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Thrombophilia: Women-Specific Reference Ranges Can Prevent Misdiagnosis in Women
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Guest: Dr. Caroline Veen. Dr. Veen is currently a graduate student in the Department of Hematology at the Erasmus University Medical Center, Rotterdam.

Randye Kaye: Hello, and welcome to this edition of "JALM Talk" from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Thrombophilia is a state where inherited or acquired abnormalities of the hemostatic system are present that predispose to thrombosis. During normal pregnancy, major changes and hemostasis occur such as increasing concentrations of most clotting factors, decreasing levels in natural anti-coagulants and impaired fibrinolytic activity. Collectively, these can induce a thrombophilic state, especially in the last trimester. These normal changes in hemostasis resulting from hormonal influence protect women from fatal hemorrhage during delivery.

Complications during pregnancy can contribute to several abnormal physiological thrombotic states including preeclampsia (PE). Preeclampsia is characterized by a maternal hypercoagulable state with intravascular coagulation, microthrombosis in several organs and impairment of the uteroplacental circulation.

The development of preeclampsia during pregnancy can have detrimental effects to both the mother and fetus. The diagnosis of preeclampsia and postpartum thrombophilia remains challenging for certain populations and the use of universal reference ranges may be misleading in these women. Several studies have already highlighted the influence of age, sex, and oral contraceptive hormone use for a coagulation reference intervals. The development and adoption of gender-specific reference intervals for pregnant women is essential for accurate identification of thrombophilic states.

"Thrombophilia: Women-Specific Reference Ranges Can Prevent Misdiagnosis in Women" was published in the March 2018 issue of *The Journal of Applied Laboratory Medicine*. This work presents the establishment and impact of female-specific reference intervals for a variety of coagulation markers during pregnancy.

The first author is Dr. Caroline Veen. Dr. Veen is currently a graduate student in the Department of Hematology at the Erasmus University Medical Center, Rotterdam. She obtained her medical degree from the VU University in Amsterdam in 2013 and worked for two years in the Department of Internal Medicine and the Emergency Department. She's our guest for today's podcast. Welcome, Dr. Veen.

Let's start with this question, why are women's health issues so important in thrombosis and hemostasis?

Dr. Caroline Veen: Yes, well, thank you for the introduction and for your question.

Women's health issues are so important in thrombosis and hemostasis, specifically, because women experience unique situations, such as the menstrual cycle, pregnancy and delivery, in which disturbances of hemostasis may lead to bleeding problems or thrombosis. For example, it's known that over 80% of young women with Von Willebrand disease, which is an inherited disorder of primary hemostasis, experience menorrhagia and postpartum hemorrhage, which is defined as blood loss of more than 500 milliliters within 24 hours after delivery. It's also still one of the major causes of maternal deaths in the world and the prevalence is steadily increasing in many higher resource countries as well.

Furthermore, pre-existing coagulation disorders are known risk factors for postpartum hemorrhage. But it's shown that even mild hemostatic abnormalities can increase the risk for severe postpartum hemorrhage. And with regard to thrombosis, pregnancy is associated with an increase in concentrations of most regulation factors but also decrease in concentration as some of the natural anticoagulants which together induce a thrombophilic state, especially in the last trimester of pregnancy and the use of hormonal contraceptives also increase levels of coagulation factors.

So, this leads to a pro-coagulant risk profile and several studies have shown that currently used combined oral hormonal contraceptives increase the risk of thromboembolism two to sixfolds. So yeah, in order to keep on improving patient care, women-specific health issues deserve emphasis in the field of thrombosis and hemostasis, from my opinion.

Randye Kaye: Okay, thank you. So, keeping that in mind, do you think we should consider female-specific reference ranges for all laboratory tests?

Dr. Caroline Veen: Yes, that's a very important question, but I think it depends on the clinical relevance of the test for the target patient population. There are, of course, several factors that can cause differences in reference ranges between groups, and sex being an important factor, as the major difference of course, between men and young women is the presence of female sex hormones, which can have an influence on different test results.

And as we have shown in this study, using women-specific reference ranges can prevent misclassification or overdiagnosis of different diseases. But there are, I think, several arguments also not to have reference ranges for each different variable that can effect on these reference ranges. First of all, as I mentioned, it's important to take the clinical relevance into account. Some differences are small, can be considered not being clinical relevant and the International Federation of Clinical Chemistry and Laboratory Medicine recommends estimating reference ranges on at least 120 subjects. And enrolling this many subjects is difficult, it's costly, very time-consuming and lastly, taking into account, all the different variables that can have an influence on reference ranges. Think of age, but also dietary habits, or the environment, use of medication, muscle mass, it's simply not possible to calculate reference ranges for each of these different variables.

So, inclusion of each variable specific reference range, including sex, to my opinion, should primarily be based, I think, on the clinical relevance for the charted population.

Randye Kaye: Okay, thank you. So, it's certainly not across the board always important or easy to get, but certainly sometimes, it's important. If we consider female-specific reference ranges in thrombosis and hemostasis, should we also consider adjusted reference intervals for women who are using oral contraceptives?

Dr. Caroline Veen: Me and my supervisor had a lot of discussion about this specific issue. So, in the best scenario, of course, especially with regard to hemostasis, we would like to have different values for women with and without the use of hormonal oral contraceptives because of the earlier-mentioned influence of contraceptives on hemostasis.

However, as we see in our center, the diagnostic process of congenital thrombophilia in this case, but also the more rare coagulation disorders, is very challenging and is not necessarily carried out in routine laboratory in the Netherlands. So, therefore, our physicians are often consulted by physicians from regional hospitals and

information about the use of oral contraceptives may not always be known to the consult physician.

And because the contraceptive is still used in such a large group of young women -- I believe a few years ago, it was more than one-third of the young women in the Netherlands. In this study, we decided to include women using oral contraception in the women-specific reference ranges.

Randye Kaye: Okay, thank you and one final question, at which time point after pregnancy, would you recommend testing women for thrombophilia?

Dr. Caroline Veen: Also, a very important issue to be addressed. When I look into our clinic, we usually advise to test women at least three months after pregnancy, because then we believe all the effects of pregnancy and hemostasis have diminished. And initially in this study, we also wanted to investigate differences in hemostatic factors three and six months after pregnancy but unfortunately, the study design was not appropriate to answer this question.

There are some studies and there's one study published in 2016, where the authors investigated reference ranges in healthy population and they stated in their results that values 8 to 12 weeks after delivery were not different from healthy, non-pill using women and this was tested in a group of over 160 women.

A lot of studies however, when they investigate hemostatic variables after pregnancy, only measured coagulation factors the first days after delivery, usually the first one, two or three days, and not much is known about the period these days and eight weeks after pregnancy. So, I would recommend based on several studies to test for thrombophilia, for hemostasis in general, at least eight weeks after delivery.

Randye Kaye: That was Dr. Caroline Veen, from Erasmus University Medical Center in Rotterdam, talking about "Thrombophilia: Women-Specific Reference Ranges Can Prevent Misdiagnosis in Women" from the March 2018 issue of JALM for this podcast.

Thanks for tuning in for "JALM Talk," see you next time and don't forget to submit something for us to talk about.