

SAFETY OF WITHHOLDING HEPARIN IN PREGNANT WOMEN WITH A HISTORY OF VENOUS THROMBOEMBOLISM

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ABSTRACT

Background Women with a history of venous thromboembolism may be at increased risk for venous thromboembolic events during pregnancy. In these women, the decision to give or withhold heparin in the antepartum period is controversial, because accurate estimates of the frequency of recurrent thromboembolic events if antepartum heparin is withheld are not available.

Methods We prospectively studied 125 pregnant women with a single previous episode of venous thromboembolism. Antepartum heparin was withheld, but anticoagulant therapy was given for four to six weeks post partum. Our primary objective was to determine the rate of antepartum recurrence of venous thromboembolism. Laboratory studies were performed to identify thrombophilia in 95 women.

Results Three of the 125 women (2.4 percent) had an antepartum recurrence of venous thromboembolism (95 percent confidence interval, 0.2 to 6.9 percent). There were no recurrences in the 44 women who had no evidence of thrombophilia and who also had a previous episode of thrombosis that was associated with a temporary risk factor. Among the 51 women with abnormal laboratory results or a previous episode of idiopathic thrombosis, or both, 3 (5.9 percent) had an antepartum recurrence of venous thromboembolism (95 percent confidence interval, 1.2 to 16.2 percent).

Conclusions The risk of recurrent antepartum venous thromboembolism in women with a history of venous thromboembolism is low, and therefore routine antepartum prophylaxis with heparin is not warranted. (N Engl J Med 2000;343:1439-44.)

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PREVIOUS venous thromboembolism (a collective term for deep venous thrombosis and pulmonary embolism) is a recognized risk factor for venous thromboembolism in nonpregnant patients after anticoagulation therapy is discontinued.¹ The risk diminishes with time after the initial event. The risk is higher if the past episode was unprovoked,² and the risk may be higher if the past episode was associated with biochemical abnormalities indicating thrombophilia than if it was associated with a reversible risk factor.³ Although infrequent, venous thromboembolism during pregnancy is an important cause of maternal death.^{4,5} Women with prior venous

thromboembolism are believed to have a higher risk of venous thromboembolism in a subsequent pregnancy, but estimates of recurrence rates vary from 0 to 13 percent.

The higher estimate has prompted some authorities to recommend anticoagulant prophylaxis during pregnancy and during the postpartum period in women with prior venous thromboembolism.⁶⁻⁸ However, the risk is likely to be lower than previously suggested, because objective testing was rarely used to confirm the diagnosis of venous thromboembolism (resulting in an overestimate), and retrospective studies involved nonconsecutive patients,^{9,10} with the lower estimates coming from prospective studies.¹¹⁻¹³ Anticoagulant therapy during pregnancy is problematic, because coumarins can cause embryopathy, and heparin, although safe for the fetus, is expensive and inconvenient and can cause bleeding⁶ and osteoporosis.^{14,15}

In view of these considerations, and a recent overview that claimed that fatal pulmonary embolism as the initial manifestation of recurrence is rare, particularly in patients with good cardiopulmonary reserve,¹⁶ the routine use of heparin prophylaxis in pregnant women with previous venous thromboembolism should be challenged. We performed a prospective cohort study to evaluate the safety of withholding antepartum heparin prophylaxis in women with a single previous episode of venous thromboembolism.

METHODS**Patients and Clinical Tests**

We conducted a multicenter, prospective cohort study of consecutive, eligible women between July 1994 and September 1998. To be eligible for the study, women had to be enrolled before 20 weeks' gestation and have a history of a single episode of deep-vein thrombosis of the leg diagnosed by either compression ultrasonography or venography, or pulmonary embolism diagnosed by either lung scintigraphy or pulmonary angiography. Women were excluded if they had any of the following: known thrombophilia (deficien-

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cy of antithrombin, protein C, or protein S, or presence of antiphospholipid antibodies, the factor V Leiden mutation or the prothrombin G20210A mutation), an ongoing need for anticoagulant therapy, or venous thromboembolism within three months before the current pregnancy. All women underwent bilateral compression ultrasonography of the deep veins on entry into the study. Antithrombotic treatment was not administered ante partum. Within 24 hours after delivery, all the women were given 5000 or 7500 U of unfractionated heparin subcutaneously twice daily and a first dose of warfarin. Heparin treatment was discontinued at discharge, regardless of the international normalized ratio. Warfarin was given for four to six weeks post partum in doses adjusted to achieve a target international normalized ratio of 2.0 to 3.0. The women were seen in the clinic when warfarin treatment was discontinued, and there was follow-up by telephone at three months post partum.

