CLINICAL INQUIRIES

How can we best treat and monitor VTE during pregnancy?

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EVIDENCE-BASED ANSWER

Unfractionated heparin and low-molecular-weight heparin are equally effective for the treatment of acute venous thromboembolism (VTE) in pregnancy (strength of recommendation [SOR]: **C**; based on expert opinion and 1 low-power cohort study). Low-molecular-weight heparin may be associated with fewer bleeding events than unfractionated heparin (SOR: **B**; extrapolated from a randomized controlled trial of thromboprophylaxis in pregnancy).

Unfractionated heparin for treatment of VTE should be given by IV bolus followed by continuous infusion, maintaining the activated partial thromboplastin time (aPTT) in therapeutic range for at least 5 days, followed by subcutaneous heparin 2 or 3 times daily to maintain aPTT levels 1.5 to 2.5 times normal for at least 3 months (SOR: **C**, expert opinion). Low-molecular-weight heparin should be initially dosed based on weight as for nonpregnant patients, then adjusted to goal peak antifactor Xa levels of 0.5–1.2 IU/mL (SOR: **C**; expert opinion). The US Food and Drug Administration has labeled warfarin as category X, indicating that it is contraindicated during pregnancy due to fetal loss and probable teratogenicity.

CLINICAL COMMENTARY

Safety is most important when treating pregnant women

We have enough evidence to conclude that unfractionated heparin and low-molecular-weight heparin are both effective treatments for acute VTE in pregnant women. Unfortunately, we don't know whether 1 treatment is safer or more effective than the other. The safety issue is the most important consideration in treating pregnant women. A large number of patients would need to be studied to identify a small but significant difference between the 2. We as clinicians would want to know if 1 therapy had even a slightly increased risk of a catastrophic harm. Clinical experience is not enough to tell us that; we need more research.

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Evidence summary

Pulmonary embolism remains one of the leading causes of maternal mortality in developed nations. For nonpregnant populations, low-molecular-weight heparin has equal efficacy as unfractionated heparin with a lower overall mortality.[1,2]

The only direct comparison of unfractionated with low-molecular-weight heparin for treatment of VTE in pregnancy was a prospective cohort study of 31 patients.[3] For the initial week of treatment, the unfractionated heparin group received an IV bolus followed by infusion titrated to aPTT levels (goal 70–100s), while low-molecular-weight heparin group received subcutaneous dalteparin 115 IU/kg twice daily adjusted to target antifactor Xa levels of 1 to 1.5 IU/mL 3 hours after injection. After 7 days, both groups received prophylactic doses of dalteparin throughout the remainder of pregnancy. There were no significant differences in outcome including bleeding or fetal effects. No cases of thrombocytopenia or pulmonary embolus were seen. There was 1 case of progressive thrombosis for a patient on low-molecular-weight heparin.

One randomized controlled trial compared unfractionated with low-molecular-weight heparin for VTE prophylaxis among 107 high-risk pregnant patients.[4] The unfractionated heparin group received 7500 IU subcutaneously twice daily adjusted to aPTT levels, while the dalteparin group received weight-adjusted doses to target antifactor Xa levels >0.2 IU/mL at 3 hours. No thromboembolic complications occurred in either group (95% confidence interval, 0 to 2 in both groups). Minor bleeding complications were significantly more common with unfractionated heparin than with low-molecular-weight heparin. Two bleeds requiring transfusion and 2 lumbosacral compression fractures were also observed in the unfractionated heparin group, compared with none in the dalteparin group (difference not statistically significant).

Heparinoid metabolism appears to significantly alter in pregnancy. Several studies of low-molecular-weight heparin for the treatment of VTE in pregnancy used target antifactor Xa levels of 0.5 to 1.5 at 3 hours and found patients often need doses greater than those used for nonpregnant patients.[3,5–7] The only study of unfractionated heparin for the treatment of VTE in pregnancy used aPTT levels extrapolated from nonpregnant patients, with a mean heparin dose of 25,430 IU/d, similar to mean doses for nonpregnant patients.[3]

There are no studies of repeat lower extremity ultrasounds for pregnant patients; however, 1 study of nonpregnant patients revealed proximal extension of deep venous thrombosis despite anticoagulation predicted increased risk of pulmonary embolism.[8]

Recommendations from others

Both the American College of Obstetrics and Gynecologists[9] and the American College of Chest Physicians[10] recommends treating acute VTE in pregnancy with either weight-adjusted-dose low-molecular-weight heparin (goal antifactor Xa levels, 0.5–1.2) throughout pregnancy or full-dose intravenous unfractionated heparin, followed by adjusted-dose unfractionated or low-molecular-weight heparin, for the remainder of the pregnancy and at least 6 weeks postpartum.

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FAST TRACK

Low-molecular weight and unfractionated heparin are both effective treatments for acute VTE in pregnant women