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Fever and pleuritis in a postpartum patient

A 27-YEAR-OLD WHITE WOMAN seeks medical attention for a constellation of symptoms, including fever, left lateral chest pain on inspiration, and a general sense of not feeling well. Seven days previously, she had given birth to her second child, a healthy, full-term boy. This was her second pregnancy and it was uncomplicated; a caesarian section was performed because her first pregnancy required this owing to cephalopelvic disproportion. She has had no significant medical problems, and her family history contributes no relevant information. She has no drug allergies, and her only current medication is a multivitamin once daily.

On physical examination, the patient appears ill and anxious. Her blood pressure is 96/52 mm Hg bilaterally, heart rate 96 beats per minute and regular, respiratory rate 22 and nonlabored, and temperature 38.3 °C. No adenopathy, sinus tenderness, or posterior pharyngeal erythema is noted. Auscultation of the heart reveals an S4 gallop with a regular rhythm and no murmur. Inspiratory rales are heard in the middle of the left lung. The abdominal incision is healing, and the edges are approximated; there is mild incisional tenderness and erythema. No fluctuance is observed. The left groin is tender to deep palpation and contains no obvious masses. Multiple new, small venous telangiectasias are noted on the anterior and medial left thigh and calf (*Figure*). The legs are not edematous or tender.

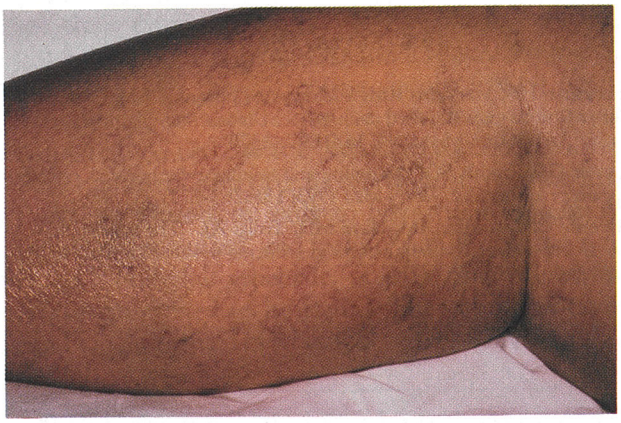

FIGURE. Venous telangiectasias in a postpartum patient.

1 On the basis of how frequently these diagnoses occur during or soon after pregnancy, what is the most likely diagnosis?

- ❑ Endometritis
- ❑ Pleuropulmonary bacterial infection
- ❑ Urinary tract infection with urosepsis
- ❑ Deep venous thrombosis and pulmonary thromboembolism
- ❑ Aortic dissection

Although each of these diagnoses is plausible, venous thromboembolic disease is the most common cause of morbidity and mortality during pregnancy and the puerperium. Previously believed to be most common in the third trimester of pregnancy and the puerperium, venous thromboembolism appears to occur with equal frequency throughout pregnancy. Aortic dissection is unusual in pregnancy, occurring mostly in patients with Marfan's syndrome or other rare conditions. Infectious diseases occur infrequently in the postpartum period and are less common than thromboembolism in pregnancy and the puerperium.

2 What should be the next step in the management of this patient?

- ❑ Impedance plethysmography; if normal, antibiotic therapy
- ❑ Warfarin therapy for 12 weeks
- ❑ Venous duplex ultrasonography; if normal, ventilation-perfusion lung scanning
- ❑ Pulmonary angiography
- ❑ Heparin, 5000 units subcutaneously twice daily

Since deep venous thrombosis and pulmonary embolism are the most likely diagnoses, a definitive, noninvasive diagnostic test should be performed. Warfarin therapy by itself without a formal diagnosis is not adequate. Heparin at a low dosage is a reasonable method to *prevent* venous thromboembolism but is inadequate to *treat* it. Proceeding directly to pulmonary angiography forgoes an opportunity to secure a diagnosis noninvasively.

Impedance plethysmography is a reasonable test when performed routinely by skilled technologists. However, it yields many false-positive results. For example, in the third trimester of pregnancy, a positive study may represent thrombosis or extrinsic compression by the gravid uterus. A negative result does not exclude thrombosis, as calf vein thrombi may still exist. Therefore, antibiotic therapy would not be an appropriate next step.

Venous duplex ultrasonography is another excellent noninvasive diagnostic test, demonstrating 94% sensitivity and 97% specificity. However, this test may miss isolated thrombi in the iliac vein and calf vein. Therefore, a negative test mandates further investigation; in this case, a ventilation-perfusion lung scan would be reasonable.

3 Duplex ultrasonography reveals a thrombus in the left common and superficial femoral veins, and the perfusion scan documents a lingular and left lower lobe defect, interpreted as representing a high probability for pulmonary embolus. A continuous intravenous (IV) infusion of heparin is started. Which of the following is *incorrect*?