Clinical follow-up was conducted as follows. Women who had symptoms or signs of deep-vein thrombosis during pregnancy underwent serial compression ultrasonography of the proximal veins, and the results were compared with the base-line images. If the base-line images were normal and there was a noncompressible segment, deep-vein thrombosis was diagnosed.¹⁷ If the base-line compression ultrasonogram was abnormal and no new changes were found, ultrasonography was repeated in seven days. If a new noncompressible segment was identified, it was considered diagnostic of recurrence. If serial testing raised the suspicion of a new noncompressible segment, venography with lead shielding of the fetus was performed; a persistent intraluminal defect was considered diagnostic of recurrence. Women with symptoms or signs of pulmonary embolism underwent ventilation-perfusion lung scanning. Pulmonary embolism was ruled out if the perfusion scan was normal and was diagnosed if the result was interpreted as indicating a high probability of pulmonary embolism. For other, nondiagnostic lung-scan patterns, the clinician had the option of performing serial compression ultrasonography or pulmonary angiography with appropriate shielding of the fetus. In all cases, when deep-vein thrombosis or pulmonary embolism was suspected and ruled out, anticoagulant therapy was withheld. All cases of suspected symptomatic recurrence were assessed by an independent central adjudication committee.

Blood samples were obtained from 95 women on entry into the study. Plasma was separated by centrifugation and stored at -70°C until assayed; peripheral-blood leukocytes were stored for analysis for possible mutations. Assays for factor V Leiden,¹⁸ the prothrombin G20210A mutation,¹⁹ protein C,²⁰ protein S,²¹ antithrombin,²² anticardiolipin antibodies,²³ and lupus anticoagulant²⁴⁻²⁶ were performed in a central laboratory. For factor V Leiden and the prothrombin G20210A mutation, the test results were based on genetic analysis that determined whether any abnormal genes were present. The criteria for the diagnosis of deficiencies were less than 66 percent of normal activity for protein C, less than 24 percent for free protein S antigen, and less than 80 percent for antithrombin activity. Lupus anticoagulant was considered to be present if the lupus-sensitive activated partial-thromboplastin time (Diagnostica Stago, Asnières, France) and dilute Russell's-viper venom time (DRVV, American Diagnostica, Greenwich, Conn.) were abnormal. Abnormal results were confirmed by either hexagonal phospholipid (Staclot LA, Diagnostica Stago) or DRVV Confirm (American Diagnostica) tests. Anticardiolipin antibodies were considered to be present when the serum antibody concentrations exceeded five standard deviations above the mean (Anticardiolipin Test, Readds, Westminster, Colo.). Since the plasma free concentration of protein S is reduced in pregnant women, the measurements were repeated at least three months after the discontinuation of postpartum treatment with coumarins in the women whose concentrations were low during pregnancy. Only women with persistently low concentrations were considered to have inherited protein S deficiency. The tests were not performed until the trial was completed. The protocol was approved by the institutional review boards of the participating centers, and written informed consent was obtained from all study subjects.

Statistical Analysis

We calculated 95 percent confidence intervals for each point estimate of clinical events. Odds ratios and the corresponding 95 percent confidence intervals were calculated with Confidence Interval Analysis software (version 1.1, *British Medical Journal*, London). We anticipated a 6 percent rate of recurrence of antepartum venous thromboembolism, and on the basis of this estimate, we sought to enroll a sample large enough to exclude the possibility that the true recurrence rate was 10 percent or more. Thus, if the upper limit of the 95 percent confidence interval was less than 10 percent, it would be reasonable to recommend withholding antepartum heparin prophylaxis. We initially planned to enroll 250 women, but we stopped the trial after enrolling 125 women because the single planned interim analysis ruled out a true recurrence rate of 10 percent. We did not calculate a statistical penalty when we stopped the study early, and the 95 percent confidence intervals are therefore uncorrected and thus marginally narrower than they should be.

