Journal of Medical
Screening

Editorials

Should we screen for factor V Leiden?

The explosive coagulation cascade is held in check by antithrombin and the protein C system. In the latter, activated protein C inactivates coagulation factors V and VIII in the presence of its cofactor, protein S. Deficiencies of antithrombin, protein C, and protein S are not common but are well described and are associated with thrombosis. A fourth inherited cause of thrombosis became apparent four years ago when Dahlback and colleagues discovered the phenomenon of resistance to activated protein C. They identified a middle aged man with a personal and a family history of thrombosis whose activated partial thromboplastin time was not prolonged as expected when exogenous activated protein C was added to his plasma.[1] One year later the molecular defect was identified as a point mutation in factor V.[2] The mutation was a G to A substitution at nucleotide position 1691. This results in the arginine at position 506 being replaced by a glutamine, and the mutant factor V has become known as factor V Leiden. This mutation explains the phenotype because activated protein C inactivates normal factor V by an initial cleavage at arginine 506, which is now prevented.

Factor V Leiden has become important because of its prevalence. In white European and North American subjects this mutation is present in about 5% of the population (which means that about 1 in 1600 will be homozygotes). This seems to be due to a founder effect and it is rare in the rest of the world.[3] In the past the gene must have offered a selective advantage, but now we are concerned about its association with an increased risk of thrombosis. It is found in 20% of all cases of deep vein thrombosis (DVT) and in those cases where there is a family history of DVT it is found in 50%. The increased risk of thrombosis has been estimated from the Leiden thrombophilia study, in which the odds ratio for thrombosis was seven for heterozygotes and 80 for homozygotes.[4]

The initial test for resistance to activated protein C was based on the activated partial thromboplastin time. This test costs about £2, and in expert hands it has been reported to have a sensitivity of 90% and a specificity of 95% for the factor V Leiden mutation.[5] Such a test would have a negative predictive value of 99.4% and a positive predictive value of 48.6% when the prevalence in the population tested is 5%. However, in the routine service laboratory the sensitivity and specificity are rather less than those quoted above. Fortunately, a modification of the activated protein C resistance test, diluting the patient's plasma in factor V deficient plasma, results in the sensitivity and specificity approaching 100%.[6] This increases the cost to about £4 a test but means that the currently more expensive DNA testing can be used for confirmation of positive results rather than screening. If mass screening were to become routine then, possibly, modern techniques could dramatically reduce the cost of DNA testing.

Environmental factors also increase the risk of thrombosis. The main categories are immobilisation and female hormones. In the first category a major problem is postoperative venous thromboembolism, in the second are included the combined oral contraceptive pill, pregnancy, and hormone replacement therapy. Should we screen for factor V Leiden and if so when? We do not yet have data to show how it modulates postoperative risk, but after surgery we should continue to make sure that all patients are considered for prophylaxis, and this is likely to remain the best strategy. Screening all pregnant women and giving some form of prophylactic anticoagulation to one in 20 women during pregnancy and the puerperium would be extremely expensive and associated with considerable morbidity and mortality. There is no evidence that the benefit would outweigh the risk, which for an individual woman with factor V Leiden remains low.

We do have data from the Leiden thrombophilia study on the interaction between factor V Leiden and the thrombotic risk imposed by the combined oral contraceptive pill. In this analysis the combined oral contraceptive pill had an odds ratio for thrombosis of four, the factor V Leiden mutation an odds ratio of eight, and for both together the odds ratio was 35.[7] The fourfold increase in risk due to the combined oral contraceptive pill in this study, in which a mixture of pills was used, is in keeping with the threefold and sixfold increases in risk estimated for pills without and with gestodene or desogestrel (CMO's Update 8). On this basis some have argued that we should screen for factor V Leiden before prescribing the pill. Assuming the risk of

Table 1 Cases of venous thromboembolism per 100 000 women years

	Without COC	*With COC*	*Excess cases*
All women	5	20	15
Normal controls	4	15	11
Factor V Leiden	30	130	100

COC=combined oral contraceptive pill.

Table 2 Risk of VTE for women taking the combined oral contraceptive pill for 10 years

	All (%)	*Normal controls (%)*	*Factor V Leiden (%)*
Absolute increase in risk	0.15	0.11	1.00
Probability of no VTE reduced:			
From	99.95	99.96	99.70
To	99.80	99.85	98.70
NNT for 10 years for one extra event	667	909	100

VTE=venous thromboembolism, NNT=number needed to treat.

venous thromboembolism in women of this age distribution is five per 100 000 (CMO's Update 8) then using these odds ratios (and assuming 5% of the population have factor V Leiden) we can construct table 1. We thus have an estimate of the excess cases of venous thromboembolism due to use of the combined oral contraceptive pill and the role of factor V Leiden.

We have the facts but how they are presented can have a marked effect on how they are interpreted,[8] so in table 2 the risk of thrombosis in women who use the pill for 10 years is presented in different ways. For an individual woman the issue is subjective, but I think most people would agree that the risk is not excessive even in women with factor V Leiden. In the United Kingdom three million women take the pill, and we can estimate that the pill results in 450 extra episodes of venous thromboembolism and nine deaths a year (assuming a mortality of 2%). Denying the estimated 150 000 women with factor V Leiden the pill would prevent 150 episodes of venous thromboembolism and three deaths a year.

These figures do, however, have one important assumption, which is that other methods of contraception do not increase the risk of venous thromboembolism by having a higher failure rate. If denying women with factor V Leiden the pill results in an increase in pregnancies then the overall number of thromboses may increase as pregnancy is a greater thrombotic risk than taking the pill. It is instructive to note that the recent pill scare in the United Kingdom resulted in a significant increase in the number of abortions (British Pregnancy Advisory Service). On balance, screening women without a personal or family history of thrombosis does not seem advisable.

The same arguments can be used for the analogous situation of hormone replacement therapy. The increased risk of thrombosis with hormone replacement therapy is about threefold (similar to the second generation combined oral contraceptive pill). The background risk has doubled because of the older age group, but the absolute risk in women who do not have a personal or family history of thrombosis is low and screening cannot be justified.

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