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<https://reachmd.com/programs/cme/role-fetal-fibronectin-identifying-risk-reducing-burden-unplanned-preterm-birth/7937/>

Released: 03/01/2016

Valid until: 07/07/2018

Time needed to complete: 15 Minutes

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## The Role of Fetal Fibronectin in Identifying the Risk and Reducing the Burden of Unplanned Preterm Birth

### ANNOUNCER OPEN:

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Dr. Chang:

Hello, I'm Dr. Gene Chang. I am an Associate Professor in the Department of OB/GYN and Director of the Maternal-Fetal Medicine Fellowship at the Medical University of South Carolina in Charleston.

Joining us today via Skype from Columbus, Ohio is my colleague Dr. Stephanie Costa. Stephanie is a physician at MaternOhio Clinical Associates-Kingsdale Division, a large single specialty OB/GYN practice of 45 doctors in Central Ohio. She's also the Chair of the Department of OB/GYN at Riverside Methodist Hospital in Columbus.

Dr. Costa:

Hi, Gene, how are you today?

Dr. Chang:

I'm good. We're here today to talk about the role of fetal fibronectin in identifying and reducing the burden of unplanned preterm birth. Some of the topics we're going to cover today will include:

1. What are the short- and longer-term burdens and risks of an unplanned preterm birth?
2. What is fetal fibronectin, what's its normal role in pregnancy, and why is it considered a risk factor or a risk marker for an unplanned preterm birth?
3. How is FFN obtained, measured and reported, and what levels are associated, or considered abnormal, and associated with an increased risk for unplanned preterm birth?

So, Dr. Costa, to begin our discussion, in your practice, what do you see as short- and longer-term burdens and risks of an unplanned preterm birth?

Dr. Costa:

Well, preterm delivery and admissions to the intensive care unit, the neonatal intensive care unit, are becoming huge, and despite our

advances in medicine, we're still seeing a large number of preterm births. I'm not sure how it is in South Carolina, but here in Ohio our neonatal intensive care units are overflowing, and patients are frequently getting transferred out of the city because of a lack of neonatal beds. So, we know that preterm birth is the leading cause of neonatal morbidity. It's also the leading cause of antenatal admission for pregnant women.

The burden of preterm delivery is huge, and a study by the Institute of Medicine estimated that the annual cost in the United States to treat preterm birth is over \$26.2 billion. If you look at that in another way, that averages out to over \$51,000 per child. We know that preterm birth accounts for 70% of neonatal deaths, and it also accounts for 25 to 50% of long-term neurologic impairment in children.

Dr. Chang:

Yes, that's definitely a big deal. It's funny; we've kind of lagged behind our colleagues in neonatology in the sense that we haven't done a great job at reducing spontaneous preterm birth, while what they've done is really increase survivability of really extremely premature babies, and so, the tradeoff is we're seeing lots of babies in higher-level nurseries for a longer period of time who go on to have lots of different problems. And really, the impact on society down the road is going to be significant both from a cost standpoint and really also from the different services that these kids are going to need down the road.

Dr. Costa:

Right, it's a huge burden not only to society but to each of those individual families.

Dr. Chang:

Yes, absolutely.

Dr. Costa:

Gene, I've got a question for you. Tell me, what exactly is fetal fibronectin? What's the normal role of fetal fibronectin during pregnancy, and why can it be considered a marker for unplanned preterm birth?

Dr. Chang:

Sure, great question. So, fetal fibronectin is a matrix glycoprotein that really exists at the interface between the fetal membranes and the uterus, and it's excreted by the fetal membranes and acts as an adhesive, so we tell patients it's like the glue between the pregnancy and the uterus. And why it's so significant is, typically, in the late second trimester and early third trimester, you don't really find it in cervicovaginal secretions. So, when that interface between membranes and uterus is disturbed, as would happen during preterm labor in someone who's destined to deliver, what you will see is you'll start being able to detect fetal fibronectin in cervicovaginal secretions and, therefore, it is really something that's associated with an increase in the risk of preterm birth.

Dr. Costa:

Right, because normally, that level of fetal fibronectin would be declining as the pregnancy went on, correct?

Dr. Chang:

Yes, absolutely, so you don't see it. So, the normal state is not to find it, and so the abnormal state, when you find it, is where you have to be concerned. And ultimately, as we'll talk about later, it's really the normal state we're looking for and the normal state that is most reassuring.

