MATERNAL911®

# Venous ThromboEmbolic Disease

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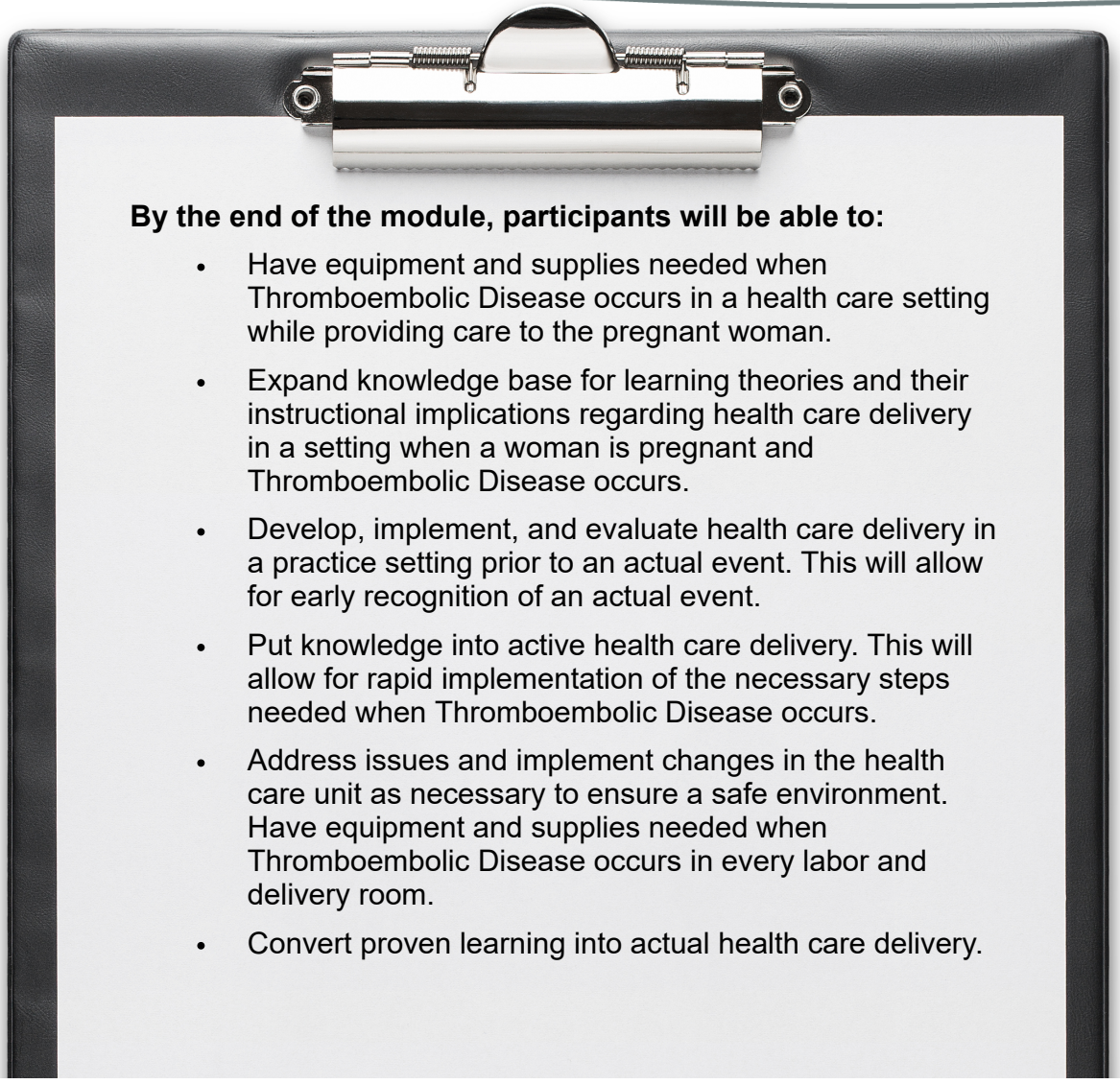
**Course Description:**

Venous thromboembolic (VTE) disease is a high acuity, low occurring process that when recognized can be managed. The course will help by giving understanding of the disease and its management. VTE is a detrimental disease process that is life threatening for the women it effects. The VTE course will provide knowledge for treatment of the pregnant woman while keeping the fetus safe.

**Approximate Time to Complete:** 70 minutes

***Click here to download a print version of this course.***



**By the end of the module, participants will be able to:**

- Have equipment and supplies needed when Thromboembolic Disease occurs in a health care setting while providing care to the pregnant woman.
- Expand knowledge base for learning theories and their instructional implications regarding health care delivery in a setting when a woman is pregnant and Thromboembolic Disease occurs.
- Develop, implement, and evaluate health care delivery in a practice setting prior to an actual event. This will allow for early recognition of an actual event.
- Put knowledge into active health care delivery. This will allow for rapid implementation of the necessary steps needed when Thromboembolic Disease occurs.
- Address issues and implement changes in the health care unit as necessary to ensure a safe environment. Have equipment and supplies needed when Thromboembolic Disease occurs in every labor and delivery room.
- Convert proven learning into actual health care delivery.

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**Venous ThromboEmbolic Disease**

*Collectively deep venous thrombosis (DVT) and pulmonary embolism (PE) are referred to as venous thromboembolic disease (VTE).*

*Well established risk factors for VTE, DVT and PE are pregnancy and the puerperium.*

- Fortunately, the prevalence of VTE in pregnancy is low.
- The diagnosis of VTE occurs 1 in 500 - 2000 pregnancies within the United States [1-7].
- The incidence of VTE was 85 per 100,000 pregnancies in a retrospective case-control study of 395,335 pregnant women at 24 weeks of gestation [14].
- An overall incidence of VTE was 200 per 100,000 women-years in a population-based inception cohort study over a 30 year period [5].
- Compared to PE, DVT was three times more common [5].

# Occurrence

***PE accounts for 9% of maternal deaths and is the seventh leading cause of maternal mortality [9-11].***

- In comparison, black women have a three to four times higher pregnancy related mortality rate than white women.
  - Deaths from VTE are higher in black women and the reasons for this cannot be directly attributed to increased rates of VTE [8].
- The largest racial disparity occurs with pregnancy related mortality in the maternal and child health indicators [11].

***Carefully consider the risk assessment protocols available and adopt them in a systematic way to reduce the incidence of VTE in pregnancy and postpartum.***

***Click here to learn more about occurrence of VTE.***

# Occurrence

From the late 1990's to early 2000, the incidence of VTE appears to decrease, largely due to a decrease in postpartum VTE incidence [5, 12].

- This change is unclear but could be due to the general increase in the use of thrombo-prophylaxis in the postpartum period.

However, VTE associated pregnancy hospitalizations between 1994 and 2009 reports an increase of 14% with a concomitant increase in comorbid conditions such as obesity and hypertension among those admitted for VTE [13].

DVT's account for 75-80% of VTE cases in pregnancy, with PE accounting for the other 25%. One half occurs in pregnancy and the other half postpartum [43].

- When comparing to non-pregnant women, there is an incidence 4 to 50 times higher in pregnancy to develop a VTE [1-6, 93].
- A personal history of thrombosis is the most important risk factor for VTE in pregnancy, increasing a woman's risk 3-4 fold [36].
- VTE has the highest risk in the postpartum period with higher than usual prevalence in the left lower extremity and pelvis.
- Further risk occurs in women with inherited thrombophilias.

- Compared to the nonpregnant population, the risk of VTE is higher in all stages of pregnancy, however, it is greatest in the postpartum period.
  - Equal distribution of VTE across trimesters of pregnancy are found in most studies [1, 2, 13-17].
  - However, there has been two large retrospective studies showing predominance in the first trimester (50% before 15 weeks) and third trimester (60%) [18, 19].

The list below includes factors that increase the risk of VTE antepartum, but are less well described:

- Multiple Gestation [20]
- Varicose veins [21]
- Inflammatory bowel disease [20]
- Urinary tract infection [20]
- Diabetes [20]
- Sickle Cell Anemia [67]

- Hospitalization for non-delivery reasons (particularily those >3 days) [21]
- Body mass index (BMI) ≥3kg/m2 [21]
- Increased maternal age ≥35 years [21]

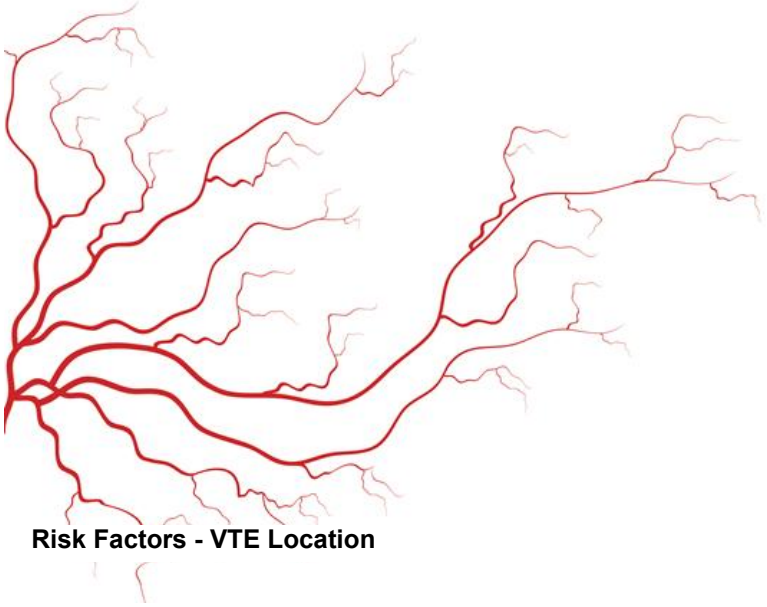
- As previously mentioned, the risk of VTE is 2-5 times more common postpartum compared to the antepartum period [22-24].
- For the first six weeks postpartum, the risk is highest and slowly declines to rates approximate to that of the general population by 13-18 weeks [22].

