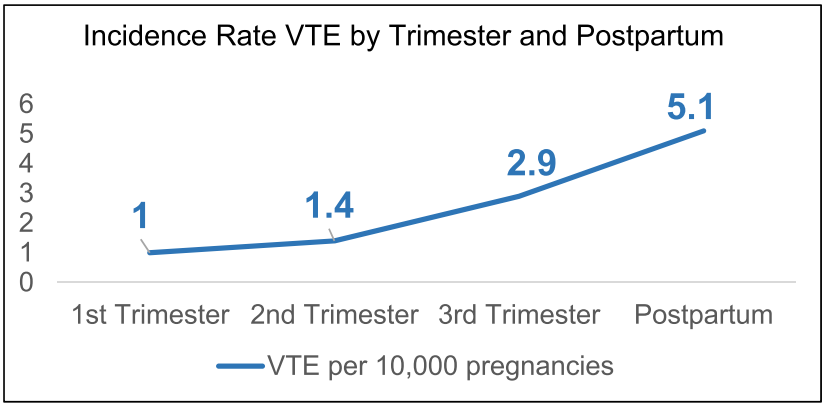
VTE in Pregnancy: Incidence and Biologic Basis

VTE Incidence Pregnancy & Postpartum

Deep vein thrombosis (DVT): **1 in 1000**

Pulmonary embolism (PE): **1 in 2500**

↑ VTE risk starts in the 1st trimester! When prophylactic anticoagulation is indicated, **START EARLY!** No later than 8 weeks gestation



VTE risk is highest in the first 6 weeks postpartum and returns to baseline after 12 weeks postpartum

Hypercoagulability in Pregnancy



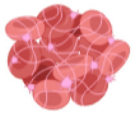
Decrease	Stable	Increase
Protein S	Antithrombin Protein C (may slightly ↑) Factor XI (may slightly ↓) Factors II, V, IX (may slightly ↑)	D-dimer Fibrinogen Factors VII, VIII, X, XII, XIII Von Willebrand (↑ 2-4 fold)!

Most hematologic parameters return to baseline levels 6-8 weeks postpartum, but some remain abnormal through at least 8 to 12 weeks after delivery.

VTE Risk Factors in Pregnancy and Postpartum

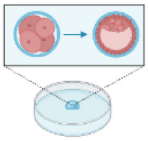
Systemic lupus erythematosus and antiphospholipid syndrome

Prior VTE – unprovoked or provoked (surgery or estrogen-related)



Heart disease (valvular, cardiomyopathy, other)

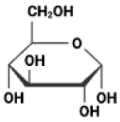
Family history of VTE (first degree relative)



Assisted reproductive technology

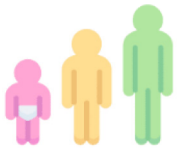
Obesity

May-Thurner: Right iliac artery compresses left iliac vein or other anatomic anomalies



Gestational diabetes

Sickle cell disease[8]



Grand multipara (≥5 prior pregnancies) or first pregnancy at ≥35 years of age

Labor & Delivery Risk Factors

- Preeclampsia and eclampsia
- Preterm labor
- Placenta previa
- Placental abruption
- Caesarean section
- Postpartum hemorrhage

Suspected PE in Pregnancy: Diagnostic Approach

Clinical Prediction Tool

Keep in mind: HR increases in pregnancy (normal physiology!)

Pregnancy-Adapted Geneva Score

1. *Age ≥ 40* ***(+1)***
2. *Surgery (under general anesthesia) or lower limb fracture in past month* ***(+2)***
3. *Prior VTE* ***(+3)***
4. *Unilateral lower limb pain* ***(+3)***
5. *Hemoptysis* ***(+2)***
6. *Pain on lower limb palpation or unilateral edema* ***(+4)***
7. *HR > 100 bpm* ***(+5)***

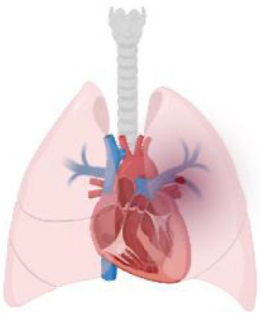
	Prevalence PE
0-1 points:	**2.3%**
2-6 points:	**11.6%**
≥ 7 points	**61.5%**

How is this helpful?
While this scoring system has not been validated as a method to determine who needs a CT scan, it provides a pre-test probability that clinicians may find useful in conjunction with clinical gestalt and the YEARS diagnostic algorithm.

