The Obstetric Medicine Listserv: review of controversies surrounding thrombophilia testing

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Summary: A woman with no significant personal or family history of thrombosis asked her internist to obtain a thrombophilia work-up prior to starting the combined oral contraceptive for dysmenorrhoea, after another physician advised her to have the test. The case was sent to an international email discussion group where the consensus was that testing should not be done. The responses of the group and review of this controversial topic are presented.

Keywords: thrombophilia, factor V Leiden, oral contraceptives

Dr. Carson maintains an email discussion group comprised of members of the International Society of Obstetric Medicine and the North American Society of Obstetric Medicine. The group was created in 2009, grew from 90 to over 200 members, and responses have come from 23 cities in at least 13 different countries in Asia, the Middle East, Europe, North America, Central America, and Australia and New Zealand. Dr. Jorn is a general and obstetric internist who, with Dr. Carson, is the co-coordinator of the Obstetric Medicine Interest Group at the Society of General Internal Medicine in the US. This article is based on a discussion initiated by a group member regarding the controversial and sometimes emotional topic of thrombophilia testing in the setting of potential oral contraceptive use in a young woman.

'Logic Is Making Mistakes With Confidence' – Fortune Cookie Paraphrasing Manley's Maxim.

CASE REPORT

An 18-year-old woman of normal weight presented, with her mother, to the office of her internal medicine physician to discuss the use of oral contraceptives to manage severe dysmenorrhoea that had not responded to non-hormonal management. She was not anticipating sexual activity in the near future. There was no personal or family history of thrombotic events suggestive of heritable clotting disorders. After becoming aware of an anecdotal patient death presumably related to a combined oral contraceptive (COC) and an undiagnosed thrombophilia, the patient's dermatologist suggested that the daughter be tested for clotting disorders prior to starting

COCs for any reason. This internist was familiar with the data and the potential treatment implications related to obtaining these tests in a low-risk patient, but the dilemma was that the dermatologist planned to order a thrombophilia screen if the internist did not. After a lengthy discussion with the patient and her mother, reviewing the risks of true/false-positive and negative tests, the uncertain clinical implications of a 'true positive,' and a lot of internal conflict, the internist ordered the thrombophilia tests, deciding it was better for them to be obtained by a physician familiar with the potential implications. Once the test results were available, the internist posed the case and question to the Obstetric Medicine online discussion group: Knowing the results of the testing (regardless of whether it was appropriate to order), how should the results guide future management for this patient regarding contraception and future pregnancy?

Test results:

Low-activated protein C ratio (APC-R) indicative of the presence of APC resistance. DNA-based testing demonstrated heterozygosity for factor V Leiden (R506Q) mutation. No evidence of lupus anticoagulant (LAC), dysfibrinogenaemia, or intravascular coagulation and fibrinolysis. Normal or elevated antithrombin, protein C or protein S. The patient does NOT have the prothrombin G20210A mutation. The pathologist added: 'If indicated, consider testing for serum anticardiolipin antibodies (IgG and IgM) and plasma homocysteine'.

BACKGROUND

Thrombophilias have been defined as disorders 'likely' to predispose to thrombosis.¹ In the setting of venous thromboembolism (VTE) or some obstetric complications, testing for antiphospholipid antibody syndrome or inherited protein deficiencies (protein C, S, antithrombin) may provide guidance

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for clinical care, but the controversy surrounds two genetic variants. The prevalence of Factor V Leiden (FVL or the R2 A4070G mutation) is 12–15% among those with VTE compared with ~5% of controls, and the respective rates for the prothrombin gene mutation (G20210A; Factor II 20210) are 6–8% versus 2%.^{2,3} These associations were found in the pregnant and non-pregnant population, but newer data suggest that testing for these abnormalities will not direct clinical care among patients with VTE and obstetric complications. It is worth mentioning that elevated homocysteine levels are not associated with an increased risk for VTE.^{4,5}

These retrospective associations prompted the publication of guidelines promoting ordering of these tests as a screen to identify women at higher risk for VTE associated with pregnancy or COCP use, and a positive result meant that women were told to avoid all hormonal contraceptives, or were given thromboprophylaxis with heparin for the duration of their pregnancies.⁶ Recent consensus statements do not promote universal screening of women for FVL/prothrombin before therapy with a COCP, but the definition of the population that should be tested is vague.⁷

COCP RISK

Initial retrospective data were used to estimate that, compared with non-pregnant and FVL-negative women, heterozygosity for FVL increased the risk of VTE in non-pregnant women by a factor of 10, and exposing a heterozygote to pregnancy or a COCP would increase the VTE risk by 50–100.⁸ However, it is estimated that 20,000 FVL-positive women would have to be denied COCPs to prevent one fatal pulmonary embolism (PE).⁹ Additionally, the theoretical benefit of VTE avoidance, even if appropriate, will result in the use of less reliable birth control. Intrauterine devices (IUDs) are reasonable alternatives, but they are not available or appropriate for all women. If the COCP users switch to condoms, it could result in an increase of unintended pregnancies, up to 11,800/100 person-years.¹⁰ The net result of withholding COCPs for FVL-positive women, owing to the risk of VTE during those unintended pregnancies, would be an increase in the VTE rate.

