

## Thromboembolic Disease in Pregnancy

The following section is entitled “**Thromboembolic Disease in Pregnancy**”. This section deals with some of the basic concepts important in diagnosis, management and investigation of thrombotic disease during pregnancy. The section begins with a *learner handout* with space for the learner to make their own notes. The *learner handout* is followed by the *teaching script* for the educator. A table reviewing the known hypercoagulable states and the effect that pregnancy has on testing for them is included with the handout and teaching script. The section then concludes with several cases for discussion and a brief bibliography for this topic.

**THROMBOTIC DISEASE IN PREGNANCY**

**THROMBOTIC DISEASE  
IN PREGNANCY**

---

---

---

---

---

---

**Pregnant women are at an increased risk for thromboembolic disease.**

**Pulmonary embolism is the major nonobstetric cause of maternal mortality.**

---

---

---

---

---

---

**Women with underlying hypercoagulable states may often present with thrombosis for the first time during pregnancy.**

**These underlying hypercoagulable states are also associated with an increased risk of fetal loss, IUGR, and preeclampsia.**

---

---

---

---

---

---

**THROMBOTIC DISEASE IN PREGNANCY**

**DVT and PE**

**90% of deep venous thrombosis during pregnancy occur on the left side.**  
**A significant proportion of DVT in pregnancy occurs in the pelvic veins and, therefore, may not be picked up by routine testing.**  
**Ovarian vein thrombosis can also occur.**

---

---

---

---

---

**DVT and PE - Presentation**

**Pulmonary embolism in pregnancy may have a more subtle presentation than in the general medical population.**

**ABG and A-a gradient are often normal.**  
**Tachycardia is often not present.**

---

---

---

---

---

**DVT and PE - Investigation**

- CUS, IPG, and venography can be done safely and with reliable results in pregnancy.**
- Ventilation perfusion scans and pulmonary angiograms can be done safely during pregnancy.**
- Pelvic vein ultrasound, CT scan and MRI are all tests that can be used to look for pelvic clot.**
- IVC filters can be placed in pregnancy.**

---

---

---

---

---

## THROMBOTIC DISEASE IN PREGNANCY

### DVT and PE - Management

- Treatment of acute DVT/PE in pregnancy is done initially with a weight-based intravenous heparin protocol.
- Because coumadin should not be used in pregnancy, the patient eventually will be discharged on twice daily subcutaneous injections of heparin.
- Heparin is adjusted to achieve a “mid-interval” (6 hours after dose) PTT of 60-80 seconds.
- Duration of treatment is controversial but should be at least 3 months.

---

---

---

---

---

---

---

---

### DVT and PE - Prophylaxis

- Women who have had a previous DVT/PE probably require prophylactic heparin during their pregnancy and for 6 weeks postpartum because of an increased risk of recurrence.
- We recommend 5000u SC q12h in the first trimester, 7500u SC q12h in the second, and 10,000u SC q12h in the third trimester and postpartum.

---

---

---

---

---

---

---

---

### Low Molecular Weight Heparin

- DVT Prophylaxis with LMWH
  - no evidence that this is superior to unfractionated heparin in efficacy but *may* have less risk of osteoporosis and thrombocytopenia.
  - more expensive than unfractionated herparin.
  - prefilled syringes make dose adjustments difficult.
  - monitoring of heparin levels may still be necessary because of increased clearance of LMWH in pregnancy.

---

---

---

---

---

---

---

---

**THROMBOTIC DISEASE IN PREGNANCY**

**Low Molecular Weight Heparin**

- **Dosing and efficacy of LMWH has not been studied in pregnancy for *acute* DVT/PE**

---

---

---

---

---

---

**Testing for Underlying Hypercoagulable Defects**

- **The hypercoagulable states presently described are:**
  - **Resistance to activated protein C**
  - **The antiphospholipid syndromes (APL Ab, ACL Ab and the lupus like inhibitor)**
  - **Protein S deficiency**
  - **Protein C deficiency**
  - **Antithrombin 3 deficiency**
  - **Hyperhomocysteinemia**
  - **Prothrombin mutation (G->A nucleotide 20210)**

