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Recent Updates on the Role of Noninvasive Prenatal Screening in Optimizing Fetal Outcomes

Narrator:
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Dr. Birnholz
This is ReachMD and I’m Dr. Matt Birnholz. Today I’ll be talking with Dr. Ronald Wapner and Dr. Martin Chavez on the topic of noninvasive prenatal testing, an important means for clinicians to assess the chromosomal health of a pregnancy via maternal blood samples. It can be offered to all pregnant women, regardless of their risk of chromosomal aneuploidy. Dr.’s Wapner and Chavez will be addressing some key questions that have arisen as NIPT has become more and more accepted as a screening tool for chromosomal aneuploidies. Dr. Chavez and Dr. Wapner, welcome to the program.

Dr. Chavez:
Thank you very much.

Dr. Wapner:
Thank you for having us.

Dr. Birnholz:
Let’s begin with a brief overview of the serum analyte and ultrasound tests that have traditionally been used to screen for aneuploidies. So, Dr. Wapner, can you talk about these tests and how effective they’ve been in this regard?

Dr. Wapner:
It’s been recognized that women having a pregnancy in which the fetus has a chromosome abnormality and, in particular, we’re talking about Down syndrome, trisomy 18 or trisomy 13, have different levels of certain biochemicals compared to women that are having an unaffected pregnancy. In addition, we know that when we do an ultrasound of a fetus that has Down syndrome or trisomy 21, there is extra fluid on the ultrasound behind the neck of the fetus. So, because of these differences in biochemicals, because of this different amount of fluid in the Down syndrome pregnancy, we can increase or decrease a woman’s risk that the pregnancy is affected. So, say that we take a woman whose initial risk based on her age, because the risk increases as a woman’s age increases, is, say, 1 in 300. If some of the chemicals are in the direction that they would be for Down syndrome, and if there is extra fluid behind the neck, that risk may go up significantly higher. Alternatively, if all the chemicals are closer to those that a normal woman having an unaffected pregnancy would have, we could actually lower her risk from, say, 1 in 300 to 1 in 1000, or even 1 in 10,000. Until recently, every woman between 10 and 12 weeks or so of pregnancy had a blood test, had these biochemicals measured, had an ultrasound that measured the amount of fluid behind the fetus’s neck, and then had a better risk assessment using all of those results rather than one. This has proved to be very successful because if we assume that if the woman’s risk is greater than that of a 35-year-old woman, which would be 1 in 270, and that is her results after we analyze all of these things—if it’s greater than 1 in 270, we would call her high-risk, and then she would be offered a diagnostic test, such as amniocentesis or CVS. If we use that cutoff, the women that we call high-risk

would have about 85% of all the Down syndrome pregnancies. So really, using that, the screening would identify 8.5 out of every 10 trisomy 21 pregnancies. The cost of that, however, since this is just a screening test, not a diagnostic test, is certain women that have a normal pregnancy would also be in the high-risk range, and that would be about 3-5% of the women. So, we call the detection rate or the number of Down syndrome pregnancies we identify the sensitivity. So the sensitivity of this biochemical and ultrasound screening would be about 85% and the specificity would be approximately 95%, and the specificity of 95% says that there is a false positive rate of around 5%. So, that's very, very good identification, but as we'll hear in just a few minutes, there now are tests that can do that even better.

Dr. Birnholz:
So, Dr. Chavez, let me turn to you then for helping us understand the role of amniocentesis and chorionic villus sampling, or CVS, as Dr. Wapner alluded to. How do these two procedures differ from the serum analytes and ultrasound tests in diagnosing fetal aneuploidies?

Dr. Chavez:
I think the biggest difference, is that when we counsel our patients that the screening test is just that, a screening test, a probability test. When we go into the direction of an amniocentesis or a chorionic villi sampling or CVS, we then are looking at a diagnostic test, an amniocentesis can be done as early as 15-16 weeks and depending on what information we want, typically up to 22 weeks, so this way we have time to get information to our patient to have all options available. A CVS is usually done anywhere from 10 to 13 weeks The only differing part, other than the gestational age, is going to be that we don't get information about open neural tube defects, which we can get with an amniocentesis. The risk profile for both of these is very similar, we're talking about probably less than 0.5 to 1% of having a complication with these procedures. We're looking with some of these screening tests specifically for certain genetic disorders, aneuploidies, whether it's trisomy 21, trisomy 18 or trisomy 13, with an amnio or a CVS, we have the option of testing a lot more. We're able to test every single chromosome and, in addition to that, even dive in deeper at the microarray level.

