Factor V Leiden: should we screen oral contraceptive users and pregnant women?

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The factor V Leiden mutation is the most common genetic risk factor for deep vein thrombosis: it is present in about 5% of the white population. The risk of deep vein thrombosis among women who use oral contraceptives is greatly increased by the presence of the mutation. The same seems to be true of the risk of postpartum thrombosis. Several authors have called for all women to be screened before prescription of oral contraceptives and during pregnancy. Such a policy might deny effective contraception to a substantial number of women while preventing only a small number of deaths due to pulmonary emboli. Moreover, in pregnancy the ensuing use of oral anticoagulation prophylaxis might carry a penalty of fatal bleeding that is equal to or exceeds the risk of death due to postpartum thrombosis. It might pay, however, to take a personal and family history of deep vein thrombosis when prescribing oral contraceptives or at a first antenatal visit to detect women from families with a tendency to multiple thrombosis.

Our recent reports on an increased risk of venous thrombosis in women who use oral contraceptives and are also carriers of a thrombogenic mutation (factor V Leiden)[1,2] prompted discussions about the possible benefit of screening for this coagulation defect before oral contraceptives are prescribed.[3-8] Also, the spectre of screening in other risk situations, such as pregnancy, is being raised.[5,9] We believe that some perspective on the epidemiological data is necessary.

Venous thrombosis is a rare event, especially in young people, and, if limited to the limbs, is benign. By calculating back from a population based case-control study, we estimated that the incidence rate of venous thrombosis of the legs in women aged 15 to 49 years is 2.1 per 10 000 women years.[1] Although estimates on the prevalence of the factor V mutation vary, a fair approximation is that about 5% of the white population will be carriers. The mutation leads to a relative resistance of coagulation factor V to breakdown by activated protein C (APC resistance). This reduces the efficiency of the blood's own anticoagulation system and therefore increases the propensity to venous thrombosis.[10]

Oral contraception

In our earlier study[1] we estimated that the incidence of deep vein thrombosis of the legs among women who did not use oral contraceptives and were not carriers of the mutation was 0.8 per 10 000 women years; this increased to 3.0 per 10 000 women years among women who used oral contraceptives and to 5.7 per 10 000 women years among carriers of the factor V mutation. Among women who had both risk factors (carriers of the factor V mutation who used oral contraceptives) the incidence became 28.5 per 10 000 women years. These differences point to a synergistic effect as the additional risk for both risk factors together is greater than the sum of each of the separate increases in risk; in fact the relative risks are almost multiplicative.[1] The calculation of incidences from our case-control study was approximate, however, and the relevant relative risks had wide confidence intervals. In a pharmacoepidemiological linkage study in Britain, as well as in a back calculation from the Oxford data of the World Health Organisation's case-control study on venous thrombosis, the incidence of venous thrombosis among non-users of oral contraceptives—about 0.4 per 10 000 woman years[11,12]—was lower than we had calculated, which might be due to the investigation of slightly younger age groups (15 to 40 or 44 years) or to differences in case definition and ascertainment.

The worst outcome for a young woman with deep vein thrombosis is that she develops fatal pulmonary emboli. The case fatality of venous thrombosis among people aged less than 40 years in hospitals in the United States is estimated at 2%.[13] This estimate is an overall figure and includes people with severe trauma or who have had major surgery, possibly with repetitive and massive pulmonary embolism. It might be too high when applied to young women who develop thrombosis during the use of combined oral contraceptives—a case fatality of 1% might be closer to reality. However, if the "worst case" 2% is multiplied by our estimate of the incidence, the use over one year of oestrogen and progestogen contraception in women who are carriers of the mutation would lead to a death rate from pulmonary emboli of 5.7 per 100 000 a year.

PREVALENCE AND RISK

This risk applies to only a small segment of the population of young women. In the Netherlands in our population based case-control study about 3% of the control group were carriers of the mutation.[14] In a study in the United States of a large group of middle aged, male physicians the prevalence of the mutation was about 6%.[15] The highest population prevalence, 15%, has been found in Greece[6] and southern Sweden.[8] In contrast, the prevalence of the mutation in Asian and African countries seems much lower.[6] In the Netherlands in 1994, 45% of women aged 15-49 years currently used oral contraceptives; peak use was 80% at age 20 to 24, but it was already 53% at age 15-19 and still about 20% over the age of 40.[16] In Britain the use of oral contraceptives is generally held to be lower—about 50% at the younger ages, and much lower at older ages.

The annual risk of death remains small, even among carriers of the mutation who use oral contraceptives. On the other hand, every year in each industrialised country a few young women die of pulmonary emboli. Some of these profound individual tragedies will be due to the combination of the pill and the mutation.

SHOULD WE SCREEN?

