Host:	This is the podcast from *Clinical Chemistry.* I am Bob Barrett. Preeclampsia is a leading cause of adverse pregnancy outcomes worldwide and remains a major cause of maternal and perinatal mortality.
	Early identification of pregnant women at risk for preeclampsia is a priority to implement preventive measures. Although some biochemical and ultrasonic graphic parameters have shown promising predictive performance, so far there is no clinically validated screening procedure.
	An article published in the March issue of *Clinical Chemistry* investigated the performance of biomarkers and ultrasonographic markers to predict preeclampsia.
	Dr. Jean-Claude Forest is the co-author of the study and the Professor of Medical Biochemistry at the Faculty of Medicine at Laval University, Chief of the Service of Medical Biochemistry and Director of the Research Center of the University Hospital in Quebec City. He is our guest in this podcast.
	Doctor some listeners may not be too familiar with preeclampsia. Please tell us a little more about this condition?
Dr. Jean-Claude Forest:	Sure. Preeclampsia is defined as the occurrence of hypertension after the 20th week of pregnancy and can be eventually accompanied by other symptoms, such as proteinuria, and also it can affect other organs, such as the liver and brain.
	On rare occasions preeclampsia may lead to eclampsia which is an acute, life-threatening complication characterized by the appearance of the tonic-clonic seizures.
	The prevalence of the preeclampsia among pregnant women varies between 2% and 7% in developed countries. It is a major cause of maternal mortality, and it is responsible for a fivefold increase in perinatal mortality.
	Adverse outcomes, such as intrauterine growth restriction and preterm birth are still responsible for significant newborn mortality and morbidity and lifelong consequences for the child may lead to enormous costs to healthcare system.

Furthermore, our team in order have reported increases of cardiovascular risk factors in women who previously suffered from preeclampsia. The actual pathophysiological hypothesis of preeclampsia involves an inadequate placentation early in pregnancy, followed by related hypoxia of the fetoplacental units, oxidative stress, and ultimately maternal endothelial dysfunction and multisystemic lesions.

But preeclampsia is not the only hypertensive disorder of pregnancy. There are at least three other disorders. The mellitus disorder, gestational hypertension occurs during pregnancy without other chemical complications.

More severe is chronic hypertension present before pregnancy on which preeclampsia could be superimposed. Hypertensive disorders of pregnancy altogether represent between 7%-12% of pregnancy in developed countries.

Preeclampsia is also quite heterogeneous. Some patients will develop preeclampsia in early pregnancy, that is before the 34th week, while the majority of women in developed countries develop preeclampsia in later pregnancy, that is after the 34th week of pregnancy.

Early onset preeclampsia represents a major challenge since it is associated with greater incidence of dramatic outcomes. Given the different disorders and this onset ambiguity, if we are to develop predictive algorithm, it is likely more effective to look at various combination of matters that are not correlated with each other.

This approach will ultimately lead to a clinical indicator, which is the best predictor for either one or all the syndromes related to hypertensive pregnancy.

Host: Well, tell us Dr. Forest, your recent systematic review looks at various combinations of biochemical and ultrasonographic markers used to predict preeclampsia. Why did you look into candidate markers, that can be measured in blood during pregnancy associated with ultrasound parameters defining various aspects of the uterine vascular system?

Dr. Jean-Claude Forest: We have many reasons for this approach. To begin with, researchers do not yet understand the

pathophysiology of preeclampsia. So, what we are measuring is not necessarily a reflection of the cause of the syndrome, but may reflect some of the earliest pathological processes.

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Investigating a number of biochemical markers with respect to various ultrasound parameters may be the most efficient way to predict which women are predisposed to developing preeclampsia.

Currently, no single parameter is robust enough on its own to be used as lone screening tool. Looking at literature related to preeclampsia, many predictive candidate markers have been evaluated and most of them relate to candidate blood markers or ultrasonographic measurements.

But in the general population, with relatively low-risk of developing preeclampsia, as we find in many developed countries, no single test at this point has been found to reach clinical usefulness, that is to effectively identify the women who are at risk of developing preeclampsia before the clinical appearance of symptoms.

Such preemptive screening would give time for appropriate preventive measures.

Host: Well now how did you conduct this systematic review, and what are its major findings?

Dr. Jean-Claude Forest: Well, as for many systematic review, we decided on the series of keywords and reviewed electronic databases. We specifically sought to report the performance of combined biochemicals and ultrasonographic markers in the prediction of preeclampsia.

Altogether, we screened 394 citations. Of those, 92 were potentially suitable for detailed evaluation and inclusion in the systematic review.

Unfortunately, many did not meet the selection criteria. In fact, 37 studies were considered relevant and included in the review. Overall, we were able to evaluate the performance of 71 combinations of ultrasonographic and biochemical markers.

The large number of combination is mainly due to the variety of biochemical markers tested in combination with ultrasonographic measurements.

One primary observation was that, many of the studies were based on fewer than 25 preeclampsic women, and only 5 studies investigated more than 100 preeclampsic women.

We also observed that there was heterogeneity of study design. So, of the 37 studies retained, biochemical and ultrasonographic markers were simultaneously evaluated in 23 studies, whereas these markers were evaluated sequentially in the remaining 14.