Dr. Birnholz:
It's an excellent preface from both of you. So, Dr. Wapner, then, in light of these traditional screening tests used for fetal aneuploidy, why don't we introduce noninvasive prenatal testing to this discussion and maybe talk about the advancements that they've brought to fetal health assessment.

Dr. Wapner:
So, when we say, "noninvasive fetal testing," what we're talking about is being able to get information about the pregnancy by drawing a blood test from the mother rather than doing one of the tests that Dr. Chavez has talked about. It was discovered about 10 years ago that floating in the mother's blood are small pieces of DNA from the fetus. As a matter of fact, at around 10 to 12 weeks of gestation, in her plasma, which is not the cells in her blood, but the fluid in her blood, there are lots of small pieces of DNA, and of all those small pieces, about 90% of them come from the mother and about 10% of those pieces actually are DNA directly from the fetus. These fragments come from the normal breakdown of our body's tissue, so most of the DNA is coming from, or shedding from, most of the organs of the mother, but, 10% is coming from shedding from the placenta. How can we analyze the fetus if we've only got about 10% of our testing material, 10% of the DNA is fetal? What we need to do is we can count using what's called sequencing each of those little pieces and ask the question, "Where did they come from?" So, we take these little pieces, we look at the sequence or the DNA, and that's just the building blocks of the DNA, the nucleic acids, and once we see those building blocks, we can say, "Okay, this piece comes from chromosome 1, this piece comes from chromosome 2, this piece comes from chromosome 21." Now, the computer can do this millions or tens of millions of times so that we actually can then get a sense of how much DNA there is from each of the chromosomes. If the mother is carrying a fetus that has Down syndrome, which is an extra number 21 chromosome, when we count all the DNA we will find a tiny little bit of extra DNA from chromosome 21 compared to the amount that's there from all the other chromosomes. We are able to make the prenatal diagnosis or we can actually improve our screening—it's not a diagnostic test, it remains a screening test—find with very good sensitivity and specificity the women who are carrying fetuses with, say, Down syndrome. Compared to the 85% with the biochemical testing, the detection rate or the sensitivity with noninvasive prenatal testing or cell-free DNA analysis is approximately 99.5%, or maybe higher. That means 9.9 out of every 10 Down syndrome pregnancies would have a positive test. The more important aspect of this test, we talked about 3 to maybe 5% of all women will get a positive test, most of them have a normal pregnancy. The false positive rate with the cell-free DNA analysis is 1 per 1000, so there is a dramatic decrease in the number of women that will be getting false results. So we can do the same thing by asking how much DNA is from chromosome 18 or we could do the same as asking how much extra DNA is from chromosome 13. Although it's 99.9 sensitivity or 99.5 for trisomy 21, it's a little less for trisomy 18, it's even a little less for trisomy 13, we also can do the same for the X and Y chromosomes and identify what we call sex chromosome abnormalities. So, once we have the technology of being able to sequence little pieces of DNA, we now have a much better test for doing our screening. But again, let me remind people that this is still a screening test; there will be people that will have a positive noninvasive test that still will have a normal pregnancy.

Dr. Birnholz:
And while we're on this subject, can you refresh us a little bit on the concept of positive predictive value and how it applies to NIPT?