- ❑ Assays for protein C and protein S should be obtained before starting warfarin therapy
- ❑ A prolonged activated partial thromboplastin time (APTT) and a low platelet count before heparin therapy is instituted suggest an underlying hypercoagulable state
- ❑ Prophylaxis against thrombosis will be required in future pregnancies to prevent recurrent deep venous thrombosis
- ❑ The APTT is reliable as the sole method for determining the intensity of heparin anticoagulation in pregnant patients
- ❑ Warfarin should be given for 3 to 6 months to maintain an International Normalized Ratio (INR) of 2 to 3

Although pregnancy is considered a hypercoagulable state, underlying congenital or acquired abnormalities in hemostatic factors (procoagulants and naturally occurring anticoagulants) should be identified. Protein C, factors VII and VIII, and fibrinogen increase during pregnancy, while protein S decreases. The triad of recurrent fetal loss, thrombocytopenia, and venous-arterial thrombosis suggests the antiphospholipid antibody syndrome. A false-positive rapid plasma reagin test for syphilis, lupus anticoagulants, and circulating anticardiolipin antibodies characterize this syndrome.

Although the APTT is the test most often used to monitor the intensity of heparin effect, pregnancy may make it less reliable. Since factors VII and VIII and fibrinogen rise dramatically throughout pregnancy, the APTT may remain short despite adequate plasma heparin concentrations. In this setting, heparin levels, as determined by anti-Xa assays of heparin, are more reliable; the target heparin concentration is 0.2 to 0.4 IU/mL. Attempting to achieve APTT values of 1.5 to 2.0 times normal laboratory control values may be dangerous in pregnant patients, as very high heparin concentrations can result, putting both the patient and the fetus at higher risk for hemorrhagic events.

After delivery, heparin and warfarin should be given concurrently for at least 4 days (thereby depleting factor II, which has a half-life of 72 to 96 hours). The patient can receive warfarin maintenance therapy for 3 to 6 months to maintain an INR of 2 to 3. Since only negligible amounts of warfarin are expressed in breast milk, breast-feeding poses no risk to the infant.

DISCUSSION

Given the incidence of venous thromboembolic disease in pregnancy, all physicians who care for pregnant patients should know how to diagnose and

treat it. Symptoms and clinical findings are not sufficient for diagnosis, and an objective examination must be performed in any patient in whom thromboembolism is suspected. Impedance plethysmography and duplex ultrasonography have limitations in pregnancy, and limited ascending contrast venography may be required. Even though this test involves some radiation exposure, the risks of birth defects and cancer are low, especially after the first trimester.

Once a diagnosis has been established, but before heparin therapy is started, assays for protein C, protein S, antithrombin III, lupus anticoagulant, and anticardiolipin antibodies should be obtained, as should the prothrombin time (PT), the APTT, and a complete blood count. A continuous IV infusion of heparin at a full dose should be started, and samples for APTT testing drawn 4 to 6 hours after the onset of treatment. Because of the risks of embryopathy, central nervous system malformations, and fetal wastage, warfarin should be avoided throughout pregnancy. If heparin doses based on the APTT become high, the heparin concentration, determined by anti-Xa assays, should be used.

If heparin is to be used during a portion of pregnancy, the IV dose should be converted to subcutaneous injections. The total daily IV dose is calculated and divided into two or three daily injections. A concentration of heparin of 25 000 units per mL should be used to keep the volume of injected solution small. If heparin is given twice daily, the APTT or heparin level should be checked 6 hours after injection (4 hours after a three-times-a-day dose), and doses adjusted based on these results. Once the APTT is in the desired range, weekly assays are adequate.

Prophylaxis against thromboembolism in pregnancy should be considered for patients who have a history of deep venous thrombosis or pulmonary embolism and no underlying hypercoagulable state, and for patients who have a hereditary or acquired hypercoagulable state with or without a history of thromboembolism. Patients at risk who do not have an underlying coagulation abnormality should receive 5000 units of heparin subcutaneously twice daily, throughout pregnancy.

Patients with antithrombin III deficiency should receive therapeutic doses of heparin subcutaneously as patients with acute thromboembolic disease do, although this is controversial. In patients with a documented coagulation abnormality and previous thromboembolic disease, the timing of heparin prophylaxis is uncertain. Full therapeutic doses of heparin should be given at least during the third trimester and puerperium.

Side effects of heparin include hemorrhage, osteoporosis, thrombocytopenia, hyperkalemia, alopecia, and, rarely, alteration in uterine muscle contraction. Bone demineralization and osteoporosis occur in patients requiring 10 000 to 20 000 units of heparin daily for at least 5 months and appear to reverse after the drug is stopped. Mild thrombocytopenia occurs in many patients, usually within the first 48 to 72 hours of treatment, and resolves spontaneously even if heparin therapy is continued. Severe heparin-induced thrombocytopenia, which is rarer, develops after 6 to 10 days of exposure and can lead to the heparin-associated thrombocytopenia-and-thrombosis ("white-clot") syndrome. The delayed form is associated with the formation of a platelet-sensitive IgG heparin antibody. A decrease in platelets of more than 50 000 per cubic millimeter or an absolute platelet count of 100 000 per cubic millimeter or less mandates stopping heparin completely. Continuation of heparin in the face of a dropping platelet count can lead to catastrophic arterial and venous thromboses, limb loss, and death.

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SUGGESTED READING

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