---

---

---

---

---

---

**Antiphospholipid Antibodies and Pregnancy**

- **Women who meet the strict criteria for the APL Ab Syndrome can be treated with aspirin and heparin, but corticosteroids increase the chance of preterm delivery.**
- **There are no randomized controlled trials to support the use of I.V. IgG in women with a history of pregnancy loss and any autoantibody.**

---

---

---

---

---

---

## Inherited and Acquired Tendencies to Coagulation and How to Test for Them in Pregnancy

	Test	Effect of pregnancy on assay	Meaningful in the setting of acute thrombotic event?	Meaningful in the setting of heparin therapy?
<b>protein C deficiency</b>	functional protein C assay	none	no	yes
<b>protein S deficiency</b>	functional protein S assay (free protein S level)	decreases levels	no	yes
<b>antithrombin 3 deficiency</b>	antithrombin III assay	none	no	no
<b>factor V Leiden mutation (90% of R-APC)</b>	PCR for factor V Leiden mutation	none	yes	yes
<b>functional resistance to activated protein C</b>	functional assay for R-APC	increases resistance to APC (decreases ratio)	yes	no
<b>Hyper-homocysteinemia</b>	plasma homocysteine w/ or w/o oral methionine (100mg/kg)challenge	levels decreased by folate in prenatal vitamins	yes	yes
	PCR for <i>methylene tetrahydrofolate reductase</i> gene mutation	none	yes	yes
<b>Prothrombin gene Mutation 20201A</b>	PCR for <i>Prothrombin gene Mutation 20201A</i>	none	yes	yes
<b>antiphospholipid antibodies</b>	anticardiolipin and antiphospholipid antibodies ( IgM and Ig G )	none	yes	yes
<b>Lupus like inhibitor</b>	PTT, mixing study, Platelet neutralization procedure (PNP), Russel viper venom (RVV) test and TT	none	yes	no

## THROMBOTIC DISEASE IN PREGNANCY

### *Teaching Script*

Pregnant women are known to be at an increased risk for thromboembolic disease. In fact, pulmonary embolism is the major, non-obstetric cause of maternal mortality in the United States and Canada. Risk factors for thromboembolic disease in pregnancy include immobilization, obesity, smoking, surgery (including cesarean section), previous thromboembolism and the presence of an inherited or acquired hypercoagulable state.

### **Physiologic Changes that Predispose Pregnant Women to Thromboembolic Disease**

There are two important physiologic changes that occur in pregnancy that help explain the predisposition of pregnant women to venous thrombosis. The first change is “stasis” or slowed flow of blood in the large vessels of the pelvis and leg. This occurs in pregnancy because the gravid uterus can lean against the large pelvic vessels, partially obstructing flow in the deep venous system of the leg. The second change is in the blood itself. Levels of all of the coagulation factors involved in clot formation (except Factors XI and XIII) increase during pregnancy. At the same time, the levels of some of the normally occurring serum proteins which act to inhibit clot formation within blood vessels have been found to decrease during pregnancy. A decrease in a protein S that occurs in all pregnant women is the most well known of these changes.

### **Diagnosis of Deep Venous Thrombosis**

Pulmonary embolism and deep venous thrombosis occur at a similar rate throughout all three trimesters. The risk for thromboembolic disease does peak in the first 48 hours after delivery and continues from between six weeks to three months postpartum.

Typically deep venous thrombosis in pregnancy presents with unilateral leg edema, leg pain and tenderness. However, the accuracy of diagnosis of deep venous thrombosis by history and physical exam is notoriously unreliable. Interestingly, 90% of deep venous thromboses in pregnancy occur on the left side. The reason for this is not well understood but likely has to do with the position of the uterus with respect to the left iliac vein. To investigate a patient for deep venous thrombosis, all of the usual tests including compression ultrasound of the lower limbs, impedance plethysmography, and contrast venography can be safely done with reliable results. It is also important to remember that a significant proportion of deep venous thromboses in pregnancy occur in the pelvic veins and therefore may not always be picked up by routine testing such as compression ultrasound or even lower limb venogram. In those cases where a high index of suspicion is met with a negative lower limb compression ultrasound, a skilled ultrasonographer can examine the iliac and femoral veins with considerable accuracy. In the rare situation that there is still some doubt regarding the presence of pelvic clot, we have found magnetic resonance venography to be very helpful.