- Commonly cited factors that increase the risk of VTE postpartum include the following [14,17,19, 20, 22-24]:
  - Cesarean delivery (a fourfold increase risk compared to vaginal birth) [93]
  - Medical comorbidities
    - Varicose veins
    - Cardiac disease
    - Inflammatory bowel disease
  - Body mass index (BMI) ≥25kg/m2
  - Young gestational age
    - Preterm delivery <36 weeks gestation
  - Obstetric hemorrhage
  - Stillbirth
  - Increased maternal age ≥35 years
  - Hypertension
  - Smoking
  - Eclampsia or preeclampsia
  - Postpartum infection

- The absolute risk of VTE postpartum appears to be quite low after six weeks, but is certainly highest the first six weeks postpartum [20, 21, 23].
- The majority of thrombotic events are from VTE (68%) followed by stroke (28%) and myocardial infarction (4%) [20, 21, 23].
- Those with thrombotic events were more likely to be older (35 years or older), have risk factors for thrombosis (i.e. eclampsia, hypercoagulable state, smoking, cesarean section) and be white or black rather than Hispanic or Asian [20, 21, 23].

Interestingly, the majority of lower extremity DVT's occur on the left side during pregnancy and most commonly in the proximal veins (i.e. femoral). In addition, pelvic vein thrombosis is significantly higher during pregnancy and the puerperium.

There is no research describing an increased incidence of upper extremity DVT during pregnancy nor the puerperium.



**Risk Factors - VTE Location**

## Left Lower Extremity DVT

- DVT is predominantly left-sided in pregnancy (70 to 90%).
- In a study of sixty pregnant women with a first episode of VTE, there were 58 isolated left lower extremity DVT's, two bilateral and none in the right lower extremity [13].
- In a retrospective study of 124 pregnant women with a DVT, the left leg was affected in 88% of the women [25].
- The left leg large distribution has been attributed to increased venous stasis in the left leg related to compression of the left iliac vein, coupled with compression of the inferior vena cava by the gravid uterus [14, 26, 27].

## Pelvic Vein DVT

- Pelvic vein DVT is more commonly diagnosed in pregnancy than in the general population.
- The true prevalence in pregnancy is unknown and may be due to poor sensitivity of compressing the proximal vein during ultrasound for the diagnosis of thrombosis in the pelvic veins [28].

The VTE risks are higher in pregnant women who have inherited thrombophilias [4, 29-35]. Discussing these thrombophilias in detail is beyond the scope of this program.

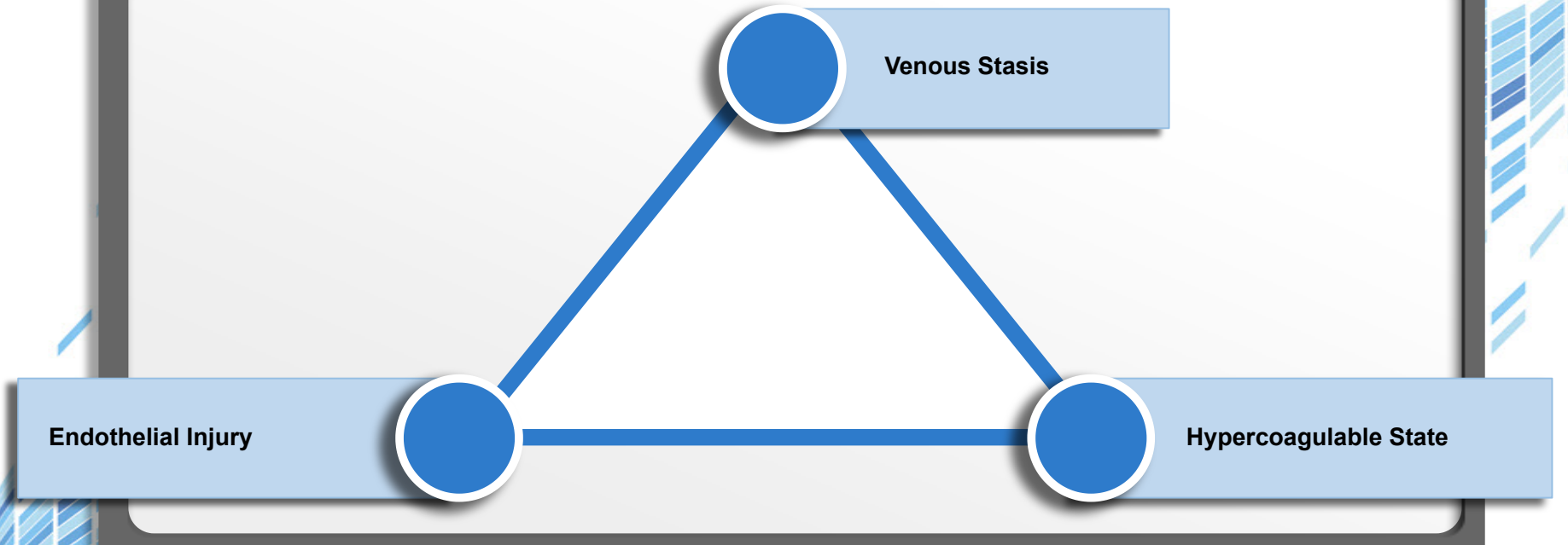
The table below reviews high versus low risk thrombophilias [36].

| Low Risk Thrombophilia | High Risk Thrombophilia |
|---|---|
| Factor V Leiden Heterozygous | Antithrombin deficiency |
| G20210A Heterozygous | Double heterozygous Prothrombin G20210A & Factor V Leiden |
| Protein C deficiency | Factor V Leiden Homozygeous |
| Protein S deficiency | Prothrombin G20210A Mutation Homozygeous |
| | Antiphospholipid Syndrome |

**Briefly, the most common inherited thrombophilias are illustrated with the following studies, with variable range in risk of VTE in pregnant patients.**

- The thrombotic risk is three times higher for pregnant women with factor V Leiden, compared to the general population [29].
- Pregnant patients with factor V Leiden deficiency and G20210A prothrombin gene mutation along with a history of prior VTE or an affected first degree relative have up to a 50-fold increased risk of VTE [35].
- Pregnant women with an inheritable deficiency of antithrombin III, protein S, or protein C have an 8-fold increase risk of venous thrombosis in the antepartum and postpartum periods combined, compared to pregnant women without a known thrombophilia [30].
- One study described a 5% risk of thrombosis during pregnancy among women with known antiphospholipid syndrome [37].

All three components of Virchow's triad are known to occur in pregnancy and postpartum [2]:




These three features likely contribute to the increased risk of VTE in pregnancy.

Two factors lead to venous stasis of the lower extremities during pregnancy:

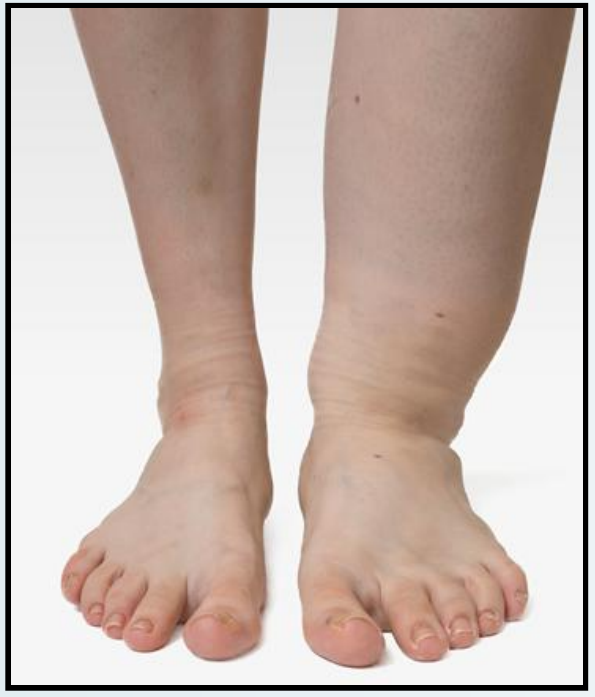
- Pregnancy-associated changes in venous capacitance
- Compression of large veins by the gravid uterus.

The increased venous stasis during pregnancy appears to occur even before the uterus has enlarged substantially.

The venous pooling and valvular incompetence are due to hormonally induced dilation of capacitance veins decreasing the linear flow velocity in the lower extremities, although blood volume and total venous return are supra-normal in pregnancy [38].

- Pathogenesis shows early changes amplified by inferior vena cava and iliac vein compression by the gravid uterus [38, 40].
- The left sided predilection of DVT in pregnancy is thought to be compounded by compression of the left iliac vein by the right iliac artery [1, 39].
- Pathogenesis for VTE in pregnancy is thought to involve endothelial injury. Delivery is associated with vascular injury and changes at the uteroplacental surface, likely contributing to the increased risk of VTE in the immediate postpartum period.
- Vascular intimal injury can be exaggerated by forceps, vacuum, or surgical delivery and amplify this phenomenon [1].