So, when we talk about FFN, can you just review how we obtain the sample, how we measure and report it, and what levels are considered abnormal and associated with an increase in the risk of spontaneous preterm birth?

Dr. Costa:

Certainly. So, FFN can be obtained either in your office or, perhaps, in triage on labor and delivery, and it's really important to perform this with a speculum exam. You can gently insert a speculum into the vagina. You don't want to use any kind of lubricant on that speculum because that can affect the results and give you a false positive. The fetal fibronectin vial comes with a sterile polyester swab. That can be rotated gently in that posterior fornix to collect the cervical vaginal secretions. You want to saturate that swab with those secretions; then you can send it off to the lab.

Now, it's important that if a patient has had intercourse within the last 24 hours that you not perform the fetal fibronectin test. Semen

can cause a false positive result. In addition, if the patient has self-administered any medicated creams or if there are any soaps in the area, that can also affect results. If you've performed a digital cervical exam or a cervical length ultrasound, either the lubricant or just the manipulation of the cervix can also cause false positive. Now, if a patient happens to have bleeding, which many of our patients that present with symptoms of preterm labor can have some bleeding, and if there's moderate or large amount of blood, then that can cause a false positive with the results. If, however, you do collect a fetal fibronectin and you send it off and there was some blood on the swab and that fetal fibronectin result comes back negative, you can be assured that those negative results are valid. It's just if you would come back positive, you're not sure if that positive is because of a true presence of fetal fibronectin or if it's falsely positive because of a presence of blood, semen, lubricant.

So, when we collect that and send it off to the lab, there's an ELISA assay performed on the specimen, it's run through a spectrophotometer, and we know that values over 50 are considered positive for fetal fibronectin. Values of an absorbance under 50 are considered negative. So, when you get that result back, it will be a clear positive or negative. There's no gray or indeterminant value.

Dr. Chang:

Right, and that's what's so helpful for us because a negative tells you exactly what you can do or not do, and conversely, a positive helps somewhat. You know, it's funny; it's not a hard test to perform with respect to just technique. We just really early on found it was a hard test to perform because people would forget to obtain the sample before doing the other things they would routinely do, but with enough training, eventually you hardwire this, and you can really train the folks around you to obtain FFNs before any other relevant exams or procedures are done on these patients. And ultimately, we think the benefit is there.

Dr. Costa:

Right. And I think for both patients and clinicians, when someone is worried about the possibility of preterm labor, we all want to know: Is she dilated? And you need to just hold off on that until you've obtained that cervical swab or the swab in the posterior fornix. I think it's important for us to realize just because you obtain the swab, it doesn't mean that you necessarily have to send it off. You could further evaluate the patient after you obtain the swab and later decide to discard the sample.

Dr. Chang:

Absolutely, and it's funny; I would estimate that probably like a third to half almost of FFNs we collect we end up discarding, because you'll do it, and then you check a patient and she may have a really reassuring exam -- or as we'll talk about in a little bit -- she might have a very normal-looking cervical length. But again, if you take the 10, 20 seconds to collect the specimen, it really can pay benefits down the road.

Dr. Costa:

Exactly. So, Gene, can you tell me a little bit about the positive and negative predictive value of the fetal fibronectin test, and then how do you use your test results with regard to disposition of that patient?

Dr. Chang:

Absolutely. So, the big thing that we kind of lean on with respect to fetal fibronectin is its negative predictive value. That means a negative test tells us that the patient is very unlikely to deliver within a week or two. At the end of the day, when you look at the negative fetal fibronectin, or the negative predictive value of fetal fibronectin, it ranges for between about 97 and 99% for prediction of those who will deliver within a week, depending on populations that are studied or the actual studies that you look at. So, what that means is a negative test tells us the patient has a 97 to 99% chance of not delivering within a week. Conversely, the positive predictive value is, unfortunately, not quite as good. It's lower; it ranges from about 12 to 40%. So, again, a positive test tells you that the patient's at risk, but it's not quite as powerful as the negative predictive value.

So, what all this means is that if we see a patient who's contracting or has some symptoms concerning for preterm labor, if we do the test and it's negative, we can reassure that patient that she's very, very unlikely to deliver and we can send her home. On the flip side, if you have a positive test, that's a patient that is going to need to be observed more carefully.