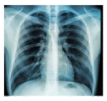
Diagnostic Algorithm

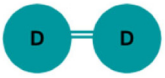
Pregnancy-Adapted YEARS Algorithm

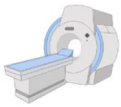
DVT missed in 0.21% (1/477)
No missed PEs



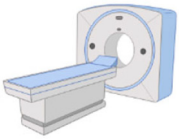
Imaging for VTE in Pregnancy





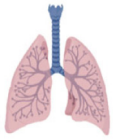


ULTRASOUND	CHEST X-RAY	D-DIMER	MRI
PROS non-invasive, no ionizing radiation **CONS** PE can occur in absence of DVT; Cannot visualize pelvic veins (iliac, gonadal) **BOTTOM LINE** First-line test for symptoms of DVT	**PROS** low dose radiation **CONS** normal chest XR does not exclude PE **BOTTOM LINE** Not useful for PE evaluation, though may identify alternative cause of symptoms	**PROS** simple blood test, no radiation; validated in pregnancy (though studies limited) **CONS** false-positive due to physiologic rise in pregnancy; false negatives occur too **BOTTOM LINE** Can be useful in combination with other data	**PROS** No ionizing radiation; ***non-contrast*** MR can detect proximal VTE missed by ultrasound (thigh, pelvis) **CONS** gadolinium use is controversial; animal studies show potential teratogenicity; MR pulmonary angiography requires gadolinium **BOTTOM LINE** Useful without contrast to diagnose proximal VTE



CT pulmonary angiography (CTPA)

Ventilation-perfusion scintigraphy (V/Q)



The preferred tests for PE in pregnancy are CTPA and V/Q

Choice of CTPA vs. V/Q depends on center availability & expertise

	CTPA	V/Q
Pros	may provide alternative dx; dose reduction techniques ↓ radiation	compared to CTPA, possible ↓ radiation to breast tissue
Cons	though no ↑ risk of fetal anomalies, *theoretical* ↑ risk of maternal breast and childhood malignancies	same theoretical risks as CTPE; potential ↑ radiation to fetus
Radiation to	0.002-0.51 (mGy)	0.2 - 0.7 (mGy)
Radiation to 	0.23 - 9.7 (mGy)	0.9 to 5.8 (mGy)
Non-diagnostic	12%	14%

Perspective: one transcontinental US flight is 0.035 mGy

Meta-analysis found no significant differences in radiation exposure or diagnostic efficiency. There is variation in radiation exposure due to differences in equipment and technical protocols across centers, as well as methodologies for calculating dose.

Lead shields may be used depending on institutional protocols. They are no longer recommended universally since they may interfere with the technology and increase the total amount of radiation needed

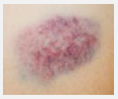
Anticoagulant Safety in Pregnancy

Medication	Considerations
Heparins	Do not cross placenta; extensive observational safety data
Danaparoid	Does not cross placenta and considered safe (can be used for heparin-induced thrombocytopenia)
Fondaparinux	Crosses placenta minimally; likely safe (limited data)
Warfarin	Crosses placenta, teratogenic; highest risk 6-12 weeks gestation and dose >5mg/daily, though toxicity outside this period and at lower doses reported
DOACs	Crosses placenta; unknown risk and safety concerns exist from limited human data

LMWH Safety Specifics

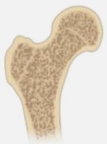
Bleeding

↑ risk bleeding peripartum including postpartum hemorrhage (PPH)
LMWH relative risk PPH: ~1.5; absolute risk of PPH varies by setting and mode of delivery; baseline risk of severe PPH in the US is 0.03%



