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The Importance of Non-invasive Prenatal Testing in All Pregnant Women

Narrator:

Welcome to CME on ReachMD. This segment entitled “The Importance of Noninvasive Prenatal Testing in All Pregnant Women” is provided by Omnia Education.

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Dr. Russell:
With fetal chromosomal abnormalities being a common cause of congenital malformation and miscarriages, screening for these abnormalities has for many years been identified by ACOG as an important component of obstetrical care. Noninvasive prenatal testing, or NIPT, provides meaning to screen women for these chromosomal abnormalities that offers high levels of sensitivity and specificity.

Join us, as Dr. Lee Shulman discusses the background of NIPT, including the advantages, risks, limitations and differences in the various screening tests that are available.

I am your host, Dr. John Russell, and I have the pleasure of speaking today with Dr. Lee Shulman, who is the Anna Ross Lapham Professor of Obstetrics and Gynecology, Chief of the Division of Reproductive Genetics and Medical Director of the Graduate Program in Genetics Counseling at the Feinberg School of Medicine at Northwestern University in Chicago, Illinois.

Dr. Shulman, welcome to the program.

Dr. Shulman:
Pleasure to be here.

Dr. Russell:
So, doctor, what types of testing are available to evaluate fetal chromosomal makeup, and how do they differ in terms of screening and diagnosis?

Dr. Shulman:
There really is a profound misunderstanding of the differences between screening and diagnosis. Screening is meant to adjust somebody's risk for a particular problem. Diagnosis tells us whether or not that individual or fetus has that particular problem or doesn't. So there are first trimester options, there are second trimester options, and there are combinations of first and second trimester options. So, for the most part, we look at biomarkers or proteins in the first trimester and in the second trimester. People may be familiar with, say, the quad screen, which looks at four different maternal biomarkers. People may also be familiar with the nuchal translucency test which we typically do in the late first trimester, and at many times combine that with another series of maternal biomarkers. Recently the availability of what we call noninvasive prenatal testing, or circulating cell-free nucleic acid testing, where we look at not so much at biomarkers but at nucleic acid ratios that give us an indication of whether there's an increased or decreased risk in certain fetal chromosome abnormalities.

So, all of these, regardless, really, of how well they do in screening, are screening processes. They should be reported as positive or negative. They should not be reported as a normal or abnormal. And we reserve the normal or abnormal reporting for diagnostic testing. Chorionic villus sampling can be done in the first and early second trimesters typically. Amniocentesis is typically done in second and sometimes the third trimester.

Dr. Russell:
So, what is NIPT, and how does it work?

Dr. Shulman:
Essentially, what NIPT looks at is nucleic acid, cell-free nucleic acid, so not fetal cells per se but nucleic acids. And we now know that most of these nucleic acids are derived from the placenta. A woman, for example, has 2 number 21 chromosomes. If we take a look at her cell-free nucleic acid, 1.36% of her cell-free nucleic acid will be 21-specific nucleic acid. So, there are obviously 22 autosomes, 2 sex chromosomes. And so we know with a percentage of 1, the percentage of 2, 3, 4, 5, 6, etc., etc. So, 21-specific nucleic acid is 1.36%. If she is carrying a fetus with Trisomy 21 -- we know that about 10% of her circulating cell-free nucleic acid is fetal in origin. And while this particular screening protocol doesn't identify fetal nucleic acid specifically, what we know is that if she -- and we believe her to have 2 chromosome 21s -- is carrying a fetus with 3 chromosome 21s, Trisomy 21 or Down syndrome, then that percentage increases from, say, 1.36 to 1.44%. And what technology has developed has been the ability to differentiate that small difference in percentage, and that really is the basis for all the commercially available NIPT screening algorithms. So, we look at 21 specific. We can look at chromosome 18 specific, chromosome 13 specific, X and Y, and more recently other genomic specific nucleic acid sequences.

Dr. Russell:
So, doctor, overall, what type of fetal aneuploidies can be screened for with NIPT, and are there any limitations as to the type of aneuploidies that it can detect?

Dr. Shulman:
The first chromosome to be screened is the one that's most commonly associated with problems, and that's chromosome 21 associated with Trisomy 21 or Down syndrome. For the most part, the commercially available products that are there screen for chromosomes 21 and chromosomes 18. Some of them also screen for chromosome 13, and others also screen for chromosome X and chromosome Y. The 5 chromosomes that are associated with the majority of chromosome abnormalities in, say, a late first, early second trimester fetus, are amenable for screening with this technology, regardless of which commercially available product one uses.
The limitation is that we understand that there are many other chromosome abnormalities. Wholesale numerical abnormalities or aneuploidies, translocations, deletions, duplications -- -- but conventional NIPT assays cannot provide information about those other chromosome abnormalities.