Dr. Costa:

Well, and I think stated another way, while you're observing that patient very carefully, it doesn't mean that that patient is likely going to deliver.

Dr. Chang:  
Right, right.

Dr. Costa:  
You know, there's a chance that they could deliver in the next week, but it's not a given.

Dr. Chang:  
Yes, absolutely. So, tell me, Stephanie, how is FFN used along with transvaginal ultrasound or a cervical exam when assessing the overall risk for a patient for spontaneous preterm birth?

Dr. Costa:  
So, they really complement each other nicely. And again, we'll just reiterate that it's important when you're considering doing a cervical length ultrasound that you obtain that fetal fibronectin prior to inserting a probe into the vagina. So obtain the fetal fibronectin swab, hold it, and then you can go ahead and perform your cervical length ultrasound. We know that women who have a cervical length greater than 30 mm, that they're at low risk of delivering within the next week. Studies have shown that less than 2% of those women will go on to deliver within that next week. We also know that for women who have a cervical length that's less than 20 mm, that they have a significant risk for delivering in the next week, and that risk can approach about 47%. So, fetal fibronectin in each of those groups may not be as beneficial because your management is most likely going to be dictated on what that cervical length is. Fetal fibronectin becomes very useful when you have that patient with the cervical length somewhere between 20 and 29 mm. We know that that's an intermediate range, and so if you had a fetal fibronectin that was positive on a patient with that intermediate range cervical length, that's someone that you would want to go ahead and make some of those interventions. If their fetal fibronectin was negative and you had that intermediate range of cervical length, you could probably feel comfortable letting them go home with close follow-up.

Dr. Chang:  
Yes, sure. I think this is definitely a case where more information is always better. Certainly, if you have a really abnormal cervical exam or really abnormal cervical length, I mean, you can make, you can make a clinical call, but unfortunately in medicine, it always seems like, instead of the extremes of what we see, we see a lot of patients in gray areas, and I think the power of FFN is it helps you take that gray area patient and at least give her a little more solid disposition, so in that sense a very cool test.

Dr. Costa:  
Gene, if you have a positive fetal fibronectin, in addition to other signs and symptoms, that could suggest a threatened preterm delivery. What kind of interventions could you take with that patient?

Dr. Chang:  
Well, the big things that we do are really all to prepare or protect the neonate. So the big, big thing is we can give corticosteroids, which will reduce the risk of respiratory distress syndrome; it will reduce the risk of fetal brain injury to some degree and some other complications. We could give magnesium sulfate for neuroprotection in patients that are really early. We can start antibiotics for prevention of GBS sepsis. And then, for the docs in the smaller hospitals in smaller towns, wherever they may be, they can at least identify the patient that needs to be transferred to a higher-level nursery. It's a big deal, in terms of really for the folks on the front line knowing what to do, and so this test can be helpful for identifying who can be sent where.

Now, one of the problems we deal with with steroids is the recognition that steroids only last for so long and that repeated doses of steroids could actually be harmful to the fetus. I'm ashamed to admit it, but back in the '90s it was very commonplace for us to admit patients at risk for preterm birth and give them steroids on a weekly basis. And after a while, we started to really become concerned about the effects of that, and we really found that there's a potential problem with giving repeated steroids, such that ACOG now recognizes that, ideally, only a single course of steroids would be given to patients between 24 and 34 weeks who are at risk for preterm birth. In some patients who get a course of steroids, a single repeated course can be given in certain circumstances, and that's reasonable. But one of the really nice things about FFN is, in particular, it helps us identify a little better than just using what we see clinically. It helps us identify patients who should not get steroids. It helps us identify the patient that we can say, "Do you know what? I think you're fine. We can just watch you and hold off on anything." And from that standpoint, I think it's a very powerful test.

Dr. Chang:

Exactly, exactly. And we're all trained to intervene, and I think it's definitely hard not to at times, but having a test that really is pretty reliable when it tells you that there is no problem is helpful and something to stand on.

Dr. Costa:

Well, and I think fetal fibronectin has demonstrated its power. It's been around enough that we really feel comfortable trusting the results of this test.