Skin reactions

Minor reactions are common, serious reactions rare
Switching LMWH agents can help



Osteoporosis

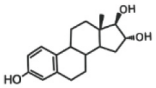
Negligible risk if used exclusively for pregnancy. A study of LMWH in pregnancy found **NO** impact on bone mineral density
In contrast, unfractionated heparin (UFH) has a greater impact on bone density loss, but this is primarily with long-term use

Heparin-induced thrombocytopenia (HIT)

Exceedingly rare
LMWH carries substantially lower risk of HIT compared to UFH
Absolute risk: ~0.2% versus 2.6%

Indications for Anticoagulation

A) Indications for Prophylactic Anticoagulation



1. History of **estrogen-provoked VTE**
2. Inherited **thrombophilia** (Conditional – See table)
3. Other **high-risk individuals** (See Note)

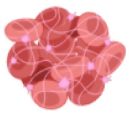
Thrombophilia	Antepartum	Postpartum
History of estrogen-provoked VTE; homozygous FVL; compound heterozygous FVL/PGM	YES	YES
Family history of VTE + homozygous PGM or antithrombin deficiency	YES	YES
Family history of VTE + protein C or S deficiency, or homozygous PGM without family history	No	YES
History of VTE with non-hormonal transient risk factor (trauma, surgery), not on anticoagulation at baseline	No	YES
Any other inherited "thrombophilia" (heterozygous FVL, heterozygous PGM, other)	No	No
Abbreviations: FVL – Factor V Leiden; PGM – Prothrombin Gene Mutation Recommendations from American Society of Hematology 2018		

Note:

Recurrent Miscarriage: prophylactic AC has NOT shown benefit for individuals w/ inherited thrombophilia & recurrent miscarriage (ALIFE trial)

Antiphospholipid Antibodies: prophylactic AC & aspirin may benefit pregnant patients who have antiphospholipid antibodies w/ history of recurrent pregnancy loss, even without prior thrombosis

B) Indications for Therapeutic Anticoagulation



1. **NEW** VTE in pregnancy or postpartum
   → Duration of therapy 3-6 months
   → Minimum 6 weeks postpartum
2. **CONTINUATION** of therapy in patient on **long-term anticoagulation** (including most patients taking reduced-dose DOAC therapy)

Prophylactic Anticoagulation

When to **start** prophylactic AC?
- First positive pregnancy test, or
- Ultrasound-confirmed pregnancy; no later than 8 weeks

When to **stop** prophylactic AC?
- 6 weeks postpartum is standard, consider extending in high-risk patients

Which medication**? LMWH** (Consider UFH in renal dysfunction)

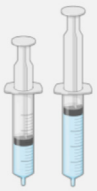
What **dose** of prophylactic AC?
- **Low-dose**, based on ***Highlow*** trial
- Consider **weight-adjusted intermediate dose** for patients with a concerning history (hemodynamically significant PE, limb-threatening DVT) as there was a non-significant trend toward increased postpartum PE in low-dose arm

1110 pregnant women with history of VTE randomly assigned

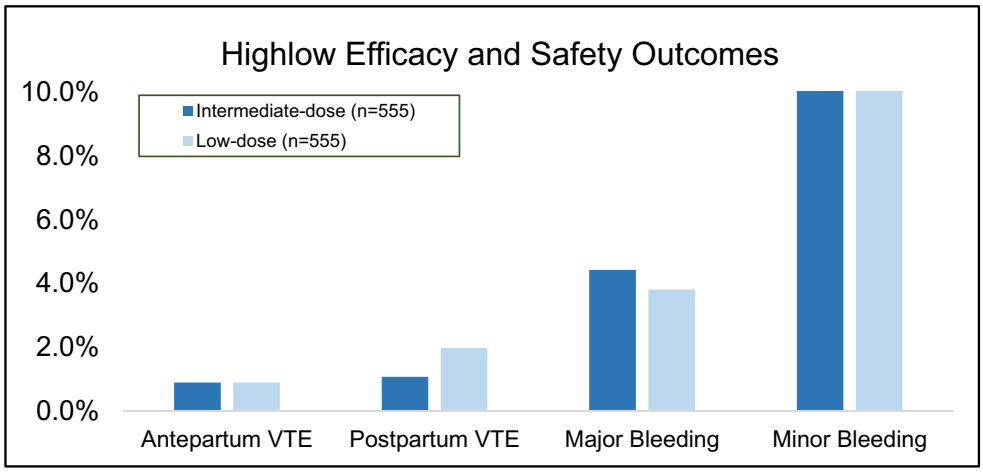
81% related to pregnancy, postpartum, or hormone-associated; others: minor or major transient risk factor, unprovoked