What advice should we give to ensure the greatest public good? If we want to be extremely risk avoiding we might screen all young women who are on the pill or who intend to start using it. Such a policy might deny

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oral contraceptives to at least 3% to 6% of women, with the ensuing risk of other problems: related strain due to unappealing methods of contraception and contraceptive failures resulting in unwanted pregnancies and their consequences.[17] Therefore, unless our estimates prove too conservative or unless other risks—such as arterial thrombosis (myocardial infarction or stroke)—are also determined by the same combination of risk factors, we do not support universal screening before prescription.

Moreover, the screening task would be formidable. From a death rate from pulmonary embolus of 5.7 per 100 000 a year, it follows that about 20 000 women positive for factor V should be denied the use of oral contraceptives during one year to prevent one death. At an estimated population prevalence of the mutation of 1 in 20, 400 000 young women would need to be screened to find them. Of course only 40 000 women need to be screened if it is assumed that the benefit accrues over 10 years of non-use of oral contraceptives; that extrapolation is uncertain as the incidence of thrombotic events is higher during the first year of use. If the population prevalence of the mutation is higher, say 1 in 10, 200 000 women would still need to be screened to prevent one death. On the other hand, if we use lower figures for the incidence of venous thrombosis, for its fatality, and for the prevalence of factor V Leiden (for example, a baseline incidence of 0.5 per 10 000 women years, a case-fatality of 1%, and a prevalence of 3%) the number of women who need to be screened to prevent one death might exceed two million.[18]

The cost and reliability of the screening test(s) are also variable: it depends to a large extent on the accuracy of the coagulation test that detects activated protein C resistance (which is the coagulation consequence of the mutation), the number of times that the coagulation test has to be followed by DNA determination, or the choice for a direct DNA determination without coagulation testing. Even at nominal laboratory costs for testing for activated protein C resistance and DNA confirmation, screening for factor V Leiden before prescription of contraceptives is unlikely to stand the competition for resources with other medical screening and therapeutic interventions.

PREVIOUS VENOUS THROMBOSIS

If a woman has already had a venous thrombosis the reasoning over whether or not to screen might be different. No data exist about young women who continue taking the pill after a first deep vein thrombosis. A previous venous thrombosis, however, is known to be a strong risk factor for a further thrombosis.[19] Evidence now exists that recurrence rates of idiopathic venous thrombosis—that is, without a clear precipitating factor such as trauma or surgery—are higher in carriers of the factor V mutation than in non-carriers.[20] These data pertain to middle aged male physicians, however, and we do not know whether they apply to young women with a history of thrombosis who use contraceptives.

In the recent past, when the factor V Leiden mutation was still unknown, most doctors were already advising young women with a history of venous thrombosis to consider other modes of contraception, such as progestogen-only pills or barrier methods, if these were acceptable to her and her partner. The advice seemed more urgent if the thrombosis had happened soon after starting oral contraceptives without any other precipitating factors, or if pulmonary emboli had developed. The wisdom of this advice is borne out by a follow up study that showed how recurrence rates of idiopathic thrombosis were lower in women who had stopped using oral contraceptives than in women who had never taken the pill.[21] (Of course if there is a clear precipitating factor—say, an arthroscopy of the knee joint—such a thrombosis will not count as heavily as a purely idiopathic one during pill use.) Doctors will continue to give the same advice to a young woman with thrombosis, irrespective of her factor V status. When the woman is a carrier of the mutation she will have a raised baseline risk, which gives firmer ground for advising her to opt for other modes of contraception. The advice might become mandatory if the woman is a homozygous carrier of the mutation: in homozygotes the risk of venous thrombosis is 50 to 80 times the baseline risk, and oral contraception might increase this to more than a hundredfold.[22] The same might be true if a woman carries two different thrombogenic mutations—for example, factor V Leiden combined with deficiency of protein C, protein S, or antithrombin.[9]

Oral contraception, pregnancy, and factor V Leiden

- Women who carry the factor V Leiden mutation and use oral contraceptives have a much greater risk of deep vein thrombosis
- Routine screening for the factor V Leiden mutation before prescription of oral contraceptives would deny effective contraception to about 5% of white women, while preventing only a small number of fatal pulmonary emboli
- If routine screening for the factor V Leiden mutation during pregnancy is followed by routine anticoagulation prophylaxis, the number of cases of fatal bleeding might equal or exceed the number of fatal pulmonary emboli that are prevented
- Taking a personal and family history of deep vein thrombosis when prescribing oral contraceptives, or at a first antenatal visit, will detect people from families with a tendency to multiple venous thrombosis and might be worthwhile