RESULTS

One hundred thirty-three women met the inclusion criteria, of whom six were subsequently excluded; five had known thrombophilia, and one had deep-vein thrombosis within three months of entry into the study. Of the 127 eligible women, 2 refused consent. The mean (\pm SD) age of the women was 30 ± 5 years, and the duration of pregnancy at enrollment was 15 ± 6 weeks. There were 131 previous episodes of venous thromboembolism (six women had previously had simultaneous deep-vein thrombosis and pulmonary embolism). Of the initial episodes, 92 were deep-vein thrombosis (25 idiopathic and 67 associated with a temporary risk factor) and 39 were pulmonary embolism (18 idiopathic and 21 associated with a temporary risk factor). The temporary risk factors for the initial episode of venous thromboembolism in the women were pregnancy in 31 women, oral-contraceptive use in 20, surgery in 16, trauma in 12, immobility in 4, and chemotherapy in 1. In women with an initial episode that was idiopathic, the mean interval between the initial event and entry into the study was 4 ± 4 years.

There were three episodes of recurrent antepartum venous thromboembolism (2.4 percent; 95 percent confidence interval, 0.2 to 6.9 percent) (Table 1). Two women had antepartum deep-vein thrombosis: one had a proximal deep-vein thrombosis at 29 weeks' gestation, and the other had deep-vein thrombosis in the calf at 28 weeks. There was a single case of pulmonary embolism at nine weeks' gestation. These three women were treated with low-molecular-weight heparin for the remainder of their pregnancies.

There were also three episodes of postpartum deep-vein thrombosis: one occurred 2 days after a complicated missed abortion with hemorrhage at 11 weeks of gestation, and the other two occurred at 3 and 8 weeks post partum. All three women were treated with anticoagulant therapy. No woman had a postpartum recurrence while receiving warfarin, and the mean duration of warfarin prophylaxis was 33 days. However, one of the three women who had a post-

TABLE 1. RECURRENT VENOUS THROMBOEMBOLIC EVENTS DURING AND AFTER PREGNANCY IN 125 WOMEN WITH PREVIOUS VENOUS THROMBOEMBOLISM.

PATIENT No.	PREVIOUS EVENT	RECURRENT EVENT	STAGE OF PREGNANCY	RESULTS OF TESTS FOR THROMBOPHILIA
1	Right deep-vein thrombosis, idiopathic	Left proximal deep-vein thrombosis	29 wk	Factor V Leiden, prothrombin G20210A mutation, and protein C deficiency
2	Right deep-vein thrombosis, temporary risk (oral-contraceptive use)	Left calf deep-vein thrombosis	28 wk	Factor V Leiden
3	Pulmonary embolism, idiopathic	Pulmonary embolism	9 wk	All test results normal
4	Left deep-vein thrombosis, temporary risk (cesarean section)	Left proximal deep-vein thrombosis	2 days post partum	Factor V Leiden
5	Left deep-vein thrombosis, idiopathic	Right calf deep-vein thrombosis	3 wk post partum	Transiently low plasma concentration of free protein S during pregnancy
6	Left deep-vein thrombosis, idiopathic	Left proximal deep-vein thrombosis	8 wk post partum	Protein S deficiency

partum recurrence might have benefited from a longer course of anticoagulant therapy, because the recurrence occurred two weeks after she stopped taking warfarin. Neither of the other two women who had a postpartum recurrence received postpartum warfarin; warfarin was withheld in one woman because of uterine hemorrhage, and the other refused warfarin and was given 12,500 U of unfractionated heparin twice daily subcutaneously without laboratory monitoring. No woman had any bleeding while receiving anticoagulant therapy.