### **Diagnosis of Pulmonary Embolism**

It is critical to be cognizant of the fact that pulmonary embolism in pregnancy may have a more subtle presentation than in the general medical population. In review of cases of pulmonary embolism in our own institution, we found that less than half of the patients with documented pulmonary embolism had widened Arterial alveolar gradients, tachycardia, or the typical pleuritic chest pain. Less than half had EKG or chest x-ray findings. The most common presenting feature is dyspnea. The commonness of dyspnea in pregnancy can make the decision about which patient to investigate for pulmonary embolism a difficult one.

To investigate a patient for pulmonary embolism, all of the usual investigations can be safely done with reliable results. Chest x-rays, ventilation perfusion scan and pulmonary

angiograms can all be done safely during pregnancy and involve a dose of radiation that is well below the general accepted maximum recommended radiation exposure in pregnancy. The ventilation perfusion scan is often diagnostic in young healthy individuals with no pre-existing lung disease. Normal lung scans effectively rule out a pulmonary embolism, while a high probability scan effectively rules pulmonary embolism “in”. In the situation that a low or intermediate probability scan is obtained, a pulmonary angiogram is often necessary to rule out pulmonary embolism. The life threatening nature of pulmonary embolism and the lifelong clinical implications of making the diagnosis of thromboembolic disease in a young person almost always warrants getting a definitive answer through the use of pulmonary angiography.

### **Treatment of Deep Venous Thrombosis and Pulmonary Embolism**

Treatment of acute deep venous thrombosis and pulmonary embolism in pregnancy is done initially with intravenous heparin in the same manner as is done for the non-pregnant patient. Heparin is a large molecule that does not cross the placenta and therefore does not have any effect upon the fetus. The risks of heparin are entirely maternal and include hemorrhage, osteoporosis, and thrombocytopenia, all of which are relatively rare and are far outweighed by the benefits of heparin therapy. After five to seven days of intravenous heparin, the patient with DVT and/or pulmonary embolism is eventually discharged on twice daily subcutaneous injections of heparin. Full anticoagulation with subcutaneous heparin is monitored with the goal of achieving a mid-interval (6 hours after a q 12h dosing), PTT of 60 - 80 seconds. In general, we begin by taking the total amount of units of heparin required over a 24-hour period to create adequate anticoagulation on intravenous heparin and divide the total number of units by two to determine the initial dose to be given every 12 hours. Duration of treatment is controversial but should be at least three months. If the patient is still pregnant after three months of therapeutic heparin have been administered, many people would continue full anticoagulation therapy while others would switch to a prophylactic dose (see below).

Although the nonpregnant patient with thromboembolic disease is managed as an outpatient on warfarin (coumadin), warfarin use is to be avoided in pregnancy. Warfarin readily crosses the placenta and has deleterious effects on the fetus. It acts as a teratogen in the first trimester and later in pregnancy coumadin is associated with an increased incidence of cerebral malformations presumably related to *in utero* cerebral bleeds in the fetus.

In the rare situation that an acute pulmonary embolism occurs in a patient who cannot undergo systemic anticoagulation with heparin, inferior vena cava filters can be placed safely in pregnancy.

The role of low molecular weight heparin (LMWH) in pregnancy is yet to be defined. Like unfractionated heparin, it does not appear to cross the placenta. It would appear to be a reasonable alternative to unfractionated heparin and although it is far more costly there is evidence to suggest it may be associated with a lower risk of thrombocytopenia, hemorrhage and osteoporosis. In nonpregnant patients, low molecular weight heparin therapy has the additional benefit of not requiring PTT monitoring. However, there is evidence to suggest the low molecular weight heparin has altered pharmacokinetics in pregnancy that may make standardized dosing in gestation inappropriate. Many clinicians advocate that the use of low molecular weight heparin therapy in pregnancy should be followed and adjusted on the basis of heparin levels (a.k.a. anti-factor Xa levels). Present packaging of the majority of low molecular weight heparins in pre-filled syringes makes such dose adjustments difficult.

