Pregnancy related thromboembolism

Rosendaal, F.R.

breast-feeding patients. I would appreciate the authors' comments on this issue.

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2. **Lee RV.** Thromboembolic disease and pregnancy: are all women equal? [Editorial] Ann Intern Med. 1996;125:1001-3.
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4. **Sturridge F, de Swiet M.** The use of low-molecular weight heparin for thromboprophylaxis in pregnancy. Br J Obstet Gynaecol. 1994;101:69-71.

To the Editor: We would like to point out a critical error by Friederich and associates (1) and to report on what we believe is the largest population study of the incidence of deep venous thrombosis and pulmonary embolism in the setting of delivered pregnancies (4 weeks postpartum). Our data suggest that the incidence is not only low but is similar to the incidence in closely age-matched nonpregnant women in another study (2).

The annual 1.8% frequency of deep venous thrombosis in nonpregnant women 20 to 40 years of age cited by Friederich and colleagues is inaccurate. As listed in the original report (2), the correct frequency is 0.018%.

We reviewed records of delivered pregnancies and postpartum periods during which deep venous thrombosis and pulmonary embolism occurred from January 1985 through January 1996 in the northern California region of Kaiser Permanente (a health maintenance organization serving 2.5 million members). A total of 280 793 deliveries occurred; among these, 251 charts were identified by International Classification of Diseases codes with concomitant diagnoses of delivered pregnancy/postpartum and thromboembolic disease. Patients were included in our study if deep venous thrombosis or pulmonary embolism was documented by venography, Doppler ultrasonography, ventilation–perfusion scanning, or pulmonary angiography. Eighty-one patients met these criteria (67 with deep venous thrombosis and 14 with pulmonary embolism); thus, the incidence of documented deep venous thrombosis or pulmonary embolism in this population was 0.029%.

As cited in Friederich and colleagues' study, previous studies have reported frequencies of these conditions of 1.3% to 7% during pregnancy and 6.1% to 23% during the postpartum period (1). Our incidence suggests a much lower frequency, as does the 0.055% frequency reported in the second largest population study of these two conditions in women giving birth; like ours, this study required objective documentation of thromboembolism (3). Most noteworthy, in nonpregnant women 20 to 40 years of age, the annual frequency of thromboembolism has been observed to be 0.018% (2). By using the Fisher exact test, we found no statistically significant difference between this incidence and the incidence of deep venous thrombosis or pulmonary embolism in our study population ($P > 0.2$).

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In response: Dr. Manoharan addresses the important issue of the use of a drug when there is no formal knowledge of safety in a specific situation. The experience with low-molecular-weight heparin in pregnancy was obtained while the pharmaceutical companies advised against use of the drug during pregnancy (1, 2). One report has indicated that low-molecular-weight heparin, like unfractionated heparin, does not appear in breast milk (3). Moreover, heparin is not easily absorbed and thus when given orally is unlikely to cause any adverse effects.

We thank Brickner and colleagues for pointing out a mathematical error that escaped our attention when we reviewed the galley proofs of our article. The numbers in the second paragraph of the introduction should read 0.018%, 0.013% to 0.07%, and 0.061% to 0.23%, respectively. Thus, Brickner and colleagues' findings agree with the existing literature on the incidence of pregnancy-related venous thromboembolism in the general population.

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To the Editor: In his editorial on thrombosis prophylaxis during pregnancy in women with hereditary or acquired thrombophilia, Lee (1) rightly asks whether all women entering reproductive life should be screened for coagulation deficiencies. For factor V Leiden, we have already answered in the negative: If mass screening for factor V Leiden were followed by routine anticoagulation prophylaxis, even a short course (say, 6 weeks) of oral anticoagulation during the puerperium might cause the death of as many young mothers as, or even more than, would have died of pulmonary emboli resulting from their thrombophilic condition (2). The recommendation that attention be paid to the personal and family history of thrombosis is borne out by the important paper by Friederich and colleagues (3), whose results pertain to women who already have one or more relatives with venous thrombosis and a coagulation defect. Lee mentions that a fear of litigation in the United States might lead to defensive testing for thrombophilia and prescribing of anticoagulation during the entire pregnancy. We hope that this will be counterbalanced by a fear of hemorrhagic side effects (although we, as Europeans, are not sure whether such side effects might also lead to litigation) (4).

Prescribers should not forget that there are different modes of prophylaxis. For example, it might be worthwhile to investigate prophylaxis with elastic stockings during or after pregnancy (alone or in combination with a very low dose of pharmacologic anticoagulation). In a meta-analysis of prophylaxis in patients having hip surgery, elastic stockings proved to be only slightly less effective than pharmacologic anticoagulation and certainly caused no bleeding (5).