Dr. Wapner:
Whenever one does a screening test, you get the two terms "sensitivity" and "specificity." What a patient really wants to know is what is her specific probability that her pregnancy has, in this particular case, Down syndrome, and that's called the positive predictive value, and that's the result that the patient gets. The positive predictive value is the likelihood, if you have a positive test, that the fetus actually has Down syndrome, the less frequent the particular disorder is, the less likely that a positive test actually means the fetus is affected. So, if you take a woman that's 35 or 40 years old, in which the risk of Down syndrome is very, very high, if she has a positive test, it's approximately 9 times out of 10, or maybe higher, that the fetus is really affected. Alternatively, if you did the exact same test with the exact same sensitivity and specificity on a 20-year-old in whom the risk may be 1 in 1000 or 1 in 2000, her positive test would mean she only has about a 30 to 50% chance that the fetus is affected, and that's just because trisomy 21 is so much less in that population, a positive test is more likely to be a false positive than it is to be a true positive. The importance of positive predictive value is, when patients get positive tests from cell-free DNA screening, because it's not diagnostic and because we know nothing has 100% positive predictive value, at least no screening test, women have to have the results confirmed by a diagnostic test, such as CVS or amniocentesis.

Dr. Birnholz:
Excellent. So Dr. Chavez, given what we now know about the high sensitivity and specificity associated with NIPT, and understanding the positive predictive value a little bit more, what about these results that are deemed failures or no-calls, what can you tell us about that?

Dr. Chavez:
Now, there is a challenging aspect of this technology there are these failures or no-call rates. What we're doing is actually putting the patient in a predicament where they might get delayed information, or not get the information that they need. There's different types of NIPT and they also have different types of failures or no-calls. But the range of these no-calls or these failures can be as low as less than 1%, but as high as 8%.

If we do get a no-call, that depending on the gestational age, depending on what the clinical scenario is and what the patient's desires are, it might be worthwhile, under certain circumstances, considering repeating it. Or offering the patient more definitive testing, and that definitive testing can either be an amniocentesis or a CVS. There have been some studies that show that these failure or no-call rates in certain patients have an increased risk of having an aneuploidy just for the fact that they ended up with a failure or no-call rate. One of the things that we've seen in certain of these studies that this can be as high as 16 to 20%, we also have to be sensitive to the fact that we're delaying getting information because some of these tests can take anywhere from 4 to 7 or 8 days to return and we're adding another 4 to 7-8 days on top of that if we're repeating it. We also want to let patients know that they do have other options, and they can pursue an amnio or CVS to get definitive information.

And if we have a no-call and we have an ultrasound finding, depending on what it is, we might want to consider an invasive test from the get-go. If we have one of these soft markers on echogenic focus, for example, where we see a small bright spot in the heart, well then maybe repeating it might be an option if everything else being low-risk for that particular patient. When we do counsel our patients concerning, NIPT, that we do mention it to them, that depending on the technology we use, it can be less than 1% or 8% at a time that we don't get results, and that it might delay getting information. Because for some patients, they say, "You know what, while that risk is small, I don't want to take that risk. I'd rather look at other technologies or other options to get the information I want."

Dr Birnholz:
That's a great tie back to the daily practice, Dr. Chavez. I'm sure a number of our listeners are going to feel like this information resonates with them.

Dr. Wapner, then, why don't we turn to the role of NIPT in whole genome reporting or in identifying microdeletions? I'd like to know when this role is indicated and for which patients.

Dr. Wapner:
When we're talking about microdeletions, we're talking about chromosomal or genetic abnormalities that don't represent an extra whole chromosome, but represent either a missing or overrepresented small piece of the chromosome, and only recently have we actually been able to detect these smaller—and they're called subchromosomal findings—and that's by a technology called microarray. It's interesting that studies using diagnostic testing and microarray have shown that maybe 1% of all pregnant women will have a pregnancy

in which the fetus has a small deletion or a small duplication, and those small deletions and duplications are called copy number variants. That number may seem high, but it's been validated by a number of studies. These microdeletions that occur in about 1% are not benign microdeletions, they occur much more frequently, they can cause problems such as autism, schizophrenia, seizure disorders, learning disorders, developmental delay, depending on which chromosome they come from and depending on their size. This is in opposition to the other question you asked, which is sequencing, and sequencing is actually a change in one of the base pairs, and that we're just beginning to explore during pregnancy and the ability to do that noninvasively would still have to be considered to be investigational. However, it's really important to realize that these changes of one base pair, if they're not inherited from the parent, in other words, they're de novo mutations, are a very common cause of birth defects and actually increase as the father's age increases.