There were nine episodes of suspected pulmonary embolism (all investigated by ventilation-perfusion lung scanning) in nine women, of which one was objectively confirmed. Suspected deep-vein thrombosis was investigated 18 times in 18 women and was objectively confirmed in 5 women. There were no episodes of fatal pulmonary embolism. Of the 41 women with an initial episode of idiopathic venous thromboembolism, 4 had recurrent venous thromboembolism, as compared with 2 recurrences among the 84 women whose initial venous thromboembolic event was not idiopathic (odds ratio, 4.4; 95 percent confidence interval, 0.1 to 36.0). Recurrence rates for these women are shown in Table 2.

Of the 95 women from whom blood was taken on entry into the study, 48 (51 percent) had one or more abnormalities. Of the 30 women who did not have blood samples taken, none had a recurrence. There were 58 abnormal test results in the 48 women who had at least 1 abnormal result: low plasma concentrations of free protein S in 30 women, heterozygosity for factor V Leiden in 11, heterozygosity for the prothrombin G20210A mutation in 7, antithrombin deficiency in 3, protein C deficiency in 3, lupus anticoagulant in 2, and anticardiolipin antibodies in 2. None of the women were homozygous for factor V Leiden or the prothrombin G20210A mutation.

Plasma concentrations of free protein S are often low during the second and third trimesters of pregnancy.^{27,28} Only 1 of the 30 women with low plasma concentrations of free protein S (Patient 6 in Table 1) had true protein S deficiency on testing during follow-up; she had a recurrent deep-vein thrombosis post partum. None of the 29 women with transiently low plasma concentrations of free protein S had a recurrence (Table 3).

Aside from the transiently low plasma concentrations of free protein S during pregnancy, there were 29 abnormal test results in 25 of the 95 women from whom blood was drawn (26 percent) (Table 3). Of these women, 22 had a single abnormal test result and 3 had multiple abnormal results. One woman had factor V Leiden, the prothrombin G20210A mutation, and protein C deficiency; one had both anticardiolipin antibodies and lupus anticoagulant; and one had factor V Leiden and protein C deficiency. Among these 25 women with abnormal test results, 4 had recurrent venous thromboembolism, as compared with 2 of the 70 women with normal test results (odds ratio, 6.5; 95 percent confidence interval, 0.8 to 56.3). Of the test abnormalities, factor V Leiden was associated with the highest odds ratio (Table 3).

Fifty-one women had an abnormal laboratory result, a previous episode of idiopathic thrombosis, or both. Three of these women (5.9 percent; 95 percent confidence interval, 1.2 to 16.2 percent) had an antepartum recurrence of venous thromboembolism. In contrast, there were no recurrences among the 44 women with normal laboratory results and a previous episode that was associated with a temporary risk factor.

DISCUSSION

We found that women with a single previous episode of venous thromboembolism had a low rate of recurrent antepartum events during a subsequent preg-

TABLE 2. RISK FACTORS AND RATE OF RECURRENT VENOUS THROMBOEMBOLIC EVENTS IN 95 WOMEN WITH PREVIOUS VENOUS THROMBOEMBOLISM.*

VARIABLE	IDIOPATHIC CONDITION AND ABNORMAL TEST RESULTS	TEMPORARY RISK FACTOR AND ABNORMAL TEST RESULTS	IDIOPATHIC CONDITION AND NORMAL TEST RESULTS	TEMPORARY RISK FACTOR AND NORMAL TEST RESULTS
Recurrent events (no.)				
Total	2	2	2	0
Ante partum	1	1	1	
Post partum	1	1	1	
No recurrence (no.)	8	13	24	44
Recurrence rate				
Percent (95% CI)	20 (2.5–55.6)	13 (1.7–40.5)	7.7 (0.01–25.1)	0 (0.0–8.0)

*CI denotes confidence interval. Temporary risk factors were pregnancy, use of oral contraceptives, surgery, trauma, immobility, and chemotherapy. Only women in whom laboratory studies were performed are included.