- During pregnancy, protein S is noted to decrease; however, with pregnancy being a known hypercoagulable state, it is associated with progressive increases in several coagulation factors including factors I, II, VII, VIII, IX, and X [1, 29, 41,42].
- A resistance to activated protein C shows a progressive increase, normally observed in the second and third trimester [36, 43] and one study showing high resistance to activated protein C associated with an increased risk for pregnancy related venous thrombosis [44].



**Clinical Features**

- Normal pregnancy and the puerperium features overlap with clinical features of DVT in pregnancy.
- Thus, it can be difficult to distinguish the clinical features associated with the hemodynamic changes of pregnancy from clinically important DVT.
- The clinical presentation of DVT in pregnancy is identical to a non-pregnant woman, other than the higher propensity to develop left-sided DVT and iliac vein thrombosis.
- When the proximal vein has a thrombus, the signs and symptoms to suggest this diagnosis are diffuse pain and swelling that may or may not be associated with erythema, warmth and tenderness of the lower extremity.
- Iliac vein thrombosis has symptoms including swelling of the entire leg with or without flank, lower abdomen, buttock or back pain [45].

**Laboratory Considerations**

- Compared to the general population, D-dimer has limited diagnostic value in pregnant women suspicious of having a DVT.
- Arterial blood gases are not routinely indicated to diagnose DVT.
- There have been extensive studies for the use of serum D-dimer, a breakdown product of cross-linked fibrin, for serum assays (enzyme linked, turbidimetric, hemaglutination).
- The negative predictive value of D-dimer in ruling out DVT is high in non-pregnant patients, particularly when combined with clinical probability models or with a negative compressive ultrasound.
- D-dimer increases during pregnancy, making this test not useful during pregnancy, although the negative predictive value remain high.
- D-dimer has limited utility in pregnancy, largely due to the natural rise in D-dimer with each trimester and slow decline postpartum.
- There are not established normal reference ranges during pregnancy, thus the altered levels of D-dimer throughout pregnancy and the puerperium are subject to misinterpretation.
    - False negative D-dimer's have been reported in pregnant women with DVT or PE [36].

- The majority of research to support the imaging for diagnosing DVT in pregnancy is extrapolated from large studies in the non-pregnant population with smaller studies suggesting similar efficacy in pregnancy.
- DVT in pregnancy is most often diagnosed by demonstrating poor compressibility of the proximal veins on compression ultrasound (CUS).
- Rarely is the diagnosis of DVT made by noting a filling defect on CT or MRI.
- In both pregnant and non-pregnant patients the proximal vein CUS is highly sensitive and specific diagnostic study for the diagnosis of DVT.
- However, CUS is less sensitive for pelvic vein thrombosis (more common in pregnant women) and for calf vein thrombosis (less common) [28].
- When CUS is negative, poor doppler flow in the iliac vein has reasonable accuracy for the diagnosis of suspected pelvic vein DVT; obtaining serial compression ultrasound is sensitive strategy utilized to follow suspected calf vein DVT in the rare circumstances it propagates normally.

*Click the left and right arrows to see more.*

## Compression Ultrasonography (CUS)

- For diagnosing symptomatic proximal vein thrombosis, in pregnant patients, poor compressibility of a thigh vein with ultrasound probe is highly sensitive (95%) and specific (>95%) [50].
- To assist in diagnosing isolated iliac vein thrombosis during pregnancy, patient positioning in the left lateral decubitus and the addition of doppler analysis for flow variation with respiration helps [46].
- When positive, the diagnosis of DVT by CUS in a pregnant patient should prompt immediate anticoagulation.
- As discussed before, CUS is less sensitive for pelvic vein thrombosis and for calf vein thrombosis [28].
- When CUS is negative, pelvic vein thrombosis may be suspected when the visualized vein is compressible, but the absence of normal changes of flow during respiration or with valsalva occur.
- Utilizing serial CUS can detect suspected calf vein thrombosis that propagates proximal as progression of pregnancy occurs.

*Click the left and right arrows to see more.*

## Serial Compression Ultrasonography

- Calf vein thrombosis can propagate proximally in approximately 20% of cases in non-pregnant patients [48].
- In non-pregnant patients, it has been validated performing day 3 and day 7 serial CUS has detected suspected calf DVT in the setting of initially negative CUS [48, 49].
- Using this modality to follow non-pregnant patients with suspected DVT with initial negative CUS, only 2% are subsequently diagnosed with DVT [48].
- This same finding has been replicated in pregnancy with a small number of prospective studies.
- A prospective study from a single center of 221 women with suspected DVT and initial negative ultrasound showed serial proximal CUS excluded DVT with sensitivity of 94.1% and negative predictive value of 99.5% at three months [50].
- In a similar pregnant population, two additional studies (one retrospective and another observational) imaged the whole leg with serial CUS and very few DVT"s detected in the follow up period after the initial negative testing [51, 52].
- In conclusion, regarding CUS, these studies suggest similar findings to what is found in the general population, showing serial CUS is valuable as a sensitive modality to image and diagnose the rare cases of calf DVT that propagates proximally during pregnancy.

*Click the left and right arrows to see more.*

## Magnetic Resonance Venography

- A modality that can detect both thigh and pelvic vein DVT with a sensitivity approaching 100% in the non-pregnant population is magnetic resonance venography [53].
- Data is limited in pregnancy.
- Data is limited in pregnancy, however, small case series of pregnant patients suggest this modality is useful for the diagnosis of pelvic and femoral vein thrombosis in situations where other non-invasive exams were equivocal [54, 55].

*Click the left and right arrows to see more.*

## Ascending Contrast Venography

- In the non-pregnant population, the gold standard for diagnosing lower extremity DVT is visualizing a filling defect by ascending contrast venography [57, 58].
- In pregnancy, venography is rarely performed due to concerns of exposure of ionizing radiation to the fetus, technical difficulties of femoral vein cannulation and decreased sensitivity for isolated ileofemoral thrombosis due to abdominal pelvic shielding [1, 47, 56].
- The alternative imaging test, CUS, approaches venography in diagnostic sensitivity and specificity without these risks, rendering contrast venography less useful for the diagnosis of DVT [1, 47, 56].

**Diagnosing VTE**

- To diagnose VTE successfully in pregnancy and the puerperium, it requires clinicians to have a high index of clinical suspicion and a low threshold to order objective confirmatory tests.
- To diagnose DVT in pregnancy, the approach is consistent with evidence-based guidelines published by the American College of Chest Physicians (ACCP) in 2012 and the American College of Obstetricians and Gynecologists (ACOG) in 2018 [67, 36].
- The ACCP and ACOG guidelines are resources for the clinician regarding testing and implementation of anticoagulation based on individual assessment of a pregnant woman suspected of having a DVT.

**Pretest Probability** | **Wells Score** | **D-dimer**

Predictive scoring systems (i.e. Wells score), the LEFt clinical prediction rule and D-dimer levels have had potential clinical probability assessment tools for the diagnosis of suspected DVT.

Unfortunately, these tools have not been validated in large prospective trials and are less useful in pregnant women compared to the general population.

Thus, the LEFt clinical prediction rule should not be used as a standalone test to exclude DVT and needs further validation in a larger population before it can be routinely applied in clinical practice.

***Click the terms to see more information.***

Pretest Probability | **Wells Score** | D-dimer

For non-pregnant patients suspected to have DVT, the Wells and modified Wells scoring systems are the most common.

Unfortunately, these are not validated for use in pregnancy and should be interpreted with much caution in this population.

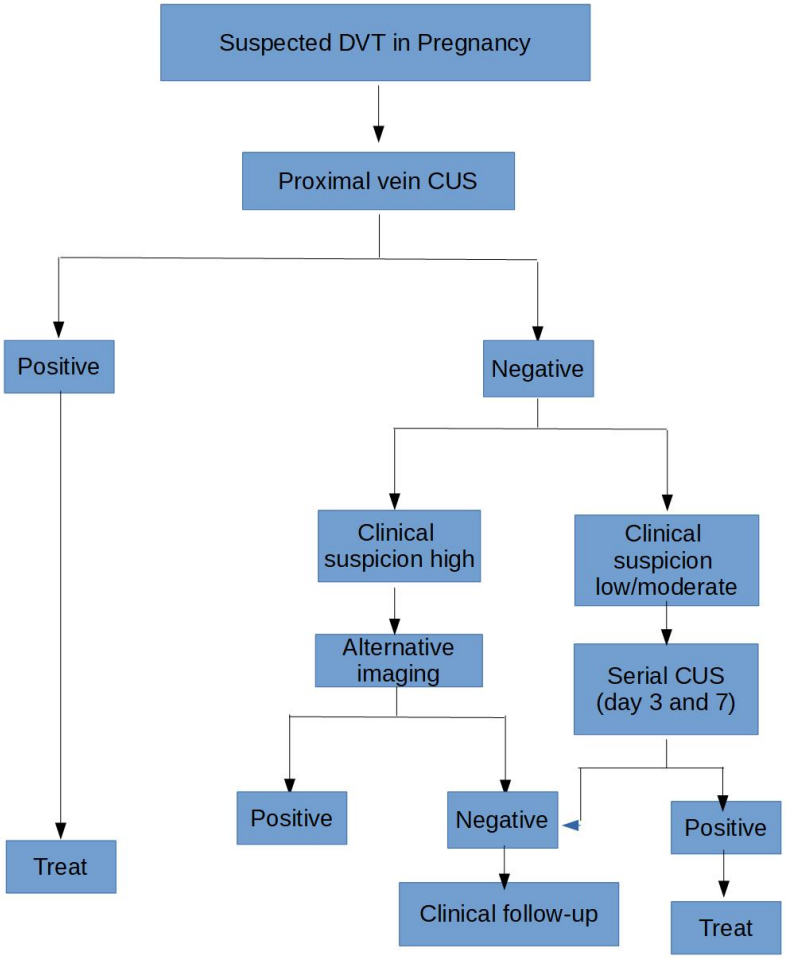
To note, some of the listed features (i.e. active cancer, recent surgery) are not likely to be present in young healthy pregnant women while other features, such as pitting edema and lower extremity tenderness, are common symptoms of pregnancy without the presence of a DVT.

