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Angiogenic Biomarkers for Risk Stratification in Women with Preeclampsia.
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Guest: Dr. Sarosh Rana from The University of Chicago.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

Preeclampsia affects approximately 8% of pregnancies worldwide and is one of the leading causes of maternal morbidity and mortality. Risks include abruption, seizures, multi-system organ failure, heart failure, and postpartum hypertension in the short term, and cardiomyopathy, stroke, and dementia in the long term. Unfortunately, diagnosis of the condition is currently limited to utilization of nonspecific signs and symptoms. However, identification of potential pathogenic biomarkers may support earlier diagnosis and ultimately improved prognosis.

A review article appearing in the June 2022 issue of *Clinical Chemistry* examined angiogenic biomarkers for risk stratification in women with preeclampsia to help address that very issue. The senior author for that paper is Dr. Sarosh Rana. She is Professor of Obstetrics and Gynecology and Section Chief of Maternal-Fetal Medicine at The University of Chicago. She is particularly interested in biomarkers in the prediction of adverse maternal and fetal outcomes and she is our guest in this podcast.

First of all Dr. Rana, let's get basic. What exactly is preeclampsia?

Sarosh Rana: Yes. So, thank you for having me and doing this podcast. So, preeclampsia is a condition in pregnancy that happens typically after 20 weeks and it is a disease that is characterized by high blood pressure, so hypertension. And classically, patients will have protein in their urine. So, it's a high blood pressure problem in pregnancy that happens after typically the 20 weeks of gestation.

Bob Barrett: And why is it important to develop new biomarkers for preeclampsia?

Sarosh Rana: Sure. So, before we talk about biomarkers, I think it's kind of important to reflect and say that preeclampsia is a common high blood pressure problem in pregnancy, so it's one of the

more common hypertensive disorders. And worldwide, it is a common cause of maternal morbidity and also maternal mortality. So, overall about 70,000 women, all pregnant women all across the world, die from complications of preeclampsia and we'll talk later about what different organ systems it can involve. And also worldwide, about 500,000 babies, or there are neonatal deaths or intrauterine fetal deaths related to preeclampsia. So, it's a pretty serious condition in pregnancy.

So, the question about developing biomarkers is a problem with some of the problems that clinically we face with preeclampsia is some of these things that we clinically use such as high blood pressures, protein in the urine, and the labs that we use to assess severity of preeclampsia. They are not very sensitive. So that means they don't really have a very high prediction for preeclampsia, so it's difficult to predict preeclampsia by some of the current existing blood tests and currently existing, for example, blood pressure that we use.

So, it's important to develop biomarkers so that we can perhaps accurately predict who are the patients who are going to develop preeclampsia and we can talk about when to predict during pregnancy. But that will eventually, if we can predict it better in terms of who's going to deliver the disease, who's not going to develop the disease, I think that will improve outcomes.

Bob Barrett: But what about some of the more common markers already in place such as proteinuria, elevated liver enzymes, and low platelet count?

Sarosh Rana: Sure. So those are some of the reflections of some of the organ systems that can be involved. So, patients with preeclampsia can present with protein in their urine so that's what it's called proteinuria. But the problem is proteinuria is that a lot of patients can have severe kind of preeclampsia and have no proteinuria, and also the degree of proteinuria doesn't really reflect the severity of disease. So, you can have a lot of proteinuria but don't really have severe disease and you can have minimal proteinuria and no proteinuria and can have severe kind of disease. So, it's not very sensitive or not specific because there can be other conditions where there can be proteinuria and patient will not have preeclampsia.

So for example, in patients who have chronic kidney disease, they can have proteinuria but they don't have preeclampsia. Patients with diabetes, they can proteinuria from their diabetes but obviously not in the context of not having preeclampsia.

So having some of these nonspecific markers, similar things for example, for elevated liver enzymes. So, liver enzymes typically in the context of preeclampsia get elevated quite late in the disease process and also again, they're not very specific to preeclampsia per se. So patients can have other liver conditions that can also result in elevated liver enzymes and same thing with low platelets. So, a combination of elevated liver enzymes and low platelets in the context of hypertension is quite specific but some of these things they get abnormal really late in the progression of disease.

