

## **Review: Safety of Withholding Heparin in Pregnant Women With a History of Venous Thromboembolism**

Brill-Edwards P, Ginsberg J, et al. Safety of Withholding Heparin in Pregnant Women With a History of Venous Thromboembolism. *New England Journal of Medicine*. 2000 Nov 16;343(20):1439-1443.

### **QUESTIONS**

What is the risk of recurrent antepartum venous thromboembolism in women with a history of previous venous thromboembolism? Is it safe to withhold heparin prophylaxis in these patients?

### **METHODS**

One hundred twenty five pregnant patients with a documented single previous venous thromboembolism and without a known thrombophilia were enrolled prior to 20 weeks gestation and were prospectively followed through their pregnancy. Prophylactic anticoagulation was withheld antepartum but it was given for 4-6 weeks postpartum with coumadin (goal INR 2.0 - 3.0). Blood samples to identify thrombophilia (antithrombin III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies, factor V Leiden gene mutation, and prothrombin 20210A gene mutation) were performed in 95 of the 125 patients but the results were not known until the study was completed. The nature of the initial thromboembolic event was classified as either idiopathic or in association with a temporary risk factor.

### **RESULTS**

There were a total of 3 recurrent antepartum thromboembolic events (2.4%, ninety five percent CI, 0.2 - 6.9%). One women developed at deep vein thrombosis (DVT) at 29 weeks gestation and was found to have Factor V Leiden, prothrombin G20210A gene mutation and protein C deficiency. A women with a DVT at 29 weeks gestation was found to have Factor V Leiden. Tests for a thrombophilia were normal in a third woman who had a pulmonary embolism (PE) at 9 weeks gestation. There were also 3 postpartum DVT's (3 and 8 weeks postpartum, and 2 days after missed abortion with hemorrhage at 11 weeks gestation). The patient with a DVT at 3 weeks postpartum had refused coumadin and was treated with 12,500 units unfractionated heparin twice daily subcutaneously and the patient who recurred at 8 weeks postpartum had stopped coumadin 2 weeks earlier. Warfarin was withheld in the woman who had the uterine hemorrhage after the missed abortion and developed a DVT 2 days postpartum.

Forty eight(51 percent) of the 95 women who were tested for thrombophilias had the following abnormalities: 30 women with decreased concentrations of free protein S (only 1 of which had a persistent abnormality on followup testing after the effect of pregnancy had been eliminated), 11 women with heterozygosity for factor V Leiden, 7 women with heterozygosity for the prothrombin G20210A gene mutation, 3 women with antithrombin III deficiency, 2 women with lupus anticoagulant, and 2 women with anticardiolipin antibodies. Three women had 2 abnormalities. Of the 25 women with abnormal test results, 4 had recurrent venous thromboembolism as compared to 2 of the 70 women with normal test results. (95 percent confidence interval 0.8 to 56.3). There were no recurrences among the 44 women who had their previous VTE in association with a temporary risk factor and had normal laboratory results. The

recurrence rate of antepartum VTE in the 51 women with abnormal lab testing or a previous episode of idiopathic thrombosis was 5.9% (ninety five percent CI 1.2 - 16.2%).

## AUTHOR'S CONCLUSIONS

The authors state that the risk of recurrent VTE is low and that routine antepartum prophylaxis with heparin is not warranted.

## COMMENTARY

The authors make the bold conclusion that heparin prophylaxis is not routinely warranted in pregnant women who have a history of a single VTE. However, caution regarding these recommendations is advised. This is a study with relatively small numbers and large confidence intervals. In addition, though the authors attempted to track patients not included in the study, it is quite possible (if not likely) that study participants were predominantly at low risk for VTE because obstetricians may not have referred women who were felt to be at high risk for recurrence.

While the overall recurrence rate for antepartum VTE was found to be low at 2.4% (95% 0.2 - 6.5%), these results are not out of keeping with previous population based studies which estimated the recurrence risk of VTE in pregnancy to be 4.0 - 12% (1,2,3). Previous recommendations for heparin prophylaxis in women with a history of VTE were based on these numbers. Such recommendations weighed the risks of recurrence (mortality and morbidity) against the risks of heparin prophylaxis (thrombocytopenia, bone loss, bleeding, and discomfort of subcutaneous administration). The risks of heparin prophylaxis includes thrombocytopenia which has been stated to be in the 1-3% range (4) but it is generally felt that the risk of life-threatening thrombocytopenia is quite low in these patients. While bone loss of 5 - 10% in up to 36% of women treated with prophylactic doses of unfractionated heparin has been reported (5), it appears that this bone loss is at least partially reversible. Osteoporotic fractures, though reported, are rare. The risk of bleeding in pregnant women on therapeutic doses of UF has been reported to be 2% (6) but the risk in women on prophylactic doses of UF is likely to be even lower. The recurrence risk of VTE includes not only the possibility of a potentially fatal event but also the 32 - 49% of developing a postphlebotic syndrome (7) which can have a major impact on lifelong quality of life. Thus, proponents of heparin prophylaxis using these previously estimated recurrence rates have felt that these risks of treatment do not outweigh the benefits of preventing VTE recurrence. This study would not seem to provide convincing evidence to alter this risk balance assessment.

These authors do attempt to stratify women for their risk of recurrent VTE. The data does suggest that some women with an underlying thrombophilia may have the highest risk. However, it is also likely that future research will identify new important thrombophilias in patients now thought to have none just as those with Factor V Leiden or the prothrombin G20210A mutation were not known to have an abnormality even 10 years ago. Thus, while it is reasonable to evaluate patients for underlying thrombophilias to aid in risk stratification, the

individual women with a “negative” workup may still be at high risk for recurrent VTE. In an attempt to further risk stratify patients, the circumstances of the original DVT (idiopathic versus an association with a temporary risk factor) were noted. Two of the 6 patients with recurrent VTE had the initial event in association with a temporary risk factor. (Both were found to have Factor V Leiden). One would do well to remember that pregnancy *itself is* a temporary risk factor that is present throughout the entire gestation and the postpartum period. At least 50% of patients with an underlying thrombophilia develop their first DVT in association with a predisposing risk factor. In young women this is likely to be oral contraceptives or pregnancy. It would not seem appropriate then to consider a previous VTE that occurred in association with temporary risk factor to have less important implications for pregnancy.

In regards to treatment, these authors recommend postpartum anticoagulation with “warfarin because of its safety, convenience, and low cost.” However, from other studies it appears that antepartum VTE occurs at least as frequently as postpartum VTE. (8,9,10,11) One retrospective study of 17,000 pregnancies found that 75% of DVT’s occurred antepartum (half by 15 weeks gestation). (9) Thus, since antepartum VTE occurs at least as often as postpartum VTE and since heparin prophylaxis seems well tolerated (as is coumadin), it does not make sense to target only the postpartum period for prophylaxis.

In summary, while the authors should be applauded for their contribution of this prospective study to the pregnancy literature, caution should be exercised in interpreting the results and recommendations. The proper management of women during pregnancy with a history of VTE remains controversial and certainly these pregnant women should be well counseled as to the risks and benefits of both withholding and of administering heparin prophylaxis during pregnancy. Clearly, more research is needed and if possible, these women should be encouraged to participate in clinical studies.

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