## **Prophylaxis**

Because of the fact that pregnancy is a state associated with an increased risk of DVT and pulmonary embolism, many individuals believe that women who have had a previous deep venous thrombosis or pulmonary embolism, regardless of its etiology, require prophylactic

heparin during their pregnancy and for six weeks postpartum. The risk of thrombosis in a pregnant woman with a previous thrombotic event is not known, nor is the exact effect that prophylactic heparin has on this recurrence risk. This is an area in need of a large multicenter investigation. At the present time, we recommend use of heparin at 5000 units subcutaneously (SC) in the first trimester, 7500 units SC q12h in the second trimester, and 10,000 units SC every twelve hours in the third trimester as our prophylactic regimen. The increased doses of heparin used in the second and third trimester are needed because of the increased volume of distribution of heparin during the latter two trimesters. When the patient goes into labor, the heparin is stopped and resumed approximately 12-24 hours postpartum.

Because the increased risk of thrombosis continues for at least six weeks postpartum, we continue heparin at a dose of 5000 units subcutaneously every twelve hours till six weeks postpartum or give the patient the option of being on warfarin after delivery for six weeks. If the patient opts for warfarin postpartum, we try to keep the INR in the low therapeutic range. Both warfarin and heparin are considered to be compatible with breastfeeding.

The use of low molecular weight heparin (LMWH) in prophylactic doses for DVT/PE prophylaxis in pregnancy is becoming increasingly common. Because of the previously described issues related to use of LMWH in pregnancy, some individuals would suggest that heparin levels be periodically checked when LMWH is used for this indication also.

## **Thrombophilias**

In addition to the previously mentioned normal physiologic changes that predispose pregnant women to thrombosis, many specific hypercoagulable defects not specific to pregnancy have been identified. It is now considered routine to test all individuals who have a thrombotic event for these abnormalities. Although many thromboembolic events in pregnancy will have no

clear underlying cause, women with either inherited or acquired hypercoagulable defects may present with thrombosis for the first time during pregnancy. In addition to their association with thromboembolic disease, many of the hypercoagulable states appear to be associated with an increased incidence of fetal loss, intrauterine growth restriction, and pre-eclampsia. This association presumably exists because of a propensity for placental thrombosis and infarction.

The inherited defects which can cause thrombosis are protein S deficiency, protein C deficiency, resistance to activated protein C deficiency (90% of which is due to Factor V Leiden mutation), antithrombin III deficiency, hyperhomocysteinemia and the prothrombin gene mutation 20210A. The acquired abnormalities which can cause thrombosis are the antiphospholipid antibody syndromes (antiphospholipid antibody, anticardiolipin antibody, and the lupus-like inhibitor). Hyperhomocysteinemia can also be acquired but is rare in pregnancy because of the use of folate containing prenatal vitamins. Table 3 reviews each of these hypercoagulable defects by listing the specific tests we recommend requesting when investigating for these abnormalities, the effect that normal pregnancy has on the results of these tests, and whether or not these tests are meaningful in the setting of heparin therapy or an acute thrombotic event.

As can be seen from the chart, none of the assays are significantly changed by pregnancy except for the protein S assay (which is normally decreased in pregnancy) and the PTT based assay for R-APC. Protein C, Protein S and Antithrombin 3 Deficiency are tested for by assays which measure the serologic levels of these factors as compared with the normal range. Resistance to activated protein C is a relatively newly recognized inherited disorder that appears to be responsible for a large number of thrombosis occurring in individuals without other recognizable risk factors. Resistance to activated protein C can be tested for by a variety of methods, but we recommend that the polymerase chain reaction (PCR) for Factor V Leiden mutation be used as the results should not be affected by pregnancy.