→ **555** assigned to weight-adjusted intermediate dose LMWH

→ **555** assigned to fixed low-dose LMWH



Median follow-up: 247 days



LMWH Dosing. Low-dose options for thromboprophylaxis, based on ***Highlow***

	Nadroparin	Enoxaparin	Dalteparin	Tinzaparin
<100 kg	2850 IU	4000 IU (40 mg)	5000 IU	3500 IU
≥100 kg	3800 IU	6000 IU (60 mg)	7500 IU	4500 IU

All doses are administered once daily. IU=international unit.

Therapeutic Anticoagulation

Options for patients taking **long-term oral-anticoagulants trying to conceive**

OPTION 1

Preconception: VKA / DOAC → 

Switch to LMWH preconceptually

PROS: ↓ need frequent pregnancy tests (↓ expense; ↑ convenient)
CONS: ↑ injections, particularly if conception not achieved quickly

OPTION 2

Early Pregnancy: DOAC → 

Switch DOAC to LMWH @ 1st positive pregnancy test

PROS: ↓ injections
CONS: DOAC safety data during pregnancy is limited
*Note: not endorsed by 2016 ISTH guidelines

⚠ OPTION 3

Preconception: DOAC → VKA

Early Pregnancy: VKA → 

Switch DOAC → VKA preconception, or continue VKA, then

Switch VKA → LMWH @ 1st +pregnancy test

PROS: Fewer injections
CONS: VKA =teratogen; may not know of pregnancy right away

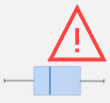
⚠ ***ISTH guidelines present option 3; however, many experts prefer options 1 and 2***

Therapeutic anticoagulation in pregnancy: Dosing and Monitoring

	Nadroparin	Enoxaparin	Dalteparin	Tinzaparin
Once daily	171 units/kg	1.5 mg/kg	200 units/kg	175 units/kg
Twice daily*	86 units/kg	1 mg/kg	100 units/kg	†100 units/kg

**There is a lack of evidence to support once versus twice per day dosing; it is possible that once per day dosing could lead to undesirably low trough levels; however, it is more convenient for patients. Shared decision making is appropriate.*
†Variable dosing strategies have been reported for twice daily Tinzaparin
The authors practice in the United States where enoxaparin is the predominant LMWH; dosing suggestions for nadroparin, dalteparin, and tinzaparin are based on literature review and an informal email survey of experts in Europe and Canada.

Is monitoring LMWH anti-Xa levels recommended?



Available evidence *does not* support the need for monitoring

The *appropriate therapeutic range is unclear* and may vary by laboratory

Consider monitoring if: extremes of weight or significant weight gain, renal dysfunction, large thrombotic burden, recurrent VTE on anticoagulation

Anticoagulation in Labor and Delivery

A) For pregnant patients on **therapeutic anticoagulation**, should you **schedule induction** or **allow spontaneous labor**?

Both are options; shared decision-making is appropriate.

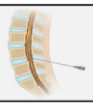
If induction planned, discontinue LMWH 24h prior.

It is not our practice to switch to UFH. In theory, this could improve access to epidural anesthesia due to shorter half life. For very high-risk patients (e.g., recent proximal DVT) a heparin infusion can be considered in early labor.