***Click the terms to see more information.***

D-dimer has limited value in pregnancy for pretest probability in diagnosing DVT. This is due to the natural rise in D-dimer levels with each trimester, even using the cut-off value of >500ng/mL (by enzyme-linked immunosorbent assay (ELISA) or RBC agglutination) [60-63].

On the other hand, a negative test (<500ng/mL) can significantly lower the clinical suspicion for DVT and aid the clinician in the decision to avoid further testing [59, 61] (**Algorithm**).

A higher cut-off value for D-dimer is not validated in pregnancy and cannot be routinely used as pretest probability tool for diagnosing suspected DVT in pregnancy.




# Diagnosis Algorithm for Suspected Deep Venous Thrombosis in Pregnancy

- All pregnant patients suspected of having a DVT should undergo evaluation with an initial test of CUS (**Algorithm**).
- As discussed, the first-line test for the diagnosis of suspected DVT in pregnancy is proximal CUS. Venography and magnetic resonance imaging are not [59].
  - In advanced pregnancy, CUS should be performed with the patient in the left lateral decubitus position.
- The CUS results and clinical suspicion help to determine if further testing needs to occur; such as doppler ultrasound of the iliac vein, magnetic resonance or contrast venography (**Algorithm**).

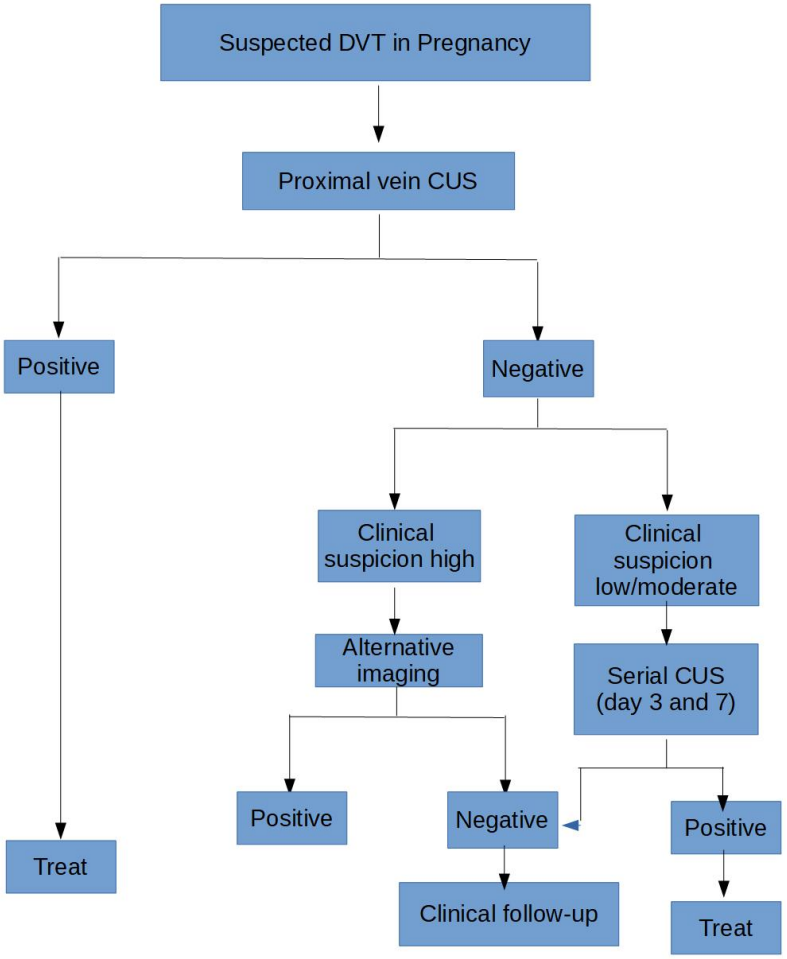
**Negative CUS**

- A negative CUS does not rule out DVT in the pregnant patient.
- Further testing depends upon the degree of clinical suspicion.
- When the initial CUS is negative, but clinical suspicion for DVT remains, there are two reasonable options:
  - Further testing concurrent with empiric anticoagulation
  - Further testing with anticoagulation reserved for confirmed cases on follow-up testing.
- There is insufficient data to guide the clinician with this decision.
- When clinical suspicion is evident, the clinician must rely upon judgment and weigh risks of untreated VTE versus bleeding in the pregnant patient.

- All pregnant patients suspected of having a DVT should undergo evaluation with an initial test of CUS (**Algorithm**).
- As discussed, the first-line test for the diagnosis of suspected DVT in pregnancy is proximal CUS. Venography and magnetic resonance imaging are not [59].
  - In advanced pregnancy, CUS should be performed with the patient in the left lateral decubitus position.
- The CUS results and clinical suspicion help to determine if further testing needs to occur; such as doppler ultrasound of the iliac vein, magnetic resonance or contrast venography (**Algorithm**).

**Positive CUS**

- When CUS is positive, the diagnosis of DVT occurs.
- Anticoagulation should be initiated.
- The bleeding risks during pregnancy and puerperium are minimal and certainly outweigh the benefits of anticoagulation for DVT.




# Diagnosis Algorithm for Suspected Deep Venous Thrombosis in Pregnancy

## Diagnosis

- With concerning signs and symptoms (i.e. suspected iliac vein thrombosis with swelling of the entire leg and buttock), it may be warranted to obtain further evaluation with doppler ultrasound directed at the iliac vein followed by magnetic resonance and then contrast venography, as needed.
- Emperic anticoagulation is suggested in these pregnant women.
- The issues with this preference places high value in the diagnostic certainty and risk of maternal death for an untreated thrombosis in pregnancy, and placing less value on risk of radiation or contrast exposure.
- For patients in whom the clinical suspicion is not high, serial CUS is preferred (performed on day three and seven) without empiric anticoagulation but with clinical follow-up throughout pregnancy.
- Preference to avoid unnecessary anticoagulation occurs when the risk of DVT is low.
    - Safety for withholding anticoagulation in this setting is assured from data with non-pregnant [48, 59, 64] and pregnant patients [50-52, 59, 61].
- Consider measuring D-dimer levels as an alternative if serial CUS is not feasible. When D-dimer is < 500ng/mL, DVT is unlikely [61].
- With ultrasound and magnetic resonance imaging, there is no measurable radiation exposure associated with these testing modalities.

**The differential diagnosis of DVT in pregnancy is similar to that in nonpregnant patients.**

- The differential includes other entities that present with erythema, warmth, edema and tenderness of the lower extremity with or without flank, lower abdomen, buttock or back.
- Many of the physiologic changes of normal pregnancy (i.e. lower extremity swelling and cramping), can mask the clinical signs and symptoms of DVT in pregnancy.
- The clinical suspicion for DVT should be high in the setting of pregnancy.
- Features highly suggestive for the diagnosis include unilateral sign and symptoms and the classic symptoms of iliac vein thrombosis; however, these are not always present.
- Such symptoms should prompt immediate investigation for DVT with compressive or Doppler ultrasound.
- It is important to note that DVT can co-exist with other conditions.
- An alternative diagnosis (i.e. cellulitis) will lower the clinical suspicion for DVT and may negate the need for diagnostic imaging.

## Prevention

- Consider discussing prophylaxis if prior DVT or thromboembolic disease (i.e. Factor V Leiden) is present
- Provide prophylaxis in pregnancy when indicated (i.e. compression stockings preop for cesarean)

## Management

- The first line management of suspected VTE is dependent on the degree of clinical suspicion for acute PE, if contraindications for anticoagulation are present and if PE, DVT or both are suspected.
- Empiric anticoagulation is indicated prior to diagnostic testing when there is a high suspicion for acute PE.
- Anticoagulant therapy is discontinued if VTE is excluded.
- If there is low or moderate clinical suspicion, empiric anticoagulant therapy prior to diagnostic evaluation should be determined case-by-case.
- When PE is suspected, but anticoagulant therapy is contraindicated, diagnostic evaluation should be expedited.
    - Anticoagulation-independent therapy (e.g. inferior vena cava filter) is indicated if VTE is confirmed.
    - Anticoagulant therapy is generally withheld when there is suspicion for DVT alone, without evidence of acute PE, until VTE is confirmed, assuming the diagnostic evaluation can be performed very timely.
- The following table reviews clinical scenarios for antepartum and postpartum management.

