Clinical Chemistry

Updates on Screening, Prevention, Treatment, and Genetic Markers for Preeclampsia

Article:
Glenn E. Palomaki, et al.
Updates on Screening, Prevention, Treatment, and Genetic Markers for Preeclampsia.
Clin Chem 2018;64:1684-89.
http://clinchem.aaccjnls.org/content/64/12/1684

Guest: Dr. Glenn Palomaki is from the Women & Infants Hospital and the Alpert Medical School at Brown University in Providence, Rhode Island.

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

Preeclampsia is a serious disorder of pregnancy that occurs by 24 weeks of gestation or later and can occur in up to 5% of all pregnancies. Maternal weight, advancing maternal age, nulliparity, a previous pregnancy with preeclampsia, and insulin-dependent diabetes are just some of the predisposing factors for developing preeclampsia. Over the past few years, development in screening, prevention, and treatment for preeclampsia have occurred and genetic studies are just now providing new insights into the etiology of this disorder.

A Q&A feature in the December 2018 issue of *Clinical Chemistry* asked three experts with different roles in this field to discuss recent advances and ongoing challenges in preeclampsia research and implementation. We're joined for this podcast by the moderator of that Q&A article, Dr. Glenn Eric Palomaki, who is a professor in the Department of Pathology and Laboratory Medicine at the Women & Infants Hospital and the Alpert Medical School at Brown University in Providence, Rhode Island.

So, first of all, Dr. Palomaki, let's get basic, what exactly is preeclampsia and what are the health consequences?

Dr. Palomaki: Preeclampsia is a condition that develops during pregnancy and classically, it's defined as an elevated blood pressure on at least two occasions, four hours apart, that develops after 20 weeks gestation, and there's usually at least one other factor such as proteinuria, renal insufficiency, liver involvement, neurological complications, thrombocytopenia, edema and so on. And this develops in somewhere between 3% to 5% of pregnancies, the rate varies because of a lot of reasons. But about 3% to 5% of pregnancies will develop preeclampsia, and in the US this rate in increasing over time. Really though, most importantly about a half of a percent, or 1 in 200, pregnancies develop early

preeclampsia. That's preeclampsia that occurs before 34 weeks gestation.

According the American College of Obstetrics and Gynecology and the United States Preventive Services Task Force, the strong risk factors for preeclampsia include things like a previous pregnancy that had preeclampsia, especially if there was an adverse outcome associated with it, multiple gestations, twin, triplets, diabetes, autoimmune diseases are the strong risk factors. The still important but more moderate risk factors include things like primipara—if it's the woman's first pregnancy—obesity, family history, being of African-American descent, age 35 and older, and just a previous adverse outcome such as low birth weight or small for gestational age.

A woman who has developed preeclampsia can rapidly develop severe preeclampsia that threatens both the fetus and the mother. In very severe cases, eclampsia can occur which is life threatening.

The only truly effective treatment for preeclampsia or eclampsia is the delivery of the fetus. If the pregnancy is very early, let's say 32 weeks, then the provider has a difficult decision to make along with the woman. Physicians then must weigh delaying the delivery to allow the fetus more time to mature, versus the possibility that the mother's condition may worsen and potentially it's possible for her to die from eclampsia from that condition.

Hundreds of women a day in the world die of eclampsia- it's relatively uncommon in the U.S., but in some third world countries, it's a really important problem for pregnant women.

Bob Barrett: What are some of the most important recent findings regarding screening and treatment for preeclampsia?

Dr. Palomaki: Well, interestingly, over the past few years, there are several lines of new evidence that have emerged. The first is the development and extensive validation of a first trimester screening test. And this screening test assigns an individualized risk of developing preeclampsia later in pregnancy, like 1 in 25, 1 in 50, 1 in 5,000. That risk model was developed by Dr. David Wright in collaboration with the Fetal Medicine Foundation in London and it differs from the way of the American College or USPSTF model. They just look at, do you have one or more of these risk factors. In this new model, it uses a Bayesian model. It takes into account that some of these factors are dependent on each other and that they are correlated. It also allows for the incorporation of ultrasound tests and biochemical results

such as the placental growth factor or PLGF, I'll be referring to PLGF more as we go on.

This model is able to identify 60, 70, maybe 75% of deliveries prior to 37 weeks that would be associated with preeclampsia, and this is at a false positive rate of 10%. You might wonder, well, what's the point of a screening test if you don't know what to do with the women that you screen positive. So, that's where the second line of evidence comes in. When that was developed there really was not an effective intervention. Many, many trials have gone on in the past looking at potential interventions at different times in pregnancy that might stop the development of preeclampsia. And one of them was aspirin, given in the first or second trimester and again, several studies were done there and it looks like that was about a 10% reduction in preeclampsia. So, it was not a very effective treatment.

