Treatment of venous thromboembolism in a 22-year-old woman taking an oral contraceptive pill

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A previously healthy 22-year-old woman presented to the emergency department with shortness of breath. She had been taking a combined oral contraceptive pill since the age of 17 years. Computed tomographic pulmonary angiography confirmed the diagnosis of pulmonary embolism and she was started on rivaroxaban. She is seeing her family physician for follow-up.

Has the patient been prescribed an appropriate anticoagulant?

Direct oral anticoagulants are the preferred initial treatment for acute venous thromboembolism in ambulatory patients without cancer. Several randomized controlled trials (RCTs) on acute venous thromboembolism have found direct oral anticoagulants to be noninferior to standard therapy — consisting of enoxaparin (low-molecular-weight heparin) followed by warfarin (vitamin K antagonist) — in reducing recurrent venous thromboembolism.[1,2] Safety outcomes of dabigatran and rivaroxaban showed no significant difference in bleeding risk compared with standard therapy, while apixaban and edoxaban reduced the absolute risk of major or clinically relevant nonmajor bleeding by 5.4% and 1.8%, respectively.[1–4]

Direct oral anticoagulants are more convenient than vitamin K antagonists, because they do not require laboratory monitoring and there are fewer drug interactions and no known food interactions. However, they are more expensive than vitamin K antagonists and dependent on renal clearance. The American College of Chest Physicians guideline recommends direct oral anticoagulants over vitamin K antagonists as first-line therapy for venous thromboembolism in patients who do not have cancer.[5]

Should the patient stop taking the oral contraceptive pill?

It appears safe to continue the combined oral contraceptive pill in patients with acute venous thromboembolism who are receiving anticoagulation. A subgroup analysis of 1888 women younger than 60 years of age who had been enrolled in an RCT of rivaroxaban versus standard therapy for acute venous thromboembolism found hormonal therapy was not associated with increased risk of recurrent venous thromboembolism during therapeutic anticoagulation.[6]

In addition, continuing the oral contraceptive pill is a simple and effective method to ensure that women who receive anticoagulation also receive contraception, which decreases the risk of fetal exposure to oral anticoagulation. Both vitamin K antagonists and direct oral anticoagulants are contraindicated in pregnancy.[5]

Immediately stopping the oral contraceptive pill in a woman who requires anticoagulation with direct oral anticoagulants may substantially worsen menorrhagia, potentially leading to decreased quality of life and iron deficiency anemia. Direct oral anticoagulants of the factor Xa inhibitor group appear to increase menorrhagia more than vitamin K antagonists. In the aforementioned analysis, abnormal uterine bleeding doubled in women who were receiving rivaroxaban compared with standard therapy, with a hazard ratio of 2.13 (95% confidence interval [CI] 1.57–2.89).[6] A subgroup analysis of a large apixaban trial found a similar effect.[7] The mechanism is unknown.

If anticoagulation is stopped, estrogen should be avoided thereafter to decrease the risk of recurrent venous thromboembolism. Progestin-only contraceptives can be considered.

For how long should anticoagulation be continued?

Anticoagulation for acute venous thromboembolism should be continued for a minimum of three months; the decision to extend anticoagulation depends on the risk of recurrent venous thromboembolism, bleeding and patient preference.

Risk of recurrence in patients with venous thromboembolism provoked by a nonsurgical risk factor, such as estrogen, is estimated at 5% within one year and 15% within five years when anticoagulation is stopped after a minimum of three months.[5] Although the annual risk of bleeding in patients on anticoagulation without risk factors is estimated at 0.8%, the case fatality from major bleeding (11.3%) is greater than from recurrent venous thromboembolism (3.6%).[5,8] Therefore, the American College of Chest Physicians guideline recommends stopping anticoagulation after three months for venous thromboembolism that is provoked by a reversible risk factor.[5]

Absent other risk factors, venous thromboembolism in this setting may be considered to have been provoked by the oral contraceptive pill. Anticoagulation may be stopped after three

months in patients who are no longer taking the oral contraceptive pill, but should be continued indefinitely as long as oral contraception is still being used.

Does the patient require anticoagulation if planning pregnancy?

It is recommended that pregnant women with a history of estrogen-provoked venous thromboembolism receive antepartum prophylaxis, and all pregnant women with previous venous thromboembolism should receive postpartum prophylaxis for six weeks.[5]

A retrospective cohort study of more than 8000 women found that women whose first venous thromboembolism was associated with pregnancy or the postpartum period had a higher risk of recurrence during a subsequent pregnancy than women with unprovoked venous thromboembolism (4.5% v. 2.7%; relative risk 1.71; 95% CI 1.0–2.8).[9] The American College of Chest Physicians considers that women with a history of venous thromboembolism related to estrogen have a moderate to high risk of recurrence.[5]

Little evidence guides peripartum prophylaxis. A systematic review of low-molecular-weight heparin evaluated 64 studies reporting 2777 pregnancies; of 1436 women receiving thromboprophylaxis with low-molecular-weight heparin, only 13 (0.9%) developed venous thromboembolism. There were no maternal deaths and a 1.98% rate of substantial bleeding, mostly owing to obstetric causes.[10] Because of these findings and low-molecular-weight heparin's long record of safety, the American College of Chest Physicians guideline recommends low-molecular-weight heparin for thromboprophylaxis in pregnancy.[5]

In the first six weeks postpartum, low-molecular-weight heparin or warfarin may be used as neither is excreted into breast milk; conversely, the excretion of direct oral anticoagulants in breast milk is unknown, so they remain contraindicated.[11] Referral to a hematologist or specialist in obstetric medicine and a specialist in high-risk obstetrics is suggested for women in whom venous thromboembolism prophylaxis may be warranted during or immediately after pregnancy.

Case revisited

Further inquiry showed the patient was using the oral contraceptive pill solely for contraception and did not want indefinite anticoagulation. The combined oral contraceptive pill was continued for several weeks during anticoagulation, at which time the patient received an intrauterine device and the oral contraceptive pill was stopped. Because estrogen exposure had been discontinued, rivaroxaban was continued for three months, then stopped. The patient was informed that she will require referral to an expert in obstetric medicine for prenatal planning, as well as thromboprophylaxis with low-molecular-weight heparin, during pregnancy and for six weeks postpartum.

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The clinical scenario is fictional.

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