Genetic Testing for DVT Risk Still Controversial

BY JANE SALODOF MACNEIL
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ATLANTA — An inherited mutation, Factor V Leiden, puts people at risk for life-threatening blood clots. Carriers can be identified with a simple blood test, so why not use it?

"Genetic testing is highly controversial. This is really not ready for prime time yet," Dr. David Ginsberg advised during a special session on venous thromboembolism at the annual meeting of the American Society of Hematology.

Factor V Leiden has been associated with risk of miscarriage and possibly other complications, but most women with the mutation have normal pregnancies, he noted. Likewise, while Factor V Leiden has been linked to increased risk of venous thromboembolism in women taking oral contraceptives, they are not contraindicated.

The central issue for Dr. Ginsberg was not whether Factor V Leiden is a risk factor, but what that means and what, if anything, would be done differently when treating patients who test positive.

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DR. WEITZ

About 5% of people of European origin have Factor V Leiden, according to Dr. Ginsberg, the James V. Neel Distinguished University Professor of Internal Medicine and Human Genetics at the University of Michigan, Ann Arbor. It "clearly increases" relative risk, compared with no mutation in Factor V, but most people with the mutation do not develop blood clots.

"Nature would not allow this to be in 5% of the population, if it was really all that bad," he said, speculating that Factor V Leiden might confer a benefit in some patients who develop venous thromboembolism. "Factor V Leiden might not always be 'bad' for you," he said.

Dr. Ginsberg cited two human studies that found deep venous thrombosis (DVT) was less likely to progress to pulmonary embolism in people with Factor V Leiden. Also, he noted that in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial evaluating recombinant human activated protein C (rhAPC), or drotrecogin alfa activated, in patients with severe sepsis, 28-day all-cause mortality was lower in 65 patients with Factor V Leiden.

Based on current knowledge, a positive test for Factor V Leiden would not change any treatments, Dr. Ginsberg continued. Patients still would receive heparin or warfarin for acute thrombosis and be given warfarin for 3½ months as prophylaxis after a first event. If patients have recurrent thromboses, warfarin prophylaxis would be extended, possibly becoming a lifelong intervention.

In the future, he suggested Factor V Leiden testing might be useful when choosing primary therapy and duration of therapy for thrombosis. Likewise, the presence of Factor V Leiden might indicate the need for thrombosis prophylaxis during pregnancy, postoperatively, and after a first thrombotic event. And women may be screened for Factor V Leiden before oral contraceptives are prescribed.

But none of this is done now, and he said more data are needed to support genotype-specific prophylaxis or therapy. Meanwhile, a positive finding could be cause for anxiety and hypervigilance. "My plea is that, until there is clear-cut evidence, testing should be used judiciously," he said.

In an interview after the session, Dr. Jeffrey Weitz, another speaker at the special session, said he "very much agreed" with Dr. Ginsberg and does not test for Factor V Leiden unless a patient insists. Most patients requesting the test have thrombosis and are referred by primary care physicians, according to Dr. Weitz of Hamilton Civic Hospitals Research Centre in Ontario. "They say, 'Does this patient have Factor V Leiden?' " he said. "I talk them out of it."

For another speaker, Melanie Bloom, a national patient spokeswoman for the Coalition to Prevent Deep Vein Thrombosis, the test is not so easy to rule out, however. Her husband, David Bloom, died of a DVT that led to pulmonary embolism while covering the Iraq war for NBC news. After his death at the age of 39, the family became aware that he had been at high risk for DVT.

When their three young daughters reach the age where pregnancy and contraception are an issue, Mrs. Bloom said she would want to know whether they have an inherited risk. "David's life could have been saved with awareness and knowledge," she said. "Less than a quarter of physicians educate high-risk patients about DVT." ■

DRUGS, PREGNANCY, AND LACTATION

SSRIs and PPHN: Refining Risk Estimates

Over the past several years, a spectrum of studies evaluating the reproductive safety of selective serotonin reuptake inhibitors has been published. It includes studies suggesting a small absolute risk for major congenital malformations associated with first-trimester exposure to these medications. Other studies have described a transient perinatal syndrome associated with exposure to SSRIs late in pregnancy, with symptoms that include jitteriness, restlessness, respiratory difficulties, and tachypnea, in approximately 25% of newborns exposed to an SSRI during late pregnancy. These studies show consistently that there is a real risk for these symptoms, which, in perhaps the most systematic study, resolved without clinical intervention (Arch. Pediatr. Adolesc. Med. 2006;160:173-6).