But then in 2012, Roberge and colleagues from Canada did a meta-analysis where they reviewed all the relevant studies and interestingly, stratified studies' impact based on the time and gestation that the aspirin was provided. And in those studies, where treatment was started in the first trimester or at least before 16 weeks, there was actually a very significant improvement in the ability of aspirin to prevent preeclampsia. They also identified the fact that the dose was important. The usually used does in the previous trials was a single 81 milligram low-dose aspirin and they determined that it would have to be essentially double in order to provide good protection against preeclampsia.

So, together the screening test provides the risk estimates in the late first trimester and then the findings that a higher dose of aspirin would be more effective in preventing preeclampsia, that provided sufficient evidence to move forward with the randomized trial.

So, in the UK and in several of European sites, they mounted a randomized double-blind placebo controlled trial which was published just recently 2017 in the *New England Journal of Medicine*. The principal investigator of that was Dr. Leona Poon of King's College, London. She, by the way is one of the participants in the *Clinical Chemistry* interview, reported that using a 150 milligram dose of aspirin, again, that's almost twice a low-dose aspirin or two low-dose aspirin taken at bedtime by the 10% of women with the highest risk according to that validated risk algorithm, reduced the rate of preterm delivery with preeclampsia less than 37 weeks by 62%. So, more than half of them were prevented. And among that group, the far more serious deliveries which would occur prior to 34 weeks were reduced by 82%. So, that's really an important reduction.

They had pretty good compliance. The compliance with treatment was 80% of the women taking at least 85% of their aspirins, and that was done by pill counting. That is, I think, one of the exciting recent developments.

Bob Barrett: Are there barriers to routine implementation of screening for preeclampsia in the first trimester in subsequent treatment with aspirin?

Dr. Glenn Palomaki: Yeah, just talk about that randomized trial, that was highly controlled and there are questions about whether that would be transferrable to a general pregnancy population. In essence, that study shows the efficacy of the program, how good it could work, but not the effectiveness of how it would work in the general population. For example, about a third of the women who were approached to be in that trial declined to participate. Well, would a third of women in the general population who are approached decline that they didn't think this is important enough, or did those third of the women decline because it was a trial and they were going to be subjected to something that they weren't sure was going to work? It's also not clear what proportion of the general population they approached. Where they the so-called compliant portion of the population? Other factors that might influence how well the algorithm works is the weight distribution. Women who are heavier weight as I said earlier are the higher risk of preeclampsia, and the same dose of aspirin may not be as effective because you really want to look at the milligrams per kilograms of dose. And the U.S. population is certainly likely to have a higher proportion of heavier women in the population and so, would -- 150 grams be sufficient?

In England and other European countries, they routinely used maternal uterine doppler pulsatility index, or the PI. That's routinely measured and it's an important component of the algorithm that was used in that randomized trial. Unfortunately, that's rarely done in the U.S. where first trimester ultrasound is routinely done in the private practitioner's office rather than the hospital and they may not have access to doppler ultrasound.

You can add additional biochemical markers, remember I told you that PLGF, the placental growth factor, was an important factor in the original algorithm. But you could add things like Pregnancy-Associated Plasma Protein A (PAPP-A) or Inhibin A may also be added to help make up the difference of not measuring the pulsatility index.

Lastly, the screening and treatment protocol has to be completed by the 15th week of pregnancy, and according to the 2016 U.S. Birth Records, only about three quarters of

the birth records indicate that prenatal care began in the first trimester. That means about a quarter of pregnancies would not be eligible for the screening and treatment that I just described in that trial. So, there's some of the issues that have to be looked at if you were to try implement this in the United States.

Bob Barrett: Well, in the U.S., what information would need to be available to allow for routine offering and reimbursement for first trimester screening in a subsequent treatment?

Dr. Glenn Palomaki: Well, first the algorithm to compute the risk is not really readily available in a format that would allow for mass screening. Optimally, that algorithm should be implemented in a hospital screening program software, so that the data entry by the primary care providers, editing interpretation and the results reporting are available to the primary care physician right away, and it needs to be scalable for the large number of women that you expect to be screened.

Another issue in the U.S. is if you look it up there's really only two doses of aspirin that are available, the 81 milligrams and the 325 milligrams. It really would be nice to have single-dose tablets around 150-160 milligrams or maybe 250 milligrams so that you could properly dose women based on their age. There are certainly will be some and perhaps many experts in the field that say you know, a single randomized placebo-controlled trial in the UK is not sufficient for implementation in the U.S. And Dr. James Martin who is, again one of the participants in the *Clinical Chemistry* interview, does believe that such a study should be attempted in the U.S.

Such a study when it was completed, would certainly contribute important information and probably lead to professional society recommendations, but in my opinion that study is going to be very costly, time-consuming, difficult to fund, and difficult to complete, especially as this information becomes more widely available, primary obstetrical providers and women will hear about aspirin and pre-eclampsia and you know, would they participate in the randomized trial?