Dr. Russell:
So, which pregnant women would you consider to be appropriate candidates for NIPT?

Dr. Shulman:
When this technology first became available this particular technology was limited to high-risk women or women who were either of advanced maternal age, which is 35 or older at their estimated date of delivery, women who had a positive conventional screening result, meaning a biomarker or a biomarker with or without nuchal translucency screen, women who had had a previous pregnancy of one of the candidate aneuploidies. So, if she had had a previous pregnancy with Down syndrome or a previous child with Down syndrome, then she would have been considered a high-risk candidate. Or, if there was, in fact, an ultrasound abnormality that could potentially would be amenable for screening with this technology. For the most part, those were the four indications, and those four indications have mostly gone forward.

Our data for the most part is mostly centered on how well this testing works in this high-risk population. I think clinicians can feel safe about offering it to a high-risk population made up of the four indications that I mentioned. As we go forward, it looks like it is starting to be applied or offered to women who are not necessarily represented by one of those four characteristics.

Dr. Russell:
If you're just tuning in, you're listening to CME on ReachMD. I am your host, Dr. John Russell. I'm talking with Dr. Lee Shulman about noninvasive prenatal testing.

So, doctor, how effective is NIPT in screening for the various aneuploidies?

Dr. Shulman:
Well, I think a general statement is that not only can NIPT screen for more chromosomal abnormalities than we have had with biomarker and nuchal translucency screening in the past, it invariably is a far better detector of fetal chromosome abnormalities than any of the

older more conventional biomarker or nuchal translucency screenings. We obviously have the most information about Down syndrome, about Trisomy 21. Detection rates are somewhere between 98 to 99+ percent. That's sensitivity. The specificity is also very high, 99%. When we take a look at things like positive predictive value, depending on which of the initial studies, we're looking at anywhere from, say, 60 to 90 to 95%. And again, positive predictive value is the ability of a screening assay, how often will a positive result be associated with, in this case, an abnormal outcome? So it's different than sensitivity, and frequently clinicians and lots of people get it confused.

Those numbers slightly decline as we go away from Trisomy 21, so when we take a look at Trisomy 18, those numbers are a little less. Sensitivity is more in the range of about 95 to 98%. Specificity is still at around 98 to 99%. Positive predictive value drops probably to about 50 to 60%. There's somewhat of a precipitous decline when we take a look at Trisomy 13, and there are actually, not so much reasons based on how common Trisomy 13 is, but rather the intrinsic nature of chromosome 13, and so sensitivity goes to about 90 to 91% in that range. Positive predictive value probably falls to about 30 to 40%. And those numbers get even lower with sex chromosome abnormalities, probably sensitivity in the range of about 70 to 80% with positive predictive values in the 20 to 40%. But I think it really is important, John, for the audience to really understand that when I talk about decline and drops, if you're comparing this to the older conventional screens, the quad screen, even the nuchal translucency and biomarker screening protocols, the sequential screens -- for example, the sequential screen, which involves blood tests in the first and second trimester and a nuchal measurement in the late first trimester -- the positive predictive value for that, which had been the standard of care for well over a decade, is only 3 to 4%. So, invariably, regardless of which commercially available product that a clinician uses, this particular screening assay is going to be far better for detecting these common chromosome abnormalities.

Dr. Russell:
So, doctor, how should a clinician discuss the results of an NIPT with a patient?

Dr. Shulman:
Well, I think first and foremost is to make sure that the patient understands that this is a screening protocol. Unfortunately, I still get patients referred to me after being told, or at least they say they were told, that this is a replacement for amniocentesis or CVS. Screening modalities are never a replacement for diagnostic modalities for a couple of reasons. First of all, we are not doing a direct analysis of fetal tissue, so we're unable to directly assess fetal tissue. Most importantly, I've mentioned already about the limitations of NIPT. When we do a CVS or an amniocentesis, we have available to us a complete chromosome analysis, and we can look for structural abnormalities in the chromosomes, and if we go on and do a microarray analysis, we can look for genomic abnormalities. And these particular situations are not possible by screening. So, first and foremost, clinicians need to make sure that the patients understand that this is screening, what the difference is between screening and diagnosis.

Obviously, a negative result is great news, meaning the risk for these common chromosome abnormalities has been reduced, reduced considerably. A positive result is obviously not good news. The risk for that particular chromosome abnormality has been considerably increased but not guaranteed, and at this point it is appropriate to initiate a discussion, either by the clinician or in referring to a maternal-fetal specialist or geneticist, a discussion of diagnostic testing and the implications of the positive result.

Dr. Russell:
Why does an inconclusive test result occur, and how can this be managed?