**See the table of clinical scenarios for antepartum and postpartum management on the next page.**

| Clinical Scenario | Antepartum Management | Postpartum Management |
|---|---|---|
| No history of VTE, no thrombophilia | Surveillance* without anticoagulation therapy | Surveillance without anticoagulation therapy or postpartum prophylaxis anticoagulation therapy if the patient has multiple risk factors VT† |
| VTE diagnosed during pregnancy | Adjusted-dose LMWH/UFH | Adjusted-dose LMWH/UFH for a minimum of 6 weeks postpartum. Longer duration of therapy may be indicated depending on the timing of VTE during pregnancy, prior VTE history, or presence of thrombophilia. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference. |
| Single provoked VTE (precipitated by a single event such as surgery, trauma, or immobility) unrelated to estrogen or pregnancy due to a transient (resloved risk factor, non thrombophilia | Surveillance* without anticoagulation therapy | Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risk factors † |
| History of single unprovoked VTE (no identified precipitating factor present; includes prior VTE in pregnancy or associated with hormonal contraception), not on long-term anticoagulation | Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH | Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen for 6 weeks postpartum |
| Low risk thrombophilia‡ without previous VTE | Surveillance* without anticoagulation therapy | Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risk factors‡ |
| Low risk thrombophilia‡ with a family history (first-degree relative) of VTE | Surveillance* without anticoagulation therapy or prophylactic LMWH/UFH | Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH |
| Low risk thrombophilia‡ with a single previous episode of VTE--Not receiving long-term anticoagulation therapy | Prophylactic or intermediate-dose LMWH/UFH | Postpartum prophylactic anticoagulatioon therapy or intermediate-dose LMWH/UFH |
| High risk thrombophilia¥ without previous VTE | Prophylactic or intermediate-dose, or adjusted dose LMWH/UFH | Postpartum prophylactic anticoagulatioon therapy or intermediate-dose LMWH/UFH |
| High risk thrombophilia¥ with a single previous VTE or an affected first-degree relative--Not receiving long-term anticoagulation therapy | Prophylactic intermediate-dose or adjusted-dose LMWH/UFH | Postpartum prophylactic anticoagulatioon therapy or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment) |
| Two or more episodes of VTE--Not receiving long-term anticoagulation therapy (regardless of thrombophilia) | Intermediate-dose or adjusted-dose LMWH/UFH | Postpartum prophylactic anticoagulatioon therapy or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment) |
| Two or more episodes of VTE--Not receiving long-term anticoagulation therapy (regardless of thrombophilia) | Adjusted-dose LMWH/UFH | Resumption of long-term anticoagulation therapy. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference. |

Abbreviations: LMWH, low molecular weight heparin, UFH, unfractionated heparin; VTE, venous thromboembolism
*VTE risk assessment should be performed prepregnancy or early in pregnancy and repeated if complications develop, particularly those necessitating hospitalization or prolonged immobility.
†First-degree relative with a history of thrombotic episode, or other major thrombotic risk factors (eg, obesity, prolonged immobility, cesarean delivery).
‡Low-risk thrombophilia: Factor V leiden heterozygote; prothrombin G20210A mutation heterozygote; protein C or protein S deficiency, antiphospholipid antibody.
¥High-risk thrombophilias include Factor V leiden homozygosity prothrombin G20210A mutation homozygosity, heterozygosity for factor V Leiden and prothrombin G20210A mutation, or antithrombin deficiency.

The following approach is generally consistent with the 2012 American College of Chest Physicians (ACCP) guidelines on VTE and pregnancy [67].

Once anticoagulation is indicated, it should be initiated using subcutaneous low molecular weight heparin (SC LMWH), intravenous unfractionated heparin (IV UFH), or subcutaneous unfractionated heparin (SC UFH) [65].

- **Warfarin**
- **Synthethic Heparin**
- **Subcutaneous LMWH**
- **IV UFH**

**Warfarin**

Generally, warfarin is not utilized, particularly in the first trimester, because of the associated teratogencity.

***Mouse-over the blue terms to learn more.***

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- **Synthethic Heparin**
- **Subcutaneous LMWH**
- **IV UFH**

**Synthetic Heparin**

- Due to the lack of safety date, synthetic heparin pentasaccharides (i.e. fondaparinux, indraparinux) are avoided.
- Another unique aspect of anticoagulation in pregnancy is monitoring; it tends to be more vigilant because less is known about the appropriate dosing with pregnancy.

***Mouse-over the blue terms to learn more.***

The following approach is generally consistent with the 2012 American College of Chest Physicians (ACCP) guidelines on VTE and pregnancy [67].

Once anticoagulation is indicated, it should be initiated using subcutaneous low molecular weight heparin (SC LMWH), intravenous unfractionated heparin (IV UFH), or subcutaneous unfractionated heparin (SC UFH) [65].

- **Warfarin**
- **Synthethic Heparin**
- **Subcutaneous LMWH**
- **IV UFH**

**Subcutaneous LMWH**

- Subcutaneous LMWH is preferred over IV UFH or SC UFH in most patients because it is easier to use and it appears to be more efficacious with a better safety profile.
- These findings are extrapolated from clinical trials in non-pregnant patients.
- In 22 randomized trials, a meta-analysis, SC LMWH decreased mortality and recurrent thrombosis.
- SC LMWH is more likely to reduce thrombus size and less likely to cause major hemorrhage [66].

The following approach is generally consistent with the 2012 American College of Chest Physicians (ACCP) guidelines on VTE and pregnancy [67].

Once anticoagulation is indicated, it should be initiated using subcutaneous low molecular weight heparin (SC LMWH), intravenous unfractionated heparin (IV UFH), or subcutaneous unfractionated heparin (SC UFH) [65].

- **Warfarin**
- **Synthethic Heparin**
- **Subcutaneous LMWH**
- **IV UFH**

**IV UFH**

- Based on clinical knowledge, IV UFH is preferred in patients with marked elevated risk of hemorrhage or persistent hypotension due to PE.
- The reasoning in pregnant women with these risks (risk of bleeding, marked hypotension) is the short half-life and near complete reversal with protamine.
- Either IV UFH or SC UFH is preferred over SC LMWH when the pregnant woman has severe renal failure.

Little information exists about the appropriate dosing of anticoagulants during pregnancy [67,68].

- Due to the limited data, it seems prudent to have additional caution when dosing these medications with more vigilant monitoring of anticoagulant activity and utilizing the weight adjusted dosing.

The following regimens are reasonable for the initial treatment of VTE during pregnancy or the puerperium.

- Regardless of the regimen, anticoagulant therapy should continue through the pregnancy.
  - **LMWH**
  - **IV UHF**
  - **SC UHF**

- Reasonable initial dosages of SC LMWH include [67, 68]:
  - Dalteparin (Fagmin ®) 200 units/kg once daily
  - Tinzaparin (Innohep ®)175 units/kg once daily
  - Dalteparin 100units/kg every 12 hours
  - Enoxaparin (Lovenox ®) 1mg/kg every 12 hours
- Dosing is then titrated to an anti-Xa level of 0.6-1.0iu/mL for twice daily administration and 1-2iu/mL for once daily [67, 69, 70].
- The anti-Xa level is first measured six hours after the third or fourth dose with every 12 hour dosing or six hours after the second or third dose when the dosing is once daily.
- Typical adjustments involve an increase or decrease by 10-25%.
- Further anti-Xa levels may be measured six hours after the third injection following the adjustments made to the medication.
- Some clinicians recheck the anti-Xa level every one to three months, once satisfactory levels are obtained; however, this is controversial because few women require dose adjustments [54].

Antifactor Xa levels are not required when LMWH is utilized for prophylactic anticoagulation because the optimal level has not been determined.

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  - **SC UHF**

- IV UFH dosing consists of initial bolus of 80 units/kg followed by a continuous infusion of 18 units/kg per hour [66].
- Every four hours this infusion is titrated to achieve therapeutic activated partial thromboplastin time (aPTT) and corresponds to an anti-Xa level of 0.3-0.7IU/mL.
- Each laboratory will have specified target ranges for the aPTT. Once this target level is reached, it should be rechecked once or twice daily.
- When long term or outpatient anticoagulant therapy is planned, the IV UFH can be transitioned to SC UFH or SC LMWH [67].

Antifactor Xa levels are not required when LMWH is utilized for prophylactic anticoagulation because the optimal level has not been determined.

Little information exists about the appropriate dosing of anticoagulants during pregnancy [67,68].

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The following regimens are reasonable for the initial treatment of VTE during pregnancy or the puerperium.

- Regardless of the regimen, anticoagulant therapy should continue through the pregnancy.
  - **LMWH**
  - **IV UHF**
  - **SC UHF**

- A reasonable initial dose of SC UFH is 17,500 units every 12 hours.
- The SC UFH dose is then titrated to achieve therapeutic aPTT, where the aPTT level corresponds to an anti-Xa level of 0.3-0.7IU/mL [67].
- The target aPTT range will be laboratory-specific.
- It is typical to have the first aPTT level measured six hours after the second dose then adjust by an increase or decrease of 10-30%.
- Measuring the aPTT level six hours after the second dose following adjustments would be appropriate.
- The aPTT may be measured after 3-4 days of treatment once a stable dose is achieved and then every few weeks.
- During the last 10 weeks of the pregnancy, more frequent monitoring is warranted.

Antifactor Xa levels are not required when LMWH is utilized for prophylactic anticoagulation because the optimal level has not been determined.

**Treatment**

- Initiating LMWH is appropriate with low risk patients in an outpatient setting. Hospitalization may be warranted with the use of IV UFH when there is a large clot, maternal co-morbidities, or hemodynamic instability. A transition to LMWH may be started as the patient becomes hemodynamically stable [36, 43]
  - Typically the transition is done after the patient has received IV UFH for 5-10 days [69].
  - Six hours after the first SC UFH dose the first aPTT can be checked and then six hours after every dose adjustment until a stable dose produces the desirable therapeutic level.
  - Once there is stable dosing of the SC UFH, the aPTT may be checked once or twice daily for 3-4 days and then every few weeks.
- The last ten weeks of pregnancy requires more frequent monitoring.