The acquired propensities for thrombosis are collectively known as inhibitors. They work by interfering with the body's normal mechanisms to prevent unwarranted intravascular clot formation. Confusingly, the inhibitors can cause elevations of PTT in the lab despite the fact that they are associated with clotting and not hemorrhage! Antiphospholipid antibodies (APL Ab) are ordered by that name and both IgM and IgG should be requested. The main two antiphospholipid antibodies identified are antiphosphatidyl serine and anticardiolipin antibodies. Higher titers of these antibodies do appear to be associated with a more significant risk of thrombosis than lower titers and IgG appears to carry more risk than IgM. The lupus-like inhibitor represents a group of disorders that can be identified by PTT, mixing studies, TT, and the Russell Viper Venom test.

## **Conclusion**

In summary, deep venous thrombosis and pulmonary embolism are seen with increased frequency in pregnancy due to increased venous stasis and changes in coagulation factors. The increased risk for deep venous thrombosis and pulmonary embolism associated with pregnancy is present at all stages of pregnancy and up to 6 weeks postpartum. The presentation and investigation for these disorders in pregnant women is much the same as it is in the nonpregnant population but it should be recognized that pregnant women may present with more subtle findings than are usually seen in the older medical population. Treatment of DVT and pulmonary embolism involves the use of heparin because warfarin is not considered safe in pregnancy. Careful consideration of the possibility of an underlying hypercoagulable state should be made, although many of these investigations may need to be deferred until after treatment has been completed, as the tests are not always interpretable in the setting of heparin therapy and or an acute thrombotic event.

### Inherited and Acquired Tendencies to Coagulation and How to Test for Them in Pregnancy

	Test	Effect of pregnancy on assay	Meaningful in the setting of acute thrombotic event?	Meaningful in the setting of heparin therapy?
<b>protein C deficiency</b>	functional protein C assay	none	no	yes
<b>protein S deficiency</b>	functional protein S assay (free protein S level)	decreases levels	no	yes
<b>antithrombin 3 deficiency</b>	antithrombin III assay	none	no	no
<b>factor V Leiden mutation (90% of R-APC)</b>	PCR for factor V Leiden mutation	none	yes	yes
<b>functional resistance to activated protein C</b>	functional assay for R-APC	increases resistance to APC (decreases ratio)	yes	no
<b>Hyper-homocysteinemia</b>	plasma homocysteine w/ or w/o oral methionine (100mg/kg)challenge	levels decreased by folate in prenatal vitamins	yes	yes
	PCR for <i>methylene tetrahydrofolate reductase</i> gene mutation	none	yes	yes
<b>Prothrombin gene Mutation 20201A</b>	PCR for <i>Prothrombin gene Mutation 20201A</i>	none	yes	yes
<b>antiphospholipid antibodies</b>	anticardiolipin and antiphospholipid antibodies ( IgM and Ig G )	none	yes	yes
<b>Lupus like inhibitor</b>	PTT, mixing study, Platelet neutralization procedure (PNP), Russel viper venom (RVV) test and TT	none	yes	no

# THROMBOTIC DISEASE IN PREGNANCY

## Case Discussion

### Case #1

A 32 year-old G<sub>1</sub>P<sub>0</sub> woman comes to you as a new primary care patient. She tells you she is seeing you because she needs a referral from her insurance company to an obstetrician. On taking her medical history she tells you that she had a deep venous thrombosis in her right lower limb two years ago that occurred after flying from Tokyo to New York. She said the diagnosis was made by ultrasound of her legs. She was treated with five days of intravenous heparin followed by three months of coumadin. She said that she had no respiratory symptoms and was not investigated for pulmonary embolism. Because she had had her deep venous thrombosis following prolonged immobilization she stated that she was never investigated for any underlying hypercoagulable defect. The patient is 30 pounds overweight and smokes one-half pack of cigarettes a day but she had quit since she found that she was pregnant five days ago. On questioning regarding her family history she tells you that both her mother and her maternal grandfather had pulmonary embolisms in their mid-40's. Her examination is completely normal.