FAMILIAL VENOUS THROMBOSIS

Should we take a family history of venous thrombosis at first prescription of oral contraceptives? Yes—the main advantage of the family history is that it may help to detect families with a "thrombophilic tendency" (that is, when several members have deep vein thrombosis, often multiple, at younger ages or without clear precipitating risk factors).[23] The factor V mutation is found in more than half of these families, and homozygotes are more common (when both parents have the mutation). Also, other rare genetic thrombophilia disorders can be detected by taking a family history: deficiency of protein C, protein S, or antithrombin. Although their rarity has precluded the exact calculation of their effect when combined with the use of oral contraceptives, the overall picture is one of a rather similar potentiation of risk. Moreover, in families with a tendency to multiple thrombosis there is more often a combination of the factor V mutation and one of the rarer mutations. Presumably, these families carry still other, presently unknown, genetic or other risk factors for venous thrombosis.[24] The detection of such families is worth while from a clinical point of view: even if no known mutations are found but there still is a clear family history of venous thrombosis, clinical wisdom might dictate caution in prescribing combined oestrogen and progestogen contraceptives. The main disadvantage of the family history is that it is not very sensitive—for example, when a person has few relatives the possibility of a family history rich in venous thrombosis is obviously much reduced. Nevertheless, if the family history is positive, the prescribing doctor has information that should certainly be taken into account.

Pregnancy

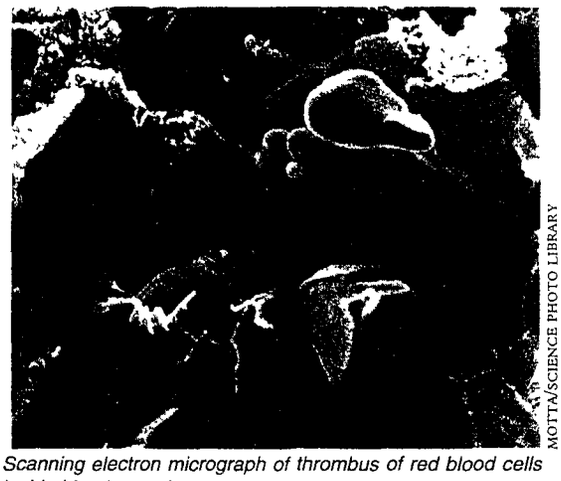
The postpartum period is when women are often at greatest risk of pulmonary emboli. Should all pregnant women be screened for the mutation? The overall maternal death rate due to pulmonary embolism has been estimated for the Netherlands over a long period (1952-79) as 5 per 100 000 deliveries.[25] Lower estimates were obtained in the early 1980s for Britain (0.3 per 100 000 deliveries (0.5 per 100 000 after caesarean section)) and the United States (1.2 per 100 000).[26,27] If half of these events were to happen among, say, the 5% women who carry the factor V mutation,[5] the risk of puerperial death due to pulmonary embolism might be as high as 1 in 2000 or as low as 1 in 15 000 among women with the mutation. In principle these events might be prevented by prophylactic anticoagulation.

Oral anticoagulation, however, carries its own risk. Under conditions of optimal monitoring, two to three patients per 100 treatment years will develop severe bleeding (necessitating admission to hospital). The risk of fatal bleeding or intracranial bleeding that leads to lifelong handicap is about 0.5 patients per 100 treatment years.[28,29] This figure applies to the overall population that receives long term oral anticoagulation, which is elderly and often has major underlying disease (malignancies) or which is in need of high intensity anticoagulation—for example, for artificial cardiac valves. In general the risk of severe bleeding during chronic treatment depends on the achieved level of anticoagulation and is lower among younger people, but it is higher among women.[28] In the experience of the Leiden thrombosis centre, which has published similar overall complication rates, the risk among younger women who receive short term anticoagulation for prophylaxis or treatment of venous thrombosis is not materially different from the overall risk (F J M van der Meer, personal communication). Perhaps this is because these courses of treatment are short, so they bear the brunt of the first weeks of treatment, when the right dosage is still being sought and bleeding complications are more frequent. As a course of prophylactic treatment takes about six weeks (about one tenth of a treatment year), a deadly or debilitating complication of postpartum anticoagulation prophylaxis might affect 1 in 2000 young mothers. This penalty of anticoagulation prophylaxis equals the highest estimate of risk of death due to puerperial thrombosis among women positive for factor V Leiden.

Such comparisons between benefits and risks are extremely tenuous, of course, and mainly illustrate our lack of knowledge. The published estimates of risk of death due to puerperial thrombosis vary widely, and the fraction wherein factor V Leiden might have a role is known only approximately. The estimate of the risk of prophylactic oral anticoagulation in young women is based on small numbers and subject to chance variation, as the indication is relatively rare. Nevertheless, the provisional balance seems to indicate that the benefit of treatment equals its penalty, which does not immediately point to the necessity of an overall screening and anticoagulation prophylaxis during and after pregnancy.