Dr. Shulman:
The reality is, is that, as I stated earlier, this particular technology has been readily available for about 4 to 5 years, and while we've had a very quick uptake in its use nationally and internationally, there's still a lot that we don't really know or understand. And if you take a look at the literature, we've seen a lot of work, even from our center and many other centers around the world, about outcomes that have not been correlated with diagnostic outcomes. And again, it gets back to the concept that this is screening. And when I speak to audiences, I actually talk about a concept that it's just screening. Trying to make this into something other than a screening assay is not a good thing for the patient or for the clinician.

So, what we have noticed is that depending on which commercially available assay -- there can be differences in this -- a percentage of tests that come back inconclusive. Initially, we felt that a lot of the inconclusive assays were perhaps as a result of increased maternal weight and as a result of that a reduced concentration of nucleic acids, and that may be true. A lot of that went into a discussion about fetal fraction and about the importance of it. And in this situation, fetal fraction may be important in the assay and in technology, but we're ultimately interested in getting a screening outcome, not necessarily learning about fetal fraction.

So, it's clear that low fetal fraction can increase the risk of inconclusive outcomes or no outcomes. I think there's been an understanding of women using heparin and Lovenox. For whatever reason there may be an increased likelihood of no results available. And again, it's just a screening assay. But what we do know is that when we take a look at the group of women who have an inconclusive NIPT result,

their risk for a chromosomal abnormality is markedly increased compared to the general screening population, and as a result, ACOG and ACMG and the International Society for Prenatal Diagnosis has strongly encouraged clinicians that when they get an inconclusive result back, and assuming it's inconclusive not based on a laboratory issue but inconclusive without really recognizing why, that these women be counseled as to a potential increased risk for a chromosome abnormality and not so much encouraged to redo the screening test but rather to counsel patients about diagnostic testing.

Dr. Russell:
In closing, Dr. Shulman, could you talk about the evolving role of NIPT in the general obstetric population?

Dr. Shulman:
John, I alluded to this earlier and, obviously, I think most people in genetics and maternal-fetal medicine who are involved in developing these assays and using these assays are probably unanimous in saying that whether we're looking in a high-risk or a low-risk population, clearly these screens provide a better screen for these particular chromosome abnormalities. That being said, because of the dynamics of developing a screening algorithm, how well this particular screen works in a high-risk population is not necessarily going to be the characteristics of this screen in a low-risk population. And again, part of this is the understanding that screening algorithms are as much of a mathematical exercise as they are a biological exercise. So, positive predictive values are going to drop. The sensitivities may drop as well. The specificities may drop. That doesn't mean that it is a bad test or it's not as good of a screen as it is in a high risk. The characteristics, the frequency of the condition we're screening for is different, is lower. So, I think people need to understand that it may not work at the same level as in a high-risk population.

I will tell you that as a clinician who's dealing with this every day in the office, part of this issue is also insurance coverage. Lots of patients may not wish to pay out of pocket for something as a low-risk patient that they may not need to pay out of pocket for if they were a high-risk patient. And so, the evolving role is hopefully to gain more information. We have some information about how NIPT performs in a low-risk population. The one paper that people allude to is Mary Norton's work published in 2015 in the New England Journal of Medicine. This international multicenter study assigned pregnant women presenting for aneuploidy screening at 10 to 14 weeks of gestation to undergo both standard screening -- with measurement of nuchal translucency and biochemical analytes -- and NIPT. 19,000 women were enrolled, with results from nearly 16,000 women available for analysis. Mean maternal age was nearly 31, and mean gestational age was 12.5 weeks. The area under the curve for NIPT was 0.999; and for standard screening this was 0.958 --- a statistically different significance P value of 0.001. Trisomy 21 was detected in 38 of 38 women – 100% -- with NIPT. While standard screening detected 30 of 38 women –79%. This also was a statistically difference with a P value of 0.008. The false positive rate in the NIPT group was 0.06%; for standard screening the FPR was 5.4%. Again this too was a statistically significant difference at the P value of <0.001. Positive predictive value for NIPT for Trisomy 21 was 80.9%, as compared with 3.4% for standard screening and again, this too was a statistically significant at a P value of <0.001.

I think many of us would agree, that there are still lots of questions that need to be answered about NIPT. But if you are looking at NIPT as a screen for fetal chromosome abnormalities and if you’re able to put that problem into its proper clinical perspective for both high-risk women as well as low-risk women, then NIPT clearly performs better than conventional biomarker assays.

Dr. Russell:
Dr. Shulman, I want to thank you very much for taking time out today to speak to us about the importance of noninvasive prenatal testing in all pregnant women.

Dr. Shulman:
John, thank you very much.

Narrator:
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