***The patient wants to know what her recurrence risk of her DVT is during the course of this pregnancy. What do you tell her?***

***Having heard this, she wants to know if anything can be done to decrease her risk of thrombosis in this pregnancy. What do you tell her?***

***She asks why she cannot just take the coumadin during this pregnancy that she took when she had a clot in the past. What do you tell her?***

***She asks you about the risks of nine months of heparin injection? What do you tell her?***

***She wants to know if heparin will harm her baby. What do you tell her?***

***Does this patient need investigations at this time for a hypercoagulable state?***

***What hypercoagulable states can you test for reliably in pregnancy?***

***What is the most likely hypercoagulable defect for this young woman to have?***

***What lifestyle modifications can she make to help decrease her risk of recurrent thromboembolism?***

***Is there any obstetrical relevance to investigating her for a hypercoagulable state?***

***She states that she has heard that most blood clots in pregnancy happen when the uterus is greatly enlarged in the third trimester and wonders if she could just take the heparin then. What do you tell her?***

The patient decides she will go take the subcutaneous heparin.

***What dose of heparin will you use? How will you monitor its efficacy?***

***What sites can she use for injection of the heparin?***

She is instructed by your nurse about how to use heparin and her follow-up CBC is normal. Her mid-interval PTT is not elevated. She does very well for the next seven months but on a follow-up visit, asks you what she should do about her heparin when she goes into labor.

***What do you tell her?***

She delivers the infant, a normal healthy male infant at 7 # 8 oz at 38 weeks gestation with normal spontaneously vaginal delivery.

***When can anticoagulation be resumed postpartum?***

***How long will she need anticoagulation post-partum and how will you administer it?***

## THROMBOTIC DISEASE IN PREGNANCY

### *Case Discussion*

#### **Case #2**

*Adapted from ACP workshop syllabus*

This 26 year old G<sub>1</sub>P<sub>1</sub> female presents for medicine consultation at 28 weeks gestation. This pregnancy has been going very well for her but she had early severe pre-eclampsia with IUGR in her previous pregnancy in 1994. Because of a history of femoral deep venous thrombosis in 1995, the patient is being treated with prophylactic subcutaneous heparin beginning at 10 weeks gestation and continued postpartum. An aPTT is drawn and found to be 60 second. She is presently on 7500 units of heparin subcutaneously q 12 hours.

***What is the most likely cause of her prolonged aPTT?***

***Is there a relationship between her history of DVT and early, severe PIH or IUGR?***

***How would you manage her anticoagulation in this setting?***

The patient complains to you of pain and swelling in her right leg. On examination she is found to have increased circumference of the right calf and thigh with labial venous distention and obvious superficial phlebitis.

***What is her most likely diagnosis?***

***How will you approach the investigations of her complaint?***

Ultrasound of the leg revealed a large right ileo-femoral deep venous thrombosis.

***How should this patient be treated?***

***What further laboratory information would you want?***

***How should she be advised about subsequent pregnancies?***

## THROMBOTIC DISEASE IN PREGNANCY

### *Case Discussion*

#### **Case #3**

*Adapted from ACP workshop syllabus*

This 28 year old G<sub>3</sub>P<sub>1</sub> Ab1 white female presents for consultation at 8 weeks gestation with a history of a subclavian vein thrombosis six weeks following the delivery of her first child two years earlier. She was treated with intravenous heparin followed by three months of coumadin therapy. She has had no recurrence of thromboembolic disease and has been off all anticoagulants since that time.

***What further historical points are needed?***

***What is her risk of a recurrence during this pregnancy?***

A family history of CVA in an 18-year-old sister who was on oral contraceptives at the time and pulmonary emboli in the mother was elicited.

***What laboratory data should be obtained?***

***How should this patient be advised regarding prophylaxis during this pregnancy?***

The patient was treated with the regimen recommended by her physician after review of laboratory studies. She underwent a term NSVD followed by a postpartum tubal ligation without immediate complications and sent home on her prophylactic regimen. She presented five days postpartum with acute abdominal pain, vaginal bleeding and a fall in hemoglobin from 11.6 to 8.0 over a 48-hour period. At laparotomy she was found to have a large hematoma at the site of her tubal ligation.