LIMITATIONS

The risk-benefit calculations may alter completely for prophylactic interventions that carry no penalty, even if they are less effective. For example, tight elastic stockings are a nuisance but only slightly less effective than pharmacological anticoagulation (at least in preventing deep vein thrombosis after hip surgery), and they certainly do not cause any bleeding.[30] In between these two extremes (full oral anticoagulation *v* elastic stockings) it remains to be determined whether



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Scanning electron micrograph of thrombus of red blood cells inside blood vessel

intermediary pharmacological regimens, such as low dose conventional heparin, low dose low molecular weight heparin, or "low intensity" warfarin (aiming at an international normalised ratio below 2.0), have a place. Data are scarce, however, about the relative effectiveness or complication rates of these agents when used for several weeks or months.

An important clinical factor that we could not take into account in this calculation is a possible difference in the risk of puerperial thrombosis between women with and without a history of thrombosis. Although the studies are relatively small, evidence exists of a roughly 10% recurrence rate of deep vein thrombosis during or after pregnancy.[21,31] If we accept a similar mortality of 2% this will tilt the balance in favour of anticoagulation prophylaxis among women with a history of thrombosis, regardless of whether they are factor V positive. Again the concern about homozygotes or women with combined defects might be stronger. For the same reasons as with use of oral contraceptive, taking the personal as well as the family history of venous thrombosis of a woman at first prenatal consultation might be worth while: it might detect individuals and families with thrombophilia where clinical judgment might be different.[32]

The family

Most advice given to carriers of factor V Leiden mutation derives from what is generally advised to members of families with inherited thrombophilia due to deficiency of protein C, protein S, or antithrombin.[33,34] Such families first come to the attention of coagulation specialists because one proband mentions that he or she is now the second, third, or fourth member of the family developing venous thrombosis without any clear precipitating factor. Often the thromboses developed at young ages or were multiple. Families with a tendency to multiple thrombosis are likely to harbour more than one genetic or environmental risk factor (or have simply had "bad luck").[9,14,24] These high risk families are rare and often receive highly personalised care in specialised centres. The situation has been completely altered, however, because of the high frequency of factor V mutation among patients with deep vein thrombosis (up to 20%). Screening for the mutation seems likely to be adopted in the routine investigation of many patients with venous thrombosis. This will yield increasing numbers of thrombotic patients with the mutation, many without a clear family history of thrombosis.

What should we tell family members, half of whom might also carry the mutation? To date we have no data on family members of consecutive patients who are not members of families with a tendency to multiple thrombosis. A woman with venous thrombosis and factor V Leiden mutation might have daughters or sisters who

take the contraceptive pill These relatives have at least one family member with venous thrombosis who carries the mutation Should we offer them screening? Perhaps they should first be told about the benefits and risks of knowing and asked about the acceptability of other forms of contraception The advice to be screened might be firmer if other first degree family members are found to have had deep vein thrombosis at young ages or without clear risk factors (which would suddenly make the family into one with a tendency to multiple thrombosis), or if the index patient is a homozygote or carries combined thrombogenic defects The clinical situation of the patient and the other family members will continue to direct the doctor's advice, rather than the mere presence or absence of a mutation

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Grand Rounds—Hammersmith Hospital

A case of laboratory acquired brucellosis

A rare condition, but laboratory transmission is a risk

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Brucellosis is now rare in Britain, and most cases are imported or contracted in a laboratory setting We present the case of a veterinary scientist who contracted the condition while working on the products of conception from animals

Case history

A 24 year old man who was studying immunology at a postgraduate medical school presented to this hospital's casualty department in July 1995 with a 17 day history of high fevers, night sweats, dry cough, and myalgia He also complained of pain and discharge from a lower left molar tooth He had no medical history and was taking no regular drug treatment. A travel and occupational history showed that he had lived in Himachal Pradesh in northern India until March 1995, when he moved to London. He had previously qualified as a veterinary surgeon, before studying for a microbiology degree between 1993 and 1995. During this time he had performed regular experiments on the products of conception from cattle and sheep to investigate possible infectious causes of abortion.

On examination at admission the patient had a fever of 38 5°C, a solitary cervical lymph node measuring 1 cm × 0 5 cm in size, a resting tachycardia of 110 beats per minute, and a palpable splenic tip. Examination of his mouth showed pus discharging from the lower left third molar tooth.

Initial investigations showed raised inflammatory markers (erythrocyte sedimentation rate 34 mm in the first hour and C reactive protein concentration of 84 U/l) and white cell count of 4 8 × 10^9/l Three blood films for malaria parasites were negative Standard liver function tests yielded abnormal results (with a raised serum alkaline phosphatase concentration of 405 U/l, a raised γ-glutamyltransferase concentration of 410 U/l, and a raised serum aspartate aminotransferase concentration of 248 U/l); the serum bilirubin concentration was at the upper end of the normal range, at 17 μmol/l.