## LABOR AND DELIVERY

When delivery is predicted (i.e. induction, scheduled cesarean), treating with SC LMHW should be discontinued 24 hours prior.

- The effects of heparin then resolve. This is particularly important for patients who desire neuraxial anesthesia and avoiding spinal hematoma upon insertion or removal of the neuraxial anesthesia catheter.

When the pregnant patient has a high risk for recurrent VTE (i.e. those with acute PE or proximal DVT developed in the past month), it may not be desirable to stop the anticoagulation therapy for 24-36 hours.

- These patients may benefit from having their SC LMWH or SC UFH switched to IV UFH.
- The IV UFH can be discontinued 4-6 hours prior to delivery [67].

Once the aPTT is in the normal range, the neuraxial catheter may be placed [71].

## Immediately Post Partum

- The regimen, SC LMWH, IV UFH or SC UFH, should be started twelve hours after cesarean delivery or six hours after a vaginal delivery, when significant bleeding has not occurred.
- Long term anticoaguation therapy options include SC LMWH, SC UFH or an oral vitamin K antagonist (i.e. warfarin).
- When warfarin therapy is the chosen option, the patient should receive both warfarin and heparin for at least five days.
- Once the international normalized ratio (INR) has been in the therapeutic range (typically two or three) for two consecutive days, then the heparin may be stopped.
- During lactation, warfarin is considered safe because it does not accumulate in breast milk to a substantial degree [75].

## Length of Therapy

The determination of length of anticoagulation should be individualized because the optimal duration is unknown.

Anticoagulation should occur for 3-6 months in women whose only risk for VTE were transient, such as pregnancy and cesarean delivery [67, 76-78].

Generally, anticoagulation therapy continues for at least six weeks postpartum [67, 79]. Patients with persistent risk factors for VTE may require longer therapy and should be individualized.

## Inferior Vena Cava Filters

Inferior vena cava (IVC) filters have been used during pregnancy with indications being the same in pregnant women as non-pregnant patients [79, 80].

- During active bleeding, following recent surgery or following a hemorrhagic stroke conventional anticoagulation is contraindicated.
- In women who develop new VTE despite being anticoagulated, conventional anticoagulation has proven ineffective.
- When a complication occurs from anticoagulation, such as significant bleeding, halting of anticoagulation therapy would be prudent.
- With a massive PE, the pulmonary vascular bed is already significantly compromised and unlikely to tolerate another insult.
- A temporary IVC filter may be placed into the IVC in women who develop VTE during pregnancy or the puerperium, since the patient population tends to be quite young and have temporary risk factors for VTE [81, 82].
- The inability to retrieve a filter placed during the third trimester of pregnancy due to the filter tilting, has been reported [83].

**Thrombolysis and Thrombectomy**

- Teratogenicity due to thrombolytic agents has not been reported, but the risk of maternal hemorrhage is high.
- As a result, thrombolytic therapy should be reserved for pregnant patients with life-threatening acute PE (i.e. persistent and severe hypotension due to the PE) [102].
- Observational studies provide the only data about the efficacy and safety of thrombolytic therapy and/or thrombectomy during pregnancy (i.e. there are no controlled trials) [86-93].
- In a review of case reports and case series (172 pregnant women undergoing treatment with thrombolytic agents) shows the maternal mortality was one percent, the incidence of fetal loss was six percent and the incidence of maternal hemorrhagic complications was eight percent [85].
- Only a few cases have been described, but the risk of postpartum hemorrhage appears to be greatest among women treated within eight hours of delivery [87-92].
- Case studies of thrombectomy report its successful use as a life saving measure when other measures have failed [92, 93].

Heparin has several side effects, including bleeding, thrombocytopenia, skin necrosis, and osteoporosis.

These adverse effects can occur even at prophylactic doses but are more likely with long term use.

**Bleeding**

**Skin Necrosis**

**Osteoporosis**

**Thrombocytopenia**

**The bleeding management during heparin therapy depends upon:**

- The location and severity of bleeding
- The degree of anticoagulants (i.e. anti Xa level or aPTT)
- The risk of discontinuing the anticoagulant

In many cases, the heparin can be stopped and restarted after the bleeding is controlled.

Consideration to insert an inferior vena cava filter (IVC) should occur if the bleeding is severe enough to prohibit resumption of anticoagulation.

The anticoagulation therapy should not be resumed if the bleeding is related to a placenta previa or abruption. However, this recommendation is based on low quality evidence.

*Click the side effects above to learn more.*

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These adverse effects can occur even at prophylactic doses but are more likely with long term use.

**Bleeding**

**Skin Necrosis**

**Osteoporosis**

**Thrombocytopenia**

**Skin Necrosis**

Heparin-induced skin necrosis is a manifestation of Heparin Induced Thrombocytopenia (HIT) and may occur in the absence of thrombocytopenia.

*Click the side effects above to learn more.*

Heparin has several side effects, including bleeding, thrombocytopenia, skin necrosis, and osteoporosis.
These adverse effects can occur even at prophylactic doses but are more likely with long term use.

**Bleeding**

**Skin Necrosis**

**Osteoporosis**

**Thrombocytopenia**

**Osteoporosis**

Long term heparin therapy, longer than seven weeks, can reduce bone mineral density by reducing bone formation.

This effect appears more common with unfractionated heparin than low molecular weight heparin.

*Click the side effects above to learn more.*

Heparin has several side effects, including bleeding, thrombocytopenia, skin necrosis, and osteoporosis. These adverse effects can occur even at prophylactic doses but are more likely with long term use.

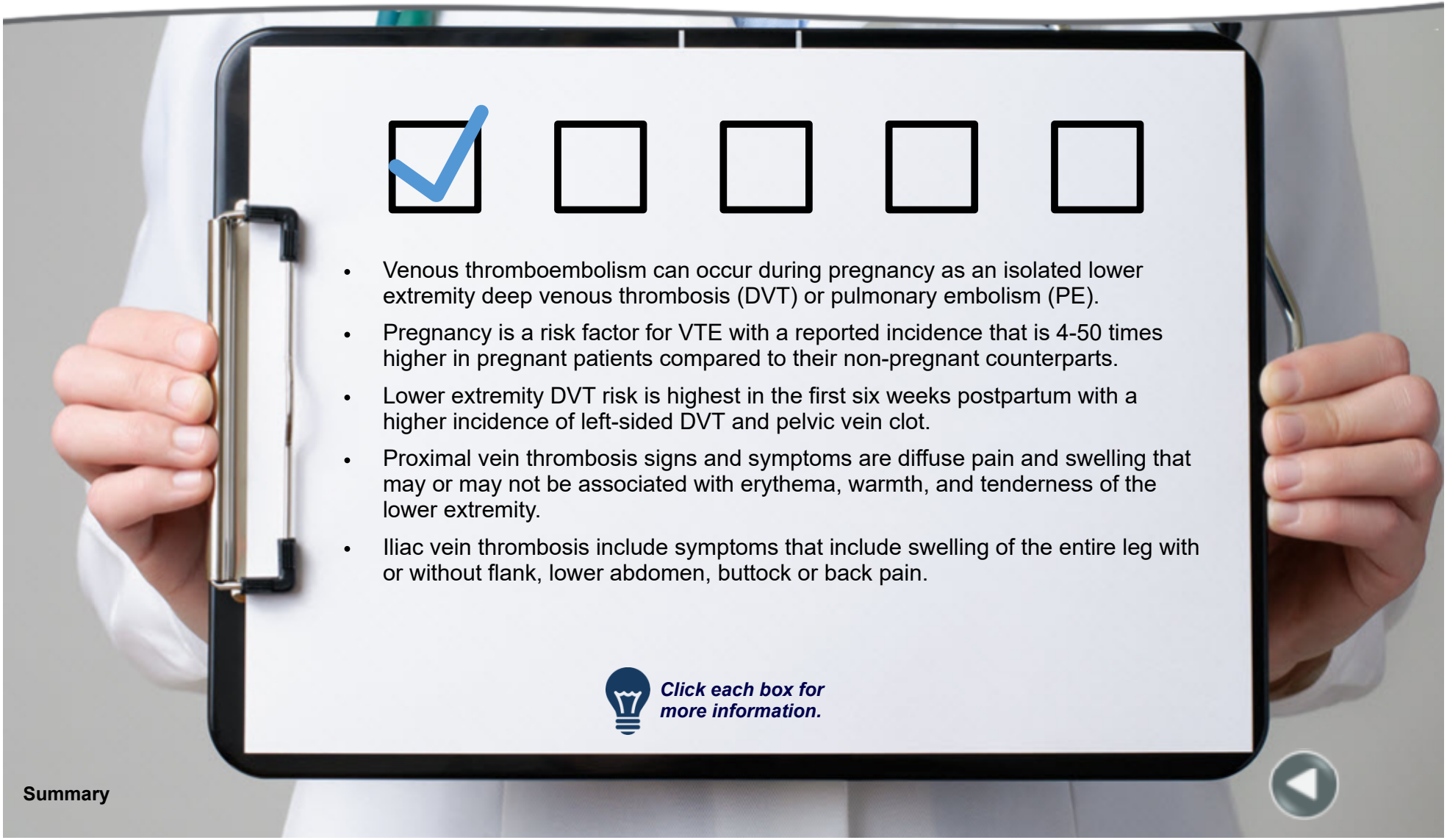
- Bleeding
- Skin Necrosis
- Osteoporosis
- Thrombocytopenia

**Thrombocytopenia**

Heparin-induced thrombocytopenia (HIT) is a potentially fatal complication of heparin therapy.