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Table. Guide to Clinical Decisions about Prophylaxis of Thromboembolism in Pregnant Women

History of Thromboembolism?		Screen for Thrombophilia?	Pharmacologic Prophylaxis?	
Personal	Family		Antepartum	Intrapartum or Postpartum
No	No	No	No	No
Yes	No	Maybe	Maybe	Yes
No	Yes	Yes	Maybe	Yes
Yes	Yes	Yes	Probably	Yes

complications in oral anticoagulant therapy an analysis of risk factors Arch Intern Med 1993 153 1557 62

5 **Imperiale TF, Speroff T** A meta analysis of methods to prevent venous thromboembolism following total hip replacement JAMA 1994 271 1780 5

In response I thank Drs Vandenbroucke and Rosendaal for reinforcing the importance of old fashioned history taking as a screening strategy for thrombophilic predisposition In a litigious venue unfortunately the availability of a quantifiable test often means that the new technique supplants the old and becomes the standard And after the presence of thrombophilia has been identified doing nothing during pregnancy (a condition highly publicized as a hypercoagulable state) is risky even when doing something like anticoagulation has clearly defined risks In light of new studies of genetic thrombophilic conditions neither the older literature about pregnancy and thromboembolism nor the literature that deals exclusively with thromboembolic disease in nonpregnant patients is a reliable source of guidance

There should be no debate about adequate heparinization for women who have thromboembolism during pregnancy or the postpartum period There should also be no debate about the universal utility of prophylactic postural and mechanical procedures (such as use of elastic stockings) for pregnant women Which pregnant women need pharmacologic prophylaxis how much prophylaxis is necessary and when prophylaxis should be administered need to be further elucidated Any clinical decisions and studies must be stratified according to the personal and family histories of thromboembolic events and according to the results of evaluation for thrombogenic predisposition (**Table**)

I am not aware of any prospective studies examining the outcome in terms of prevention of thromboembolism with varying doses of heparin during gestation I agree with Drs Vandenbroucke and Rosendaal that given the coagulation changes of pregnancy a small amount of heparin should go a long way Studies of heparin metabolism indicate that to treat active thromboembolism during pregnancy a larger dose than expected may be necessary However we do not know whether this applies to prophylaxis in a patient with a personal or familial history of thromboembolic disease

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Update in Infectious Diseases

To the Editor In the Update in Infectious Diseases Bartlett (1) states that worldwide about 1 7 billion persons currently have tuberculosis This statement implies that these persons have clinical tuberculosis In 1991 Kochi (2) estimated that approximately 1 7 billion persons were infected with *Mycobacterium tuberculosis* This figure reflected the prevalence of tuberculous infection not tuberculosis itself

In Table 2 incidence is defined as the number of deaths per epidemic period unless otherwise noted I assume that this is a typographical error and that incidence is referring to the number of cases rather than the number of deaths

In Table 5 the frequency of administration of trimethoprim–sulfamethoxazole for prevention of *Pneumocystis carinii* pneumonia and toxoplasmosis was not included

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1 **Bartlett JG** Update in infectious diseases Ann Intern Med 1997 126 48 56

2 **Kochi A** The global tuberculosis situation and the new control strategy of the World Health Organization Tubercle 1991 72 1 6

In response Dr Frankel is correct about the incidence of tuberculosis The estimate of 1 7 billion refers to the number of patients who are infected with *M tuberculosis* not the number of patients with tuberculosis itself

In Table 2 the footnote for Incidence is mislabeled This refers to the number of patients infected rather than the number of deaths The number of deaths is given in the next column With regard to Table 5 trimethoprim–sulfamethoxazole is administered once daily except as otherwise stated

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The Illusion of Deterministic Rules

To the Editor The recent article by Glassman and colleagues (1) contains several errors and may mislead readers about the promises and limitations of cost effectiveness analysis

First their Table 2 reflects a 2 5% risk for rupture with aneurysms 3 5 to 3 9 cm in diameter but their text reports a figure of 0 25% Second their Table 3 from which most of their conclusions are drawn is inaccurate A common mistake in calculating lives saved is not using a fixed reference point In this case a reasonable reference point is the number of patients who would die if no patients had surgery for aneurysms Using their example 2900 of 40 000 patients would die under those circumstances (3080 if the 2 5% risk for rupture is used for aneurysms <4 cm rather than the 0 25% we used) In either case the number of lives saved for each threshold at each of the three hospital networks is calculated relative to this reference point We believe that the correct figures are presented in the **Table** on page 166

Many of the authors conclusions are not preserved with this new table For example the authors view that the three hospital networks differ little in total number of lives saved at the 5 cm threshold for surgery is no longer supported Similarly although the authors table suggested that increasing numbers of lives are saved at the 6 cm threshold as one moves from network A to network C our table reveals the opposite The authors result could never be achieved given the different surgical mortality rates In the new table network A not only saves more lives at the 4 cm threshold it saves each life at a lower cost than network B or C

Finally we agree that cost effectiveness analyses often involve tradeoffs and that those tradeoffs can be hard to balance But hard to balance tradeoffs are not an argument against using cost effectiveness analyses to develop decision rules An important purpose of cost effectiveness analysis is to make these tradeoffs explicit Sometimes these analyses reveal that some strategies are clearly better than others The miscalculations by Glassman and colleagues understate the persuasiveness of quantitative health policy analysis After this analysis for example who would consider using a 4 cm threshold at network B or C? More lives could be saved at a lower cost by using a 6 cm threshold at network A Similarly a 5 cm threshold at network C is clearly worse than a 6 cm threshold at network A or B

We believe that few could support using the 4 cm threshold at network A after viewing this analysis Although this strategy