***How should her anticoagulation be managed?***

***What recommendations could be made regarding subsequent pregnancies had she chosen to have further pregnancies?***

# THROMBOTIC DISEASE IN PREGNANCY

## Case Discussion

### Case #4

You get a call from the emergency room regarding one of your patients who has been seen by the emergency room doctor there. She is a 21-year-old woman at 12 weeks gestation who went to the emergency room with the sudden onset of shortness of breath with pleuritic chest pain. She has just come back from a year as a student in Budapest. She has no significant past medical history and no family history of thromboembolic disease. Her vitals show a pulse of 95/min, a respiratory rate of 14/minute, a blood pressure of 110/60, and she is afebrile. Her exam is normal except for some very mild reproducible chest wall tenderness. Her chest x-ray and EKG are normal and her arterial blood gas reveals a PaO<sub>2</sub> of 95 with a PaCO<sub>2</sub> of 32, which you know to be normal in a pregnant woman. The ER doctor calls you to let you know that she would like to send your patient home to follow up with you in your office in the next few days.

### Key Points to Review

1. ***Pregnant women are at increased risk of for deep venous thrombosis and thromboembolism.***
2. ***Physical exam, chest x-ray, arterial blood gases and EKG can all be normal in the setting of an acute pulmonary embolism in a pregnant woman.***
3. ***Lower limb ultrasound can miss pelvic venous thrombosis. Ventilation Perfusion (“Lung”) scans can be safely done during pregnancy.***
4. ***Treatment of thromboembolic disease during pregnancy is done with subcutaneous heparin injections because Coumadin is contraindicated in pregnancy.***
5. ***The thromboembolic risk during pregnancy is evenly distributed throughout gestation and continues for 6 weeks postpartum. The first week postpartum is a time of particularly increased risk.***

### REFERENCE

Toglia MR, Weg JG. Venous Thromboembolism during Pregnancy.  
*New England Journal of Medicine.* 1996;335(2):108-114.

## THROMBOTIC DISEASE IN PREGNANCY

### References

**\*Toglia MR, Weg JG. Venous Thromboembolism During Pregnancy. N Engl J Med July 1996 335(2):108-13.**

**\*Bates SM, Ginsberg JS. Thrombosis in pregnancy. Curr Opin Hematol 1997 4(5):335-43**

*Two reviews of the diagnosis and treatment of thrombosis in pregnancy.*

Bonnar J , Green R , Norris L. Inherited thrombophilia and pregnancy: the obstetric perspective. Semin Thromb Hemost 1998 24 (Suppl 1):49-53

*Review and outline of the approach to preconception counseling and management of this problem in the pregnant population.*

Friederich, PW, Sanson B, Simioni P, Zanardi S, Huisman MV, Kindt I, et al. Frequency of Pregnancy-Related Venous Thromboembolism in Anticoagulant Factor-Deficient Women: Implications for Prophylaxis. Ann Intern Med Dec. 1996 125(12): 955-60.

*Methodologically sound retrospective cohort study. 4.1% of women with deficiencies of antithrombin III, protein C or protein S had a thrombosis during pregnancy vs. 0.5% of their family members without those deficiencies (hazard ration, 8.0 [95% CI 1.2 to 184]).*

Kupfermanc MJ, Eldor A, Steinman N, Manyu A, Bar-Am A, Jaffa A, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999;340(1)9-13.

*Case series have found that 40-50% of women with preeclampsia, abruptio placentae, or fetal growth restriction will have a hypercoagulable disorder. This case-control study found that 52% of women with these obstetric complications had an abnormality compared to only 17% of a control group of women with normal pregnancies.*

Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: Treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol 1996 174(5):1584-89.

*Prospective controlled trial of 50 women with at least three consecutive pregnancy losses and high titer antiphospholipid antibody. Live birth occurred in 44% of those treated with aspirin and 80% of those treated with heparin (adjusted to achieve mid-interval aPTT 1.2.-1.5 times normal) and aspirin.*

Rai R, Cohen H, Dave M, Regan L. Randomized controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ Jan.1997 314:253-57.

*Randomized trial of 90 women with three or more consecutive pregnancy losses and positive antiphospholipid antibody (low or high titer, or positive lupus anticoagulant). Live birth rate was 42% with aspirin (75mg per day) and 71% with aspirin and low-dose heparin (5000U subcutaneous unfractionated heparin twice a day). Median decrease of bone mineral density in heparin group of 5.4% as measured by DEXA of the lumbar spine.*

Cowchock FS, Reece AE, Balaban D, Branch DW, and Plouffe L. Repeated fetal losses associated with antiphospholipid antibodies: A collaborative randomized trial comparing prednisone with low-dose heparin treatment. *Am J Obstet Gynecol* 1992; 166(5):1318-23.