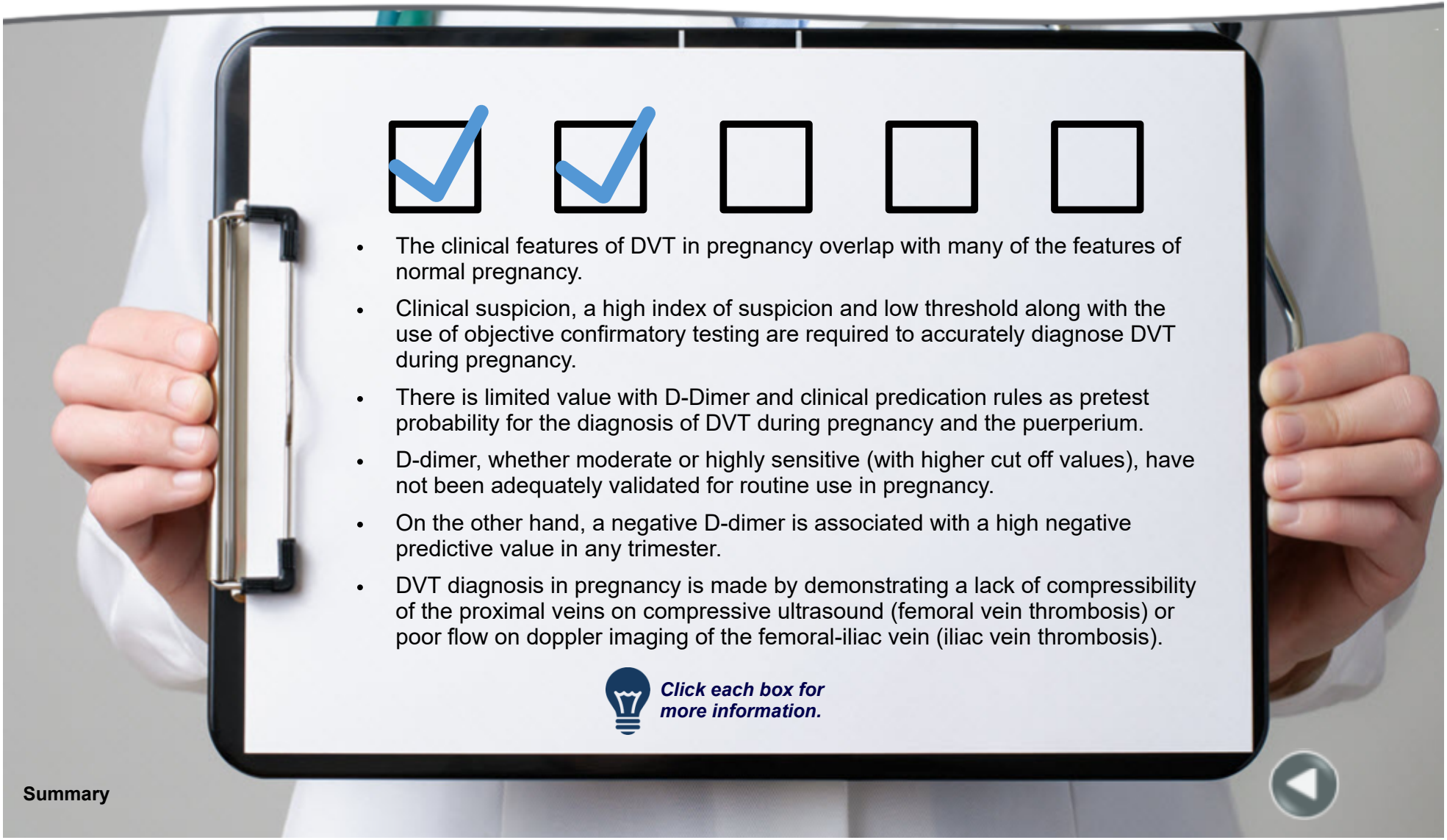
*Click the side effects above to learn more.*

*Click the right arrow to go to the next page.*



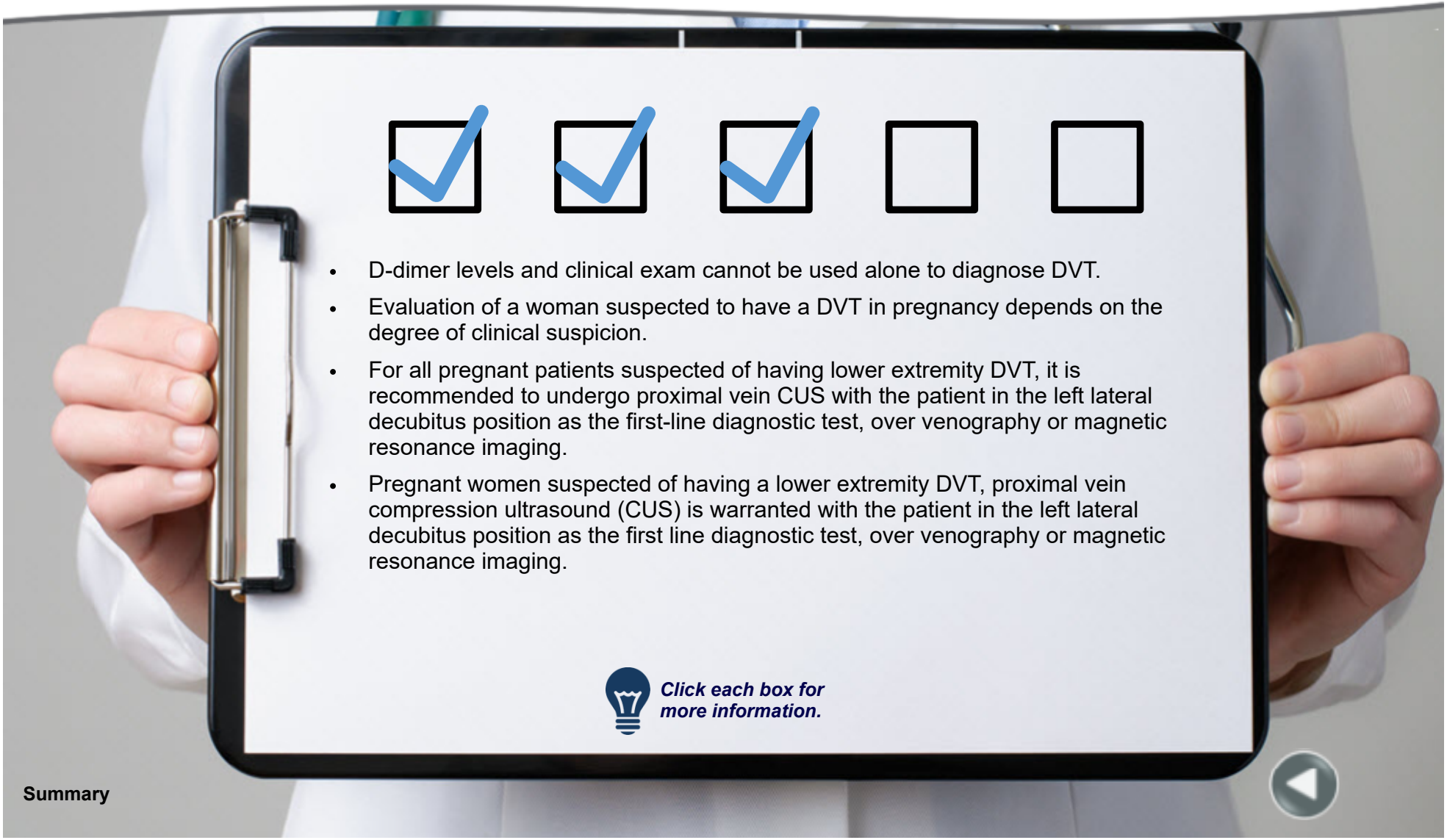
- Venous thromboembolism can occur during pregnancy as an isolated lower extremity deep venous thrombosis (DVT) or pulmonary embolism (PE).
- Pregnancy is a risk factor for VTE with a reported incidence that is 4-50 times higher in pregnant patients compared to their non-pregnant counterparts.
- Lower extremity DVT risk is highest in the first six weeks postpartum with a higher incidence of left-sided DVT and pelvic vein clot.
- Proximal vein thrombosis signs and symptoms are diffuse pain and swelling that may or may not be associated with erythema, warmth, and tenderness of the lower extremity.
- Iliac vein thrombosis include symptoms that include swelling of the entire leg with or without flank, lower abdomen, buttock or back pain.