And when we talk about biomarkers, when we have done ourselves studies to look at the prediction of some of these currently available tests including blood pressure, including protein in the urine, and including some of these labs, they're actually poor predictors of adverse outcomes happening with preeclampsia.

Bob Barrett: Doctor, what are angiogenic biomarkers and what makes them interesting in this case?

Sarosh Rana: Yeah. So thanks for asking that question. So, several years ago, there were lab studies and animal studies done that there's a protein called sFlt-1 which is soluble fms-like tyrosine kinase-1. It's an anti-antigenic protein. So it's elevated. It's high in women who are either going to develop preeclampsia or who already have preeclampsia. And on the contrary, a pro-androgenic protein called PlGF, placental growth factor, that is reduced in the women who are either going to develop preeclampsia or have preeclampsia.

So lately, there have been several studies done in United States as well as across the world, showing that women who have some signs and symptoms of preeclampsia or who are being evaluated for preeclampsia, they have a high soluble Flt PlGF ratio. So the biomarkers that we are talking about here are soluble Flt-1 and PlGF.

Bob Barrett: Is it important to find markers that will diagnose this faster in women?

Sarosh Rana: Yeah. Especially in the context of third trimester. So, when you're late in your pregnancy and you're presenting, for example, to your doctor's office with either high blood pressure or some of these other symptoms that we get, so some patients may complain of some headache. And you can imagine headache is a common symptom in general population and in pregnancy and it's very difficult to figure out where the headache is coming from, whether it's related to preeclampsia or not. Even like edema, some patients can complain of. They can complain of pain in their abdomen.

So in the context, when we are looking at patients who are coming in for evaluation of preeclampsia, measuring the androgenic biomarkers have been shown to predict development of preeclampsia. They have been shown to predict development of adverse outcomes in the mothers and their babies. They can predict preterm delivery happening within the 1 to 2 weeks. So, these biomarkers are quite abnormal in women who are at risk to develop severe preeclampsia and also at risk to have adverse outcomes.

Bob Barrett: Well finally Dr. Rana, how do you think these biomarkers will be finally used in clinical practice and when do you see that happening?

Sarosh Rana: So these markers are actually approved in some of the work that we did here in the U.S. and also obviously, lots of other work done. These markers are approved for use in pretty much most of the Europe, in Asia, in Canada, in India for example. And the way people are using it is for risk stratification. So, when you have a patient who is at high risk for preeclampsia, especially in the third trimester, people are using these biomarkers clinically as an adjunct to other tests that are currently available. So, in combination with blood pressures, in combination with some of the lab tests that we had talked about: proteinuria, liver enzymes.

When you use that in combination, you can stratify your patient who's at high risk and who's at low risk. So, when you have a patient based on biomarker levels who are at high risk, these patients you can increase their surveillance, these patients can get, for example, even admitted for intensive monitoring, planning for delivery, giving them, for example, betamethasone and steroids for fetal lung maturity. And at the same time, these biomarkers can also stratify patients as low risk.

So, you can have a patient who seemed to be at higher risk but then you measure her biomarkers and they are low-risk, those patients can be managed with, for example, reduced surveillance. There is data that it can potentially reduce the rates of iatrogenic prematurity. So the doctors, they sometimes deliver patients with increased suspicion for preeclampsia, so perhaps we can reduce some of this prematurity if we know that the patient is at low risk to have preeclampsia.

So I think the way the biomarkers are going to be used in the context of preeclampsia and hypertensive disorders will be in patients who have suspicion for preeclampsia, especially in the third trimester, they can be. Or in patients who are admitted with some sort of a hypertensive disorder. They can help us risk stratify who are the patients at high risk to develop severe preeclampsia adverse outcomes and patients

who are at low risk to develop severe preeclampsia and adverse outcomes.

Now, these biomarkers are not yet approved in the United States. We actually have several studies ongoing that hopefully we'll submit the data to the FDA and hopefully, I'm really hopeful by the end of this year or early next year we should have these markers available in the United States for clinical use.

Bob Barrett: That was Dr. Sarosh Rana, Professor of Obstetrics and Gynecology at The University of Chicago. She has been our guest in this podcast on "Angiogenic Biomarkers for Risk Stratification in Women with Preeclampsia." She is senior author of a review article on that topic that appears on the June 2022 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.