PROS of scheduled induction	CONS of scheduled induction
Improved access to neuraxial analgesia Might be associated with reduced risk PPH (low quality evidence)	Increased medicalization of delivery and *possible* increased risk of medical interventions such as caesarean Spontaneous labor before date of induction may occur regardless

Note: For patients receiving **prophylactic dose** anticoagulation, most experts prefer allowing for spontaneous onset of labor

B) If **spontaneous labor** occurs, is it safe to proceed with **neuraxial anesthesia**?



Neuraxial anesthesia can be safely performed guided by the following recommendations from Society for Obstetric Anesthesia and Perinatology. While other guidelines exist, anesthesiologists collaborating with hematologists are likely to prefer their own society's guidelines.

Prophylactic Dose LMWH e.g. enoxaparin 40 mg SQ daily	≥ 12h since last dose →
Intermediate Dose LMWH e.g. enoxaparin 60 mg SQ daily	≥ 12-24h since last dose →
Therapeutic Dose LMWH e.g. enoxaparin 1 mg/kg SQ twice daily	≥ 24h since last dose →

⚠ If the level of anticoagulation is uncertain, an anti-Xa level can be checked. While the threshold for safe neuraxial anesthesia is unknown; an undetectable level is reassuring.

Anticoagulation Postpartum and Breastfeeding

Labor & Delivery: when should anticoagulation be resumed postpartum?

Data limited; clinical judgment needed to weigh thrombosis/bleeding risks

One study showed higher rates of bleeding if therapeutic heparin resumed earlier than 9.25h after vaginal or 15h after cesarean delivery

High thrombotic-risk: low or intermediate dose heparin as early as 4h after vaginal delivery and 6h after caesarean (escalation to therapeutic dose 6-12h after vaginal delivery and 12-24h after cesarean)

Standard thrombotic-risk: 6-12h after vaginal delivery; 12-24h after cesarean

Acute VTE in pregnancy: what is the treatment duration?

At least **6 weeks post-partum** and a minimum **3-month total duration**

Breastfeeding: Which anticoagulants are considered safe?

✔ Warfarin and other vitamin K antagonists ✔ UFH and LMWH

✔ Fondaparinux and danaparoid (limited data – likely safe as heparins are present in low levels in breastmilk and furthermore have minimal bioavailability to be absorbed orally by the infant)

DOAC Safety and Breastfeeding?

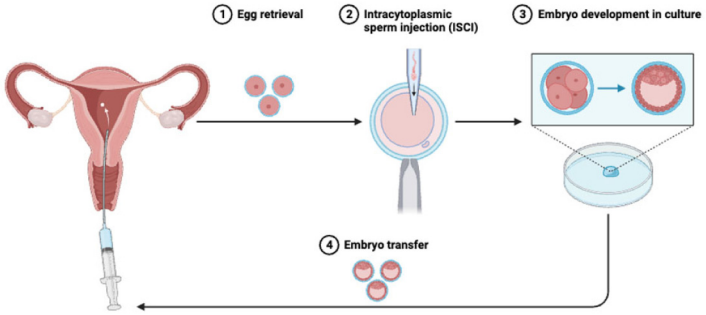
⚠ Safety data for DOACS during breastfeeding is limited. However, rivaroxaban and dabigatran levels in breastmilk are far below doses used to anticoagulate in infants. While these medications are unlikely to be harmful, experience is limited. Breastfeeding patients may consider the use of rivaroxaban or dabigatran after an informed risk/benefit discussion.

⊖ Concentrations of apixaban are slightly higher in breastmilk; furthermore, in contrast to rivaroxaban and dabigatran, apixaban has not been tested and FDA-approved for use in infants. Thus, apixaban should be avoided.

Assisted Reproductive Technology

Assisted Reproductive Technology (ART): fertility-related treatments in which eggs or embryos are manipulated

Steps involved in ART



Clomiphene or letrozole are often used for ovulation induction in patients attempting natural conception. These medications are not expected to increase VTE risk based on mechanism of action and studies in other contexts.