***Click each box for more information.***



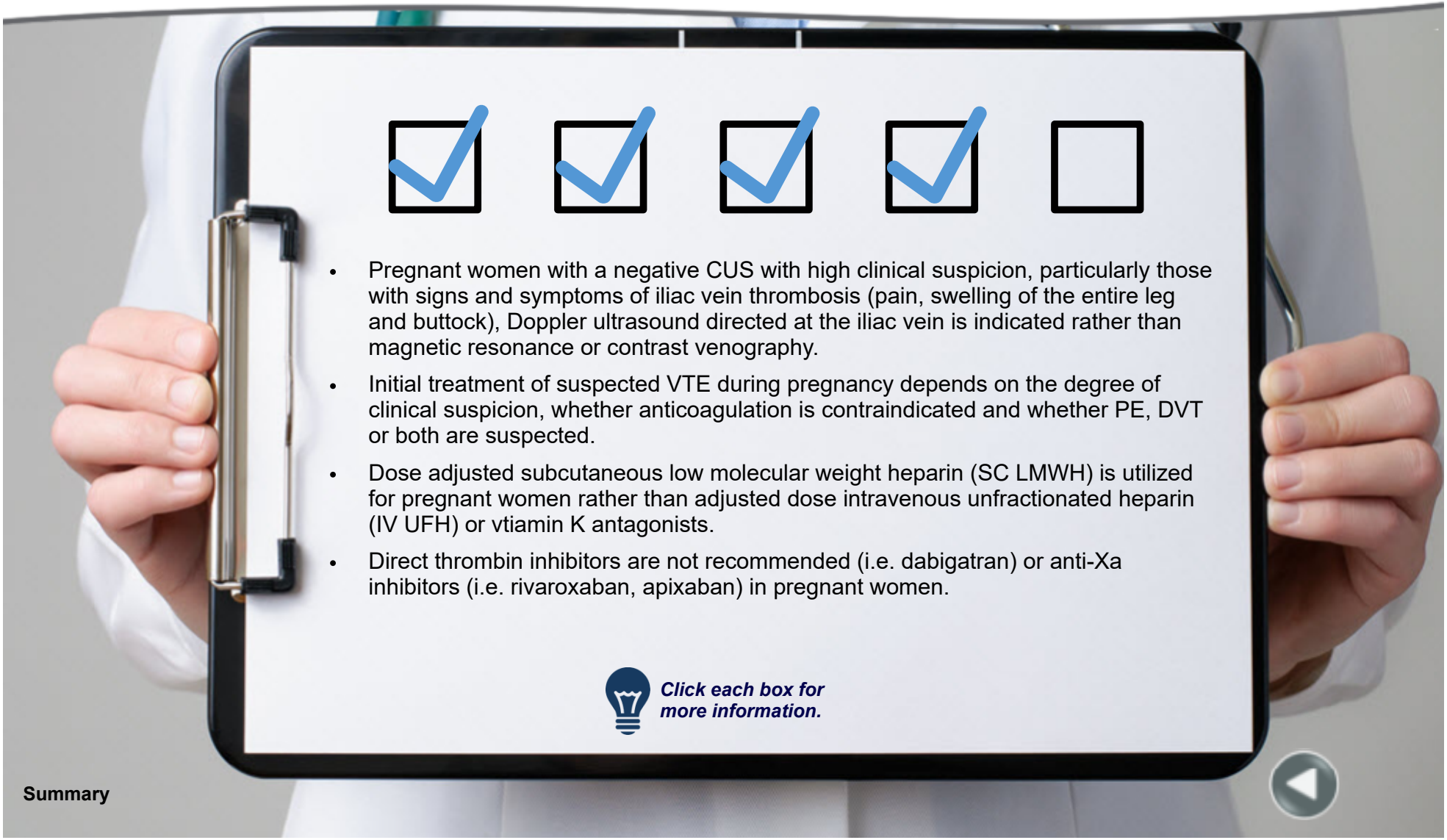
- The clinical features of DVT in pregnancy overlap with many of the features of normal pregnancy.
- Clinical suspicion, a high index of suspicion and low threshold along with the use of objective confirmatory testing are required to accurately diagnose DVT during pregnancy.
- There is limited value with D-Dimer and clinical predication rules as pretest probability for the diagnosis of DVT during pregnancy and the puerperium.
- D-dimer, whether moderate or highly sensitive (with higher cut off values), have not been adequately validated for routine use in pregnancy.
- On the other hand, a negative D-dimer is associated with a high negative predictive value in any trimester.
- DVT diagnosis in pregnancy is made by demonstrating a lack of compressibility of the proximal veins on compressive ultrasound (femoral vein thrombosis) or poor flow on doppler imaging of the femoral-iliac vein (iliac vein thrombosis).

***Click each box for more information.***



- D-dimer levels and clinical exam cannot be used alone to diagnose DVT.
- Evaluation of a woman suspected to have a DVT in pregnancy depends on the degree of clinical suspicion.
- For all pregnant patients suspected of having lower extremity DVT, it is recommended to undergo proximal vein CUS with the patient in the left lateral decubitus position as the first-line diagnostic test, over venography or magnetic resonance imaging.
- Pregnant women suspected of having a lower extremity DVT, proximal vein compression ultrasound (CUS) is warranted with the patient in the left lateral decubitus position as the first line diagnostic test, over venography or magnetic resonance imaging.

***Click each box for more information.***



- Pregnant women with a negative CUS with high clinical suspicion, particularly those with signs and symptoms of iliac vein thrombosis (pain, swelling of the entire leg and buttock), Doppler ultrasound directed at the iliac vein is indicated rather than magnetic resonance or contrast venography.
- Initial treatment of suspected VTE during pregnancy depends on the degree of clinical suspicion, whether anticoagulation is contraindicated and whether PE, DVT or both are suspected.
- Dose adjusted subcutaneous low molecular weight heparin (SC LMWH) is utilized for pregnant women rather than adjusted dose intravenous unfractionated heparin (IV UFH) or vtiamin K antagonists.
- Direct thrombin inhibitors are not recommended (i.e. dabigatran) or anti-Xa inhibitors (i.e. rivaroxaban, apixaban) in pregnant women.

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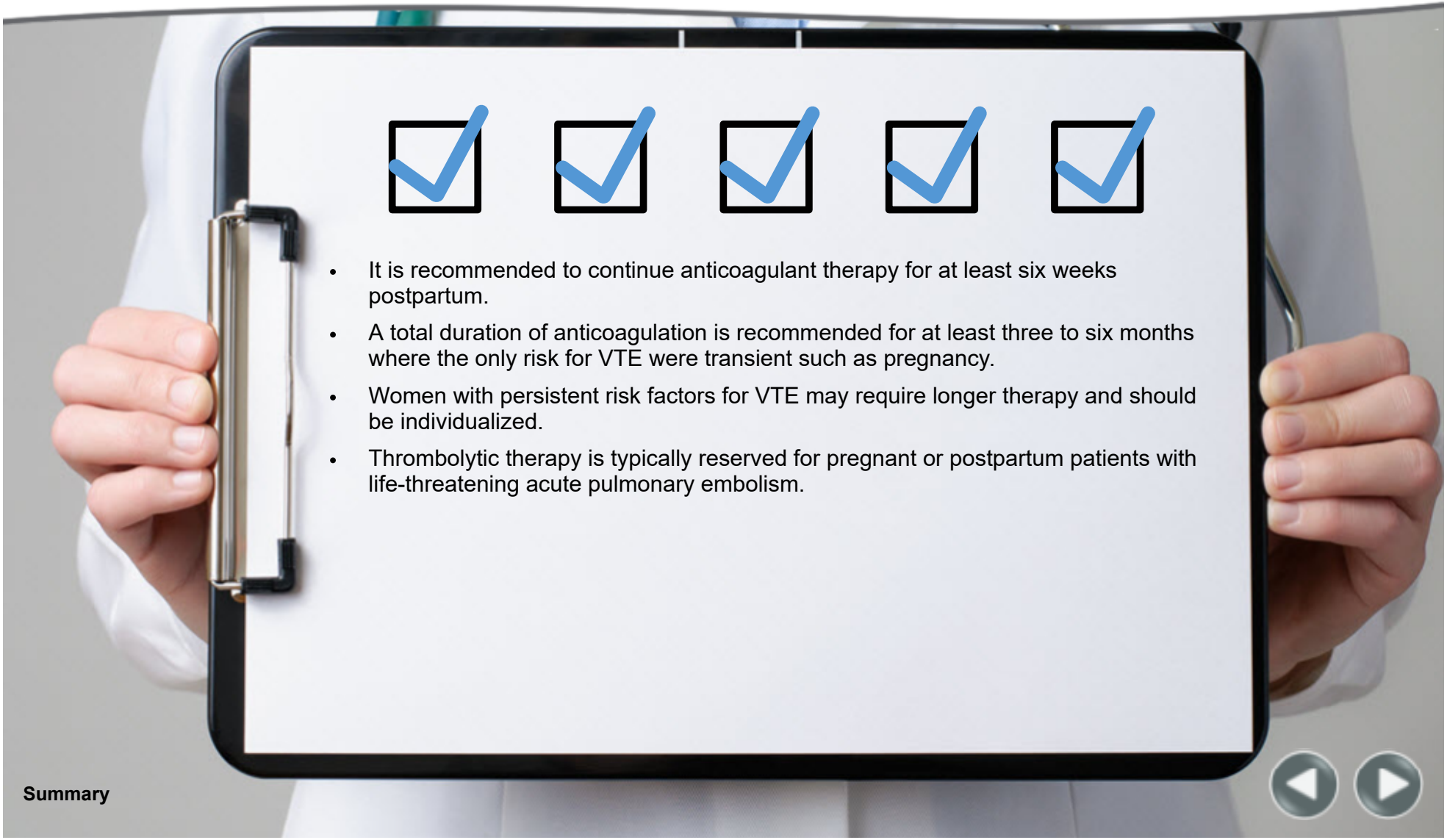

- It is recommended to continue anticoagulant therapy for at least six weeks postpartum.
- A total duration of anticoagulation is recommended for at least three to six months where the only risk for VTE were transient such as pregnancy.
- Women with persistent risk factors for VTE may require longer therapy and should be individualized.
- Thrombolytic therapy is typically reserved for pregnant or postpartum patients with life-threatening acute pulmonary embolism.

MATERNAL911®

# Congratulations!

## You have successfully completed this module.

*Click on the above 'X' to take the post-test for this course.*
*If you do not attain a passing score after two attempts at the post-test the entire program must be repurchased.*

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