*Randomized trial of 20 patients. Prednisone was associated with an increased incidence of premature rupture of the membranes and preterm delivery.*

Laskin CA, Bombardier C, Hannah ME, Mandel FP, Knox Ritchie JW, Farewell V, et al. Prednisone and Aspirin in women with autoantibodies and unexplained recurrent fetal loss. *N Engl J Med*. July 1997; 337(3):148-54.

*The population studied (n=202) did not meet strict antiphospholipid antibody syndrome criteria. However those treated with prednisone and aspirin had higher rates of preterm delivery (62% vs. 12% in the placebo group), hypertension (13% vs. 5% placebo), and diabetes mellitus (15% vs. 5% placebo). All results were statistically significant.*

Rand JH, Wu X, Andree HAM, Lockwood CJ, Guller S, Scher J, and Harpel PC. Pregnancy loss in the Antiphospholipid-Antibody Syndrome □ A possible Thrombogenic mechanism. *N Engl J Med* July 1997; 337(3):154-60

*Annexin V is a phospholipid binding protein with potent anticoagulant activity. Antiphospholipid antibodies decreased levels of annexin V and accelerated the coagulation of plasma on cultured trophoblasts. This study reveals a possible mechanism to explain the increased risk of obstetric complications in the presence of antiphospholipid antibodies.*

#### **Additional References**

Barbour LA: Prevention of deep venous thrombosis and pulmonary embolism. *American College of Obstetricians & Gynecologists Practice Bulletin*. 1998.

Catanzarite VA, Low RN, Wong DY. Ovarian vein thrombosis during cesarean section. *Journal of Reproductive Medicine* 1997; 42:315-18.

Cowchock S: The role of antiphospholipid antibodies in obstetric medicine. IN: Lee, Barron, Cotton, Coustan, Eds. *Current Obstetric Medicine* 1991; 1:229-47.

Horlocker TT, Heit JA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. *Anesth Analg* 1997; 85:874-85.

Hynson JM, Katz JA, Bueff U. Epidural hematoma associated with enoxaparin. *Anesth Analg* 1996; 82:1072-5.

Laskin CA, Bombardier C, Hannah M, et al: Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. *N Engl J Med* 1997; 337:148-53.

Nelson-Piercy C, Letsky EA, de Swiet M. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. *Am J Obstet Gynecol* 1997; 176:1062-8.

Petri M: pathogenesis and treatment of the antiphospholipid antibody syndrome. *Medical Clinics of North America* 1997; 81(1):151-77.

Price DT, Ridker PM: Factor V Leiden mutation and the risks for thromboembolic disease: A clinical perspective. *Annals of Internal Medicine* 1997; 127: 895-903.

Rai R, Regan L. Obstetric complications of antiphospholipid antibodies. *Current Opinion in Obstetrics and Gynecology* 1997; 9:387-90.

Ridker PM, Miletich JP, Buring JE, Ariyo AA, Price DT, Manson JE, Hill JA. Factor V Leiden mutation as a risk factor for recurrent pregnancy loss. *Ann Intern Med* 1998; 128:1000-3.

Shapiro GA: Antiphospholipid syndrome in obstetrics and gynecology. *Seminars in Thrombosis and Hemostasis* 1994; 20(1): 64-70.

Thomas LA, Summers RR, Cardwell MS. Use of greenfield filters in pregnant women at risk for pulmonary embolism. *Southern Medical Journal* 1997; 90(2):215-7.

Vandermeulen EP, Van Aken H, Vermeylen J. Anticoagulants and spinal-epidural anesthesia. *Anesth Analg* 1994; 79:1165-77.

Witlin AG, Mercer BM, Sibai BM: Septic pelvic thrombophlebitis or refractory postpartum fever of undetermined etiology. *The Journal of Maternal-Fetal Medicine* 1996; 5: 355-358.