So, let's talk predominantly about our ability with noninvasive evaluation to identify these microdeletions, and they're more difficult to determine than our whole chromosomes for the simple reason that they're much smaller, and that means that we have to count a lot more fragments to find tiny, little missing pieces than we would to find an overrepresented chromosome. In one approach, they count all the little fragments and they just count more and more so that they can be sure that if there's a small piece that's missing, they'll be able to identify that. The limitation right now is the power or the number of times you have to count is so high that it just becomes cost prohibitive to find anything that's smaller than 7 million base pairs. Alternatively, another technique doesn't count, but it only looks for missing pieces on certain chromosomes, and the disadvantage of that is that there could be lots of other places that are missing pieces, so you have to choose which areas you want to look at. So, the American College of OB/GYN has recommended that noninvasive screening should presently not be used to look for microdeletions. Patients that want that more detailed genetic information should have a diagnostic test in which you can look at all the DNA and you can find microdeletions as small as 200,000 base pairs. Will we be able to find microdeletions and duplications with noninvasive testing? I'm almost certain that we will, but we just have to overcome some technical difficulties and also overcome that the more sequencing you do, the more it costs.

The most common microdeletion that one might find is when we're missing a small piece of chromosome 22. That's called the 22q11 microdeletion syndrome, it's also called DiGeorge syndrome. This is a small piece of DNA, about 2.5 million base pairs that's missing, and we used to think that it was in every 1 in 4000 pregnancies. More recently, we found out that this one missing piece, and again, there's thousands of potential missing pieces, this is just the most common one, occurs in about 1 in 1000 pregnancies. In younger women it's more frequent than Down syndrome and this particular missing piece can cause severe heart defects for the fetus, it can cause cleft lip and cleft palate, but more importantly, about 90% of children that inherit this have significant learning disorders, about one-third will have very significant cognitive developmental disorders, and 1 in 4 of those children during adolescence will become schizophrenic, we now are able to find a lot of more important information by looking in more depth into the chromosomes, but it's not yet time to do that by noninvasive screening.

Dr. Birnholz:
Well clearly, based on what you've been talking about, Dr. Wapner, our focus here on microdeletions in prenatal testing is on the frontier of OB/GYN and prenatal testing. There's much more to be understood and learned.

But Dr. Chavez, when Dr. Wapner referred to ACOG's take on testing for microdeletions it seems that a number of societies have voiced their opinion. In May of 2016, there was the Society for Maternal-Fetal Medicine, as well as ACOG, both came out with this updated committee opinion on NIPT. Dr. Wapner referenced some of the general thoughts, but can you review for us a little bit of the highlights from that document and what they said regarding testing for microdeletions, specifically?

Dr. Chavez:
I think a couple of the important key points was that, one, offering this technology to a larger segment of the population including the low-risk population is a reasonable option to have a conversation with our patients. Two, I think it's also important that we have pre- and post-counselling with our patients, and to Dr. Wapner's point about we want to test things that, one, our patient is aware that we're testing for, and two, that it's going to give the most accurate information our societies have stated, particularly the one you mentioned in May of 2016 from SMFM and ACOG, that microdeletions when we're concerned or looking for them, that we should not necessarily utilize NIPT as our first option, and it's also important to realize that we don't use this technology in isolation. We want to make sure that we have a good clinical history, making sure that we have good clinical information whether from the pregnancy or whether from the ultrasound, to make sure that we help our patients get the best possible testing available. Pre- and post-counselling are probably the biggest challenges that we face now. We know that we have shortages of genetic counsellors; we know that not every clinician has access to good maternal-fetal medicine services or genetic counselling, but still the burden falls on the OB/GYN and we want to make sure that they understand that these tests should never become routine prenatal care, meaning that we tell our patients, "Oh, just go get your blood drawn and we'll review after the results come back." These tests do take the investment of counselling before the tests, not only to review what we're testing for, but the possibility of a failure or a non-reportable, and also to let the patient know that while we're trying to get information from the baby, the fetus, we're actually getting information from the pregnancy or the placenta just like we would

counsel our patients when we're performing a CVS, we would tell them that on rare occasions, anywhere from 1 or 2% might be representing just a genetic concern that's isolated to the placenta, confined placental mosaicism. Our societies are helping us offer this to many more patients, but at the same time, the challenges of counselling pre- and post- are still there.