An alternative to that might be a project that is more focused on the clinical utility and documents things like, what's the uptake rate in the population, what's the compliance in the general pregnancy population, and what's the overall effectiveness of the screening in aspirin if it was use as a relatively simple and inexpensive part of routine prenatal care. If that was successful, then that study along with the existing evidence could both contribute to show that the major savings in this would be the neonatal intensive care unit costs that are associated with pre-term

delivery due to pre-eclampsia. And they are likely to far outweigh the costs of pre-eclampsia screening and treatment. A study showing that has also been published by the group in Europe.

Lastly, just looking at NICU admissions doesn't include important reductions in things like fetal losses and long-term healthcare costs that are associated with this some of these very early deliveries. And you would hope that those things taken together would be sufficient incentive for the insurance companies to cover these costs that are associated with screening and treatment to help prevent pre-eclampsia.

Bob Barrett: It seems screening will not identify, much less prevent, all cases of pre-eclampsia. Are there any new treatments that might be able to delay delivery in cases of severe or early pre-eclampsia?

Dr. Glenn Palomaki: To your first point about the identification or prevention of all cases, as we said before, only about 1 in 4 U.S. pregnancies would not be eligible for pre-screening and treatment because they don't see a prenatal care provider in the first trimester. And of course, some women who are eligible, who are seen at 11, 12, 13 weeks, might choose to not be screened, it's obviously an option. And lastly, some women who might be screened positive might not want to take aspirin during pregnancy and that would lead to a reduction in effectiveness as well.

We have a lot of experience in prenatal screening for Down Syndrome and similar disorders. And that can give us some idea of the uptake, and most programs throughout the United States and really in Europe as well, find that the upper limit of women opting for prenatal screening for Down Syndrome is about 70%. It's likely that might be kind of the upper limit, maybe you could get a little bit higher, but that gives you a ballpark figure. And since screening will fail to detect 20% to 30% of pre-term deliveries and treatment is not 100% effective in the general population such a protocol might reduce the incidence of all pre-term pre-eclampsia by 40% to 50%.

So, maybe half of the pre-eclampsia could be prevented by a general population screening test and treatment by aspirin in the first trimester. Now, that's an important reduction, but the majority of pre-term deliveries would continue. So, there has to be either improvement in the screening algorithm, improvement in the treatment, or perhaps an alternative treatment. For those women with very pre-term deliveries, there's ongoing research on a new treatment option that has the potential to increase considerably the

length of pregnancies. That's specifically for 32 weeks and earlier right now.

There's an antiangiogenic factor, soluble FMS-like tyrosine kinase-1, or sFlt1, that's low early in the pregnancy but increases as pregnancy continues as it prepares the pregnancy for delivery. sFlt levels are higher than expected in pregnancies of pre-eclampsia that deliver early, and it's been shown in several studies that sFlt levels are the causal factor in the symptoms of pre-eclampsia in early delivery. Much of this work was done by Dr. Ananthat Karumanchi at Harvard, who also a contributor to the *Clinical Chemistry* interview. And there's a potential treatment that removes sFlt via dextran sulfate apheresis. In a preliminary small study that was performed in Germany, 11 women who developed severe pre-eclampsia between 23 and 32 weeks were enrolled.

The first six women received a single apheresis treatment and their delivery was delayed by an average of eight days. The control pregnancy average time delivery was three days. Five subsequent women were enrolled and they received two or three apheresis treatments, and the average delay in delivery was 15 days. Again, that's compared to three days. So, it's true that certainly we need larger studies to confirm these and you want to examine things like costs and long-term outcomes, but you know these are really encouraging potential treatments for those women who have imminent delivery prior to 32 weeks as a way to delay delivery and let the fetus mature.

Bob Barrett: Well, finally doctor, in the Q&A article you had three world experts address this condition. What struck you as the single essential point you would like the *Clinical Chemistry* readers and our listeners to take home?

Dr. Glenn Palomaki: Well, I was impressed with some of this new work. There have been many, many studies for decades that have not found effective treatments much less really effective screening tests, and it was nice to see all that come together in a single study. But, as a caution, like any new findings, the excitement of finding that has to be tempered by the time we all know it will take to replicate and collect sufficient evidence to allow us to implement this as part of routine care, gain the recommendations from professional organization and finally in the U.S., importantly, the insurance coverage.

Bob Barrett: That was Glenn Eric Palomaki from the Department of Pathology and Laboratory Medicine at the Women & Infants Hospital and the Alpert Medical School at Brown University in Providence, Rhode Island. The Q&A feature on pre-

eclampsia that he moderated appears in the December 2018 issue of *Clinical Chemistry*.

I'm Bob Barrett. Thanks for listening.