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However, the potential risk for a more alarming adverse effect received considerable attention when a case-control study published last year noted an association between in utero exposure to SSRIs late in pregnancy and an increased risk for persistent pulmonary hypertension of the newborn (PPHN), a cardiovascular syndrome typically occurring in term or near-term infants shortly after birth, in which infants present with severe respiratory distress. Almost 400 women whose infants had PPHN who were enrolled in Boston University's Slone Epidemiology Center's Birth Defects Study were compared with more than 400 women whose infants did not have PPHN. In utero exposure to an SSRI after 20 weeks' gestation was associated with a significantly increased risk for PPHN, but neither the use of SSRIs before 20 weeks nor use of non-SSRI antidepressants was associated with an increased risk (N. Engl. J. Med. 2006;354:579-87.)

The authors suggested that the absolute risk for PPHN associated with late-trimester SSRI exposure approached 1%. This estimate was surprising to at least some investigators, considering the prevalence of SSRI use during pregnancy through the peripartum period. An increased risk of PPHN had not been observed in previous studies of SSRIs or even anecdotally in the literature. It is somewhat inconsistent with the experience of many clinicians who regularly see this population of patients. It is also noteworthy that the results were based on only 14 cases of PPHN in infants exposed to SSRIs after 20 weeks' gestation.

The publication of this study, cited in a 2006 Food and Drug Administration public advisory, led many women and their physicians to reconsider the use of SSRIs, particularly late in pregnancy, prompting some to discontinue the medication in the third trimester. This approach puts some women at risk because of evidence showing a high risk of relapse associated with antidepressant discontinuation during pregnancy, and evidence suggesting that both history of depression and depression during pregnancy are strong predictors of postpartum depression.

Receiving little attention is another case-control study published in August, which provided useful information about prenatal and perinatal factors associated with PPHN that are far more common than SSRI exposure. The study, which also used data from the Slone database, found a strong association between PPHN and cesarean delivery, which had been reported previously in the literature and is a well-established risk factor for PPHN; late preterm or post-term birth; being large for gestational age; and black or Asian maternal race. Being overweight, having diabetes, and having asthma were other maternal factors independently associated with PPHN (Pediatrics 2007:120;272-82).

This study is important because it adds context to the issue of risk factors for PPHN. Clearly, this study suggests that there are other factors that drive the risk for PPHN that appear more predictive than the absolute risk associated with exposure to SSRIs. When one considers the relative contribution to the outcome of PPHN, it is clear that the strongest predictors do not include SSRI use, but other more common factors.

The two studies could be viewed differently: One includes a risk factor, SSRI therapy, which could be considered modifiable, compared with constitutional factors such as BMI or race. But this argument discounts the morbidity and potential effects of maternal depression, which should be considered like any other maternal illness during pregnancy.

Women and their doctors typically have an appropriately high threshold regarding medication use during pregnancy, including antidepressants.

However, SSRI use may not be a modifiable factor because failure to treat depression during pregnancy can be associated with morbidity—clearly for the mother, but potentially for the infant as well. There is some evidence (although with sparse controlled data) indicating that maternal depression can increase the risk of having a small-for-gestational-age baby or a baby with low birth weight.

Considering the amount of data that has emerged over the past several years regarding the reproductive safety of SSRIs, we might expect the clinician to feel more empowered to make decisions about antidepressant use during pregnancy. But for many clinicians, and certainly for patients, some of the data have obscured the picture somewhat rather than clarifying it—leaving it to the clinician to provide patients with the best information possible and to make these decisions about SSRI use on a case-by-case basis.

As the amount of literature on the reproductive safety of SSRIs has increased over the past several years, and because these data are somewhat inconsistent, it becomes the clinician's role to look critically at the literature and to understand not only how new data inform clinical decisions, but also the potential limitations of the data—and how ultimately, these decisions need to be made with the patient on a case-by-case basis.

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