TABLE 3. ABNORMAL TEST RESULTS AND RISK OF ANTEPARTUM AND POSTPARTUM RECURRENT VENOUS THROMBOEMBOLISM IN 95 WOMEN WITH PREVIOUS VENOUS THROMBOEMBOLISM.

TEST	RECURRENT VENOUS THROMBOEMBOLISM (N=6)*	NO RECURRENCE (N=89)	ODDS RATIO (95% CI)†
	no. of cases		
Factor V Leiden	3	8	10.0 (1.0–80.0)
Deficiencies of protein C, protein S, and antithrombin; presence of anti- phospholipid antibodies	2‡	9§	4.4 (0.2–35.4)
Prothrombin G20210A mutation	1	6	2.8 (0.7–32.9)
Transiently low plasma concentration of free protein S during pregnancy	1	28	0.4 (0.1–4.0)

*Four of the six recurrent episodes were associated with a single abnormal blood-test result, one was associated with three abnormalities, and one was not associated with an abnormal test result.

†CI denotes confidence interval.

‡One woman had protein C deficiency and one had protein S deficiency.

§Of these women, three had antithrombin deficiency, two had anticardiolipin antibodies, two had lupus anticoagulant, and two had protein C deficiencies.

nancy. The three antepartum events that occurred correspond to a rate of recurrence of 4.0 percent per patient-year of follow-up. This risk is similar to that among patients who have been treated for venous thromboembolism associated with a temporary risk factor, a subgroup with a lower-than-average risk of recurrence.^{29,30}

The strengths of our study are that it was prospective, that only women with previous, objectively documented venous thromboembolism were eligible, and that there was independent, central adjudication of clinical events. Its limitations are as follows. We did not achieve our estimated sample size because we stopped

the study early after a planned interim analysis. However, the upper limit of the 95 percent confidence interval for antepartum recurrence of venous thromboembolism was 6.9 percent, a value that reliably excludes a true rate of 10 percent.

In addition, our estimates of risk factors for the recurrence of venous thromboembolism were based on subgroup analyses, but they are likely to be accurate because they are consistent with the results of studies in nonpregnant patients. For example, none of the 44 women in our study who had normal test results and an initial episode of venous thromboembolism associated with a temporary risk factor had a recurrence

(Table 2). In contrast, women with an initial episode of idiopathic venous thromboembolism and those with an abnormal test result on screening for thrombophilia (especially factor V Leiden) appeared to be at increased risk for recurrence. However, for each calculation except that for factor V Leiden, the lower limit of the 95 percent confidence interval for the odds ratio was less than 1.0 (Table 3).

Another limitation is that the selection of women who had had one prior episode of venous thromboembolism and the exclusion of women who had had an episode of venous thromboembolism within three months before pregnancy means our results are not generalizable to pregnant women with multiple prior thrombotic events or a very recent event.

Finally, although there were no fatal cases of pulmonary embolism, even a slight increase in fatal recurrences would be unacceptable. However, in a recent study, fatal pulmonary embolism was a rare manifestation of recurrence, particularly in the absence of cardiopulmonary disease and premonitory symptoms.¹⁶ We emphasized the need for prompt investigation of symptoms of deep-vein thrombosis and pulmonary embolism to women in this study.

In summary, the low rate of recurrence in our study challenges the belief that all pregnant women with previous venous thromboembolism should receive antepartum heparin prophylaxis. However, we recommend postpartum anticoagulant therapy with warfarin because of its safety, convenience, and low cost. In pregnant women with previous venous thromboembolism who have not been tested for thrombophilia, we recommend such testing ante partum. In particular, given the high prevalence of factor V Leiden among the women in this study (11.6 percent) and the association between factor V Leiden and recurrence, testing for this abnormality is important. Conversely, we do not recommend that plasma free protein S be measured ante partum, because abnormal results are common and do not predict recurrence of thromboembolism.

None of the 44 women with a temporary risk factor and normal blood-test results had a recurrence, strongly suggesting that they need not receive antepartum heparin prophylaxis. In the other three subgroups of women, in whom the recurrence rates were higher, we recommend offering the choice of antepartum heparin or regular follow-up examinations.

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APPENDIX

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