PREGNANCY RISKS

Early studies found retrospective associations between FVL/prothrombin and pregnancy loss/placental insufficiency syndromes (preeclampsia, abruption and growth restriction), and women with a past history of these obstetric complications were offered empiric treatment with subcutaneous heparin in subsequent pregnancies. A 2002 case-control study demonstrated no association between FVL and growth restriction, and a similar 2010 study found a positive association with growth restriction but not preeclampsia.^{11,12}

No prospective studies have demonstrated that testing to identify women for FVL/prothrombin mutations and then treating with heparin has a clinical benefit greater than the potential risks. The risks of heparin include heparin-induced thrombocytopenia, decreased bone mineral density and cost. Prophylactic anticoagulation during pregnancy with low-molecular-weight heparin such as enoxaparin, costs US\$10,380 over a course of 10 months (Drugstore.com prices as of 7 November 2011 were \$2076 for 60 × 40 mg prefilled syringes). Other data suggest that the risk of significant bleeding

may actually be higher than the benefit of fewer VTE events. A large cohort study found the deep venous thrombosis rate to be 71 per 100,000 deliveries, with FVL present in 8% of the patients with thrombosis.¹³ A risk/benefit analysis using those data postulated that if one-half of the fatal PE occurred in the ~10% with FVL, the risk of VTE with FVL would be approximately one in 13,000.⁶ As the risk of intracranial bleeding leading to lifelong handicap is estimated to be one in 2000 mothers anticoagulated for at least six weeks, it appears that the risk of major haemorrhage on heparin appears to be greater than the risk of fatal PE.¹⁴

The dermatologist's implication that he would advise against using an COCP, but not against pregnancy if the patient was FVL positive, ignored three important pieces of information: (1) the attributable risk of VTE among pregnant women with FVL is 9500/10⁶, more than double the risk of 4500/10⁶ if those women took a COCP; (2) because a prospective study of non-pregnant patients with VTE found that heterozygosity for FVL did not increase the risk of recurrence over a six-year period, it appears that the actual risk of FVL is smaller than that suggested by the retrospective data; and (3) the prospective obstetric data do not link FVL to obstetric complications.^{8,15,16}

It is interesting that articles advocating FVL testing do not suggest that it will affect recommendations regarding becoming pregnant, they just suggest an unproven treatment in the form of heparin.

EMAIL DISCUSSION COMMENTS

Among 209 email discussion group members who care for women with medical issues during pregnancy, there were 13 responses from 10 countries, and all respondents agreed with the physician who submitted the case to the group: FVL screening is (was) not indicated for this patient. Some offered more than one treatment option for the patient. In terms of treating the dysmenorrhoea, five suggested a levonorgestrel-based IUD (Commercial Name: Mirena® [levonorgestrel-releasing intrauterine system] Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ 07470, Manufactured in Finland), four suggested either a progesterone-only pill or medroxyprogesterone acetate injections, and three suggested a combination COCP with proper counselling regarding the risks.

CASE REVISITED

In an effort to clarify recommendations for the patient on whom the testing was done, she was referred to a haematologist. The internist spoke with the consultant regarding her concerns and the suggestions from the email discussion group members regarding the progesterone-based IUD or progestin-only contraceptives. The haematologist recommended against hormonal contraception (without differentiating between estrogen containing or progestin-only products) but did not advise the physician or patient regarding how to approach management in future pregnancies.

CONCLUSIONS

It is important to be aware of the implications of positive test results. The comments posted by the discussion group members are in line with current evidence that does not support widespread ordering of FVL and prothrombin testing

in asymptomatic women prior to pregnancy or treatment with an COCP, and a recent editorial presents evidence supporting this approach.¹⁷ For patients with VTE, prospective data have established that FVL results should not alter the duration of anticoagulation. However, it is difficult to decline to offer a test, especially when another physician has offered to perform it, but the cost to patients and overburdened health-care systems from inappropriate testing could be enormous. The ideal solution would be publication of practice guidelines so physicians can offer testing when appropriate and know they are doing the most good for the most people, without fear that the anecdote will come back to haunt them.

DECLARATIONS

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