This reflects the complexity and the heterogeneity of preeclampsia or the lack at this point of poor-fold individual biomarker candidates.

Another notable observation is that, most of these were performed during the second trimester on small scale, high-risk populations, with few cases of preeclampsia, making it risky to draw any conclusion or derive any application for a general population with low incidents of preeclampsia.

This being said, the results published so far indicate that combinations of markers are superior to the use of a single marker. Such combinations appear to have greater sensitivity and specificity compared to single markers.

More specifically in low-risk populations, combinations, including Placental Protein 13, what we know as PP-13, Pregnancy-Associated Plasma Protein A, which is PAPP-A, Metalloproteinase-12, which is ADAM-12 or Inhibin A, measured in first or early second semester, plus Uterine Artery Doppler in second semester showed some promise with sensitivity ranging between 60% and 80% and specificity being greater than 80%.

In high-risk population, the combination of PP-13 and Uterine Artery Doppler pulsatility index in the first trimester showed 90% sensitivity and 90% specificity. However, this was found in a single study limited to 10 patients with severe preeclampsia.

Host:

Well, family practitioners and obstetricians would both certainly hope to someday predict early in pregnancy, predisposition for preeclampsia in pregnant women. What can you tell them about the availability of potential markers at this time?

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Dr. Jean-Claude Forest:	Well, based on this systematic review and the broader literature on the subject, there are really no screening procedures for preeclampsia or any other hypertensive disorder of pregnancy available at this time.
	However, recent reports suggest that the combination of some biochemical markers, ultrasonographic disease, and maternal characteristics may help identify the women at risk of preeclampsia, but this needs to be further validated.
	So, unfortunately I believe that the conclusion of an expert panel of WHO made in 2004 still applies and I cite, there is no clinically useful screening test to predict the development of preeclampsia in either low-risk or high-risk population. Further prospective longitudinal studies are needed, and I think it's still the case.
Host:	Well, where do you envision research on the developmental procedure predicting preeclampsia will go from here?
Dr. Jean-Claude Forest:	Well, although we do not know the etiology of the syndrome, we have a clearer idea of which biomarkers best reflect the physiological alternations associated with preeclampsia. These factors are involved in one or more steps of the cascades of events that occur before the onset of clinical symptoms.
	Preeclampsia is considered a two-stage disorder. It first involves reduced placental diffusion due in part to diminished vision of spiral arteries by trophoblastic cells. This is followed by reduced perfusion of the fetoplacental units and consequential oxidative stress.
	The second stage is characterized by a widespread maternal endothelial dysfunction, followed by the occurrence of the clinical symptoms in the mother. The best predictive markers will be those which can identify early in pregnancy, women just starting to develop preeclampsia.
	Recent studies have shown that maternal parameters, namely body mass index, the ethnicity, previous maternal medical and obstetrical history may be linked to preeclampsia susceptibility and be included in prediction algorithms.

There are also environmental and psychosocial elements which may play a role in increased susceptibility. We therefore envision prospective lab scale studies which are rigorously designed to evaluate the clinical usefulness of a combination of biomarkers plus individual characteristics and environmental factors in different geographic and healthcare environments.

The ultimate outcome of these efforts would be the development of nutrition screening procedures which incorporates a multivariate algorithm of selective maternal characteristic plus the measurement of biochemical and ultrasonographic markers, ultimately allowing a procedure to identify women at risk for preeclampsia who would benefit from early cognitive preventive interventions.

Host: Medical professionals were aware that until now there has been no truly effective treatment for preeclampsia, although than of course delivery, which is in fact a cause of significant morbidity and problems associated with prematurity. With this in mind, are affective preventive measures really a possibility?

Dr. Jean-Claude Forest: I think that at this stage we can say yes. Specifically the use of aspirin early in pregnancy in women who are at a higher risk of developing preeclampsia has been shown to be remarkably effective in reducing the severity of clinical symptoms or even preventing altogether the syndrome.

Our research group recently showed that ingestion of low-dose aspirins started before 16 weeks gestation could prevent up to 50% of preeclampsia, severe preeclampsia, and intrauterine growth restriction in high-risk women.

Of course, this improved maternal-child outcome closely relies on the identification of high-risk women, specifically within the first trimester of pregnancy.

Host: Well finally doctor, can you give us a glimpse as to the direction of your own research in this field?

Dr. Jean-Claude Forest: Well certainly. Our research team is currently completing a prospective study in which we recruited 8000 women during the first trimester of that pregnancy and followed them up until postpartum through collection of relevant information on personal habits, socioeconomic environment, family history,

plus the collection of biological samples throughout pregnancy.

We hope to be able to contribute to the establishment of more robust and at the same time efficient screening procedures which would help to identify the high-risk women early in pregnancy in order to implement preventive measures specifically for this group of women.

Host:

Dr. Jean-Claude Forest is Professor of Medical Biochemistry at the Faculty of Medicine at Laval University, Chief of the Service of Medical Biochemistry and Director of the Research Center of the University Hospital in Quebec City. He has been our guest into this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening.

Total Duration: 15:41 minutes