Dr. Chang:

Yes, absolutely. I think it's something we're very comfortable with and very, we're very comfortable making decisions. And, in fact, every now and then we'll get a transfer from one of the smaller outlying hospitals for patients that are concerning for preterm labor and we're worried about preterm birth, and we get them into our unit, and we see them, and we will do an FFN, and sometimes that helps us get patients home, which is a really big deal for lots of folks.

Dr. Costa:

Are you seeing, the outlying facilities, are they able to perform fetal fibronectin?

Dr. Chang:

They are, and it's taken -- it's like everything else in medicine -- it takes a little bit of time to filter down, but it has really made a difference. It helps everybody involved kind of appropriately triage patients and really make appropriate use of healthcare resources, so, from that standpoint, we've been really pleased with the test.

Dr. Costa:

I think anyone can perform a fetal fibronectin test. The question is: Is there going to be a lab in that local, little more rural hospital that's able to actually process that? Do they have the spectrophotometer so that they can actually go ahead and run the fetal fibronectin? Do you ever see patients come to your hospital with a fetal fibronectin swab in hand?

Dr. Chang:

You know, the only patients like that typically come from our offices. We have some offices really all across the Charleston area, and so sometimes they come in like that, but for the most part, patients that are transferred in from really much more rural areas, a lot of those hospitals, surprisingly, have the ability to do FFN, thankfully, and they're really starting to do it. So, again, we've been real thankful for that.

So, Stephanie, can you take us through what the standard triage might be for a woman presenting with signs or symptoms of preterm labor prior to 37 weeks?

Dr. Costa:

Sure, I can. So, this patient, it's important to take a thorough history. We want to take any kind of history of cervical surgeries such as a LEEP or laser, any kind of late second trimester procedures such as a termination, also wanting to know if they're a smoker or if they have had any history of any preterm labor or preterm births before, because you know that's a huge indicator of subsequent preterm delivery. I would also ascertain if there's ever been a history of knowing that she had a placenta previa or anything like that before you would go ahead and insert a speculum into the vagina or perform any kind of digital exam.

So, again, when you're first evaluating this patient, collect your fetal fibronectin swab first on that speculum exam, and then, following that, you may also want to do a swab to screen for rupture of membranes if the patient gives any kind of history concerning for that. Following that, you could do a cervical length ultrasound trying to determine whether or not that patient had a short, long or intermediate cervical length, and then, also do a digital cervical exam to assess for dilation, all the while also monitoring that patient for contractions and any other symptoms such as pain, you know, something that could be a sign for abruption or something more concerning.

Once you get all of those results back, you can then determine whether or not you want to send that fetal fibronectin off. If you get the fetal fibronectin back, if you've sent it off, then that can help you determine, as you outlined before, whether or not you can be comfortable sending that patient home or if you want to keep them there for those previously mentioned interventions such as steroids or magnesium sulfate.

Dr. Chang:

Yes, absolutely, and I think it also bears again repeating what you said is that, really, just because you obtain the sample doesn't mean you always have to send it. And so, sometimes you have a patient who has a very, very normal exam and is not really contracting and/or normal ultrasound, and certainly, those patients really don't need the test done, so always important to remember.

Dr. Costa:

Gene, can you tell me just in concluding, do you have any closing remarks about fetal fibronectin, any advice to our clinicians that may be listening that we haven't addressed so far?

Dr. Chang:

Well, I don't know that I have anything really significant to say in addition to what's been covered. Really, I would just want to revisit the notion that to remember that fetal fibronectin is but a part of the evaluation of a patient with symptoms of preterm labor. Just like you might see a patient with shortness of breath, you're going to rely on multiple things -- on the chest x-ray, on your physical exam, on O2 saturations and/or a blood gas. You know, it's important to get a comprehensive picture. And I think if we can get folks to think along those ways, that it's not just the cervical exam -- it's so much more when you evaluate these patients -- you want to look at multiple things including an FFN and that it can be helpful in reassuring both you and the patient. I think if you can remember those things, you're going to be in good shape.

Dr. Costa:

I agree.

Dr. Chang:

Yes, absolutely. Well, thanks for your time, Stephanie. This will conclude our discussion today on fetal fibronectin. I'm Dr. Gene Chang.

Dr. Costa:

And I'm Dr. Stephanie Costa.

Dr. Chang:

All right, signing off.

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