Dr. Birnholz:
Well doctors, I'd be remiss if I didn't bring up one other potential utility for NIPT that has been demonstrated in a number of studies as of late, and that is using NIPT as a tool to identify potential malignancies in pregnant patient. How did this come about? Dr. Wapner, can you talk about that?

Dr. Wapner:
Interestingly, it came about through serendipity. There were a few patients in whom their tests showed that there was extra material from some chromosomes and there was missing material from other chromosomes, which just shouldn't occur. So someone asked the question, "Where could this unusual DNA be coming from?" and one of the things is, we know that in tumors, tumors frequently have multiple genetic mistakes. So they asked the question, which really an incredibly good observer would ask, "Could this patient have cancer?" They did an MRI on the patient and they found, lo and behold, indeed there was a tumor, and that was causing the multiple abnormalities in the DNA. Subsequently, there have been a number of such cases that have been identified. We think of ourselves doing prenatal diagnosis and reproductive genetics, but in the cancer world, they're looking at the same exact abnormalities of DNA in order to screen the whole population for cancer. So, looking at the tumor DNA in the maternal circulation—in anyone's circulation—has become an important tool. Nobody is suggesting that NIPT is a screening test for cancer. What we're saying is, when you see these unusual patterns, then you should at least alert the patient that that's a possibility and discuss with them whether you really want to have the additional testing.

Right now, if the laboratories see this unusual pattern, not all of them are reporting that to the patients. They've taken the position that this is a test screening for trisomy 21, 18, and 13, and any additional information is not our responsibility. So, from a clinician's standpoint, you might get a result that says, "Well, it looks like this pregnancy might have both trisomy 21 and trisomy 18." You'll have 2 trisomies. That really gives the physician the responsibility to call the laboratory and say, "Are you seeing a lot more of this? Because it would be unusual even to have 2." And then if you ask, the labs will give you that information. The labs, however, over the past 3 to 5 months, have thought this over and the majority of them, if they see this unusual finding, will report it, but they didn't originally want to take responsibility for it. But it's a very interesting finding and it, indeed, has saved people's lives.

Dr. Birnholz:
Well, before we close our discussion today, I want to tie our conversation back to patient counselling at the center of this. So, Dr. Chavez, how should clinicians ultimately counsel their patients as to the use of NIPT for fetal chromosomal analysis, and especially as it pertains to informing them of test results?

Dr. Chavez:
I think that we need to realize that it's still a screening test. The other thing is that we want to set our patients' expectations correctly. The last thing we want to do is for our patients to think that NIPT is the perfect substitute for the information that we get with an amniocentesis or CVS. We want patients to realize that the technology is great, the sensitivity and specificity is fantastic when it comes to these types of aneuploidies, but if we're looking for more information, and if the patient is going to make a non-reversible decision on the pregnancy based on NIPT, that it's important that they realize that they should confirm the information they got from the technology with an invasive test, a CVS or an amniocentesis. An amniocentesis or CVS, should not be performed for every single patient, it was never meant for that. I think that more and more patients will probably end up utilizing it because, as we test more patients with NIPT, we're going to get these opportunities where we either get positives or negatives that don't match up with our ultrasound findings or these non-reportables or these other situations where we're getting confusing results.

But I'd like to also offer another option for counselling our patients during the process while they're waiting for the results. I don't think it's unreasonable to make sure that we offer our patients additional information, whether it's reading, websites, educational websites, there are societies and other organizations that are getting together now and putting together these wonderful resources for our patients, because we do have, unfortunately, a limited amount of time in our office visits. Most patients have some type of technology available to them, whether it's a computer, a tablet or a smart phone, where in a waiting room or even afterwards can look up some of the information that we gave them, either to review or to get more detailed answers from.

Dr. Birnholz:
And on that note, I would very much like to thank my guests Dr. Chavez and Dr. Wapner for joining us today to provide an overview of noninvasive prenatal testing and its role in optimizing fetal outcomes. My thanks again to you both.

Dr. Chavez:

Well, thank you for the opportunity, I appreciate it.

Dr. Wapner:
Thank you.

Narrator:
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