Step	Hormonal considerations	Prophylaxis indicated?
1. Preparation for oocyte retrieval	May involve pretreatment with estrogen-containing oral contraceptives Exogenous gonadotropins (follicle-stimulating hormone (FSH) and luteinizing hormone (LH)) are used for controlled ovarian stimulation. Ovaries produce estrogen in response to exogenous gonadotropins	*Most experts recommend prophylaxis if patient would qualify for antepartum prophylaxis on the basis of their VTE history or high-risk thrombophilia (CAPSULE 7)* AND/OR IF **ovarian hyperstimulation syndrome** occurs
2/3. Intracytoplasmic sperm injection and embryo development in culture	Patient may have a break from hormonal therapy during this time. There can be a multi-year gap between egg retrieval and embryo transfer	In many circumstances, no prophylaxis indicated during this phase
4. Embryo transfer	Following embryo transfer, exogenous progesterone and estrogen are used to promote implantation and pregnancy continuation	*IF patient qualifies for antepartum prophylaxis on the basis of their VTE history or high-risk thrombophilia (CAPSULE 7)*

Ovarian hyperstimulation syndrome (OHHS):

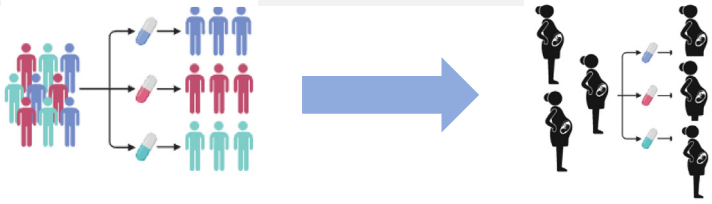
- Exuberant ovarian response to gonadotropins, evidenced by multiple follicular development, high serum estradiol concentrations, and ovarian enlargement
- Vasoactive substances lead to ↑ extravascular fluid (e.g., edema, ascites, effusions) and intravascular hypovolemia (↓ renal perfusion, end organ damage)
- Increased risk of thrombosis is likely multifactorial

Egg retrieval is a minor surgical procedure.
It is reasonable to hold LMWH for 24 hours beforehand and resume the following day, or at the discretion of the proceduralist

Continue prophylaxis for 2-4 weeks after discontinuing estrogen containing therapies

Future Directions

High quality research is urgently needed for pregnant and postpartum populations at risk for VTE and with a new diagnosis of VTE.
Most recommendations are conditional with low certainty in evidence.



Select topics warranting additional study:

1. Role of prophylactic anticoagulation for patients with sickle cell disease in pregnancy and postpartum
2. Safety and efficacy of once versus twice daily dosing for therapeutic LMWH
3. Role of anti-Xa monitoring
4. Management of anticoagulant therapy around the time of delivery (planned induction; timing of neuraxial anesthesia)
5. Safety of DOACS in pregnancy and breastfeeding

Current Ongoing Clinical Trials as of December 2023	
Trial	**Design**
Aspirin vs LMWH for postpartum VTE prevention (LEAP) Clinicaltrials.gov ID: NCT05058924	Single center pilot, randomized controlled trial assessing postpartum prophylactic anticoagulation with 3 weeks of LMWH followed by 3 weeks of aspirin compared to standard of care of prophylactic LMWH for 6 weeks
Postpartum aspirin to reduce VTE in selected high-risk patients (Pilot PARTUM) Clinicaltrials.gov ID: NCT04153760	A randomized trial of aspirin versus placebo for postpartum women at ***modest*** risk of VTE (examples: heterozygous factor V Leiden, immobilization, cesarean delivery and obesity, and others).
Assessing Women's Preferences for Postpartum Thromboprophylaxis: the PREFER-PostPartum (PREFER-PP) Clinicaltrials.gov ID: NCT05318547	This study is conducting interviews using the “standard-gamble” technique to determine threshold of risk of postpartum venous thromboembolism at which women prefer the use of short-term postpartum thromboprophylaxis with LMWH over no treatment.

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AUTHOR CONTRIBUTIONS

A.K.F. and B.S.B. made substantial contributions to this article through conception and design, drafting and revising critically for important intellectual content, and approval of the final version.

RELATIONSHIP DISCLOSURE

No conflicts of interest, financial or other, exist.

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