Good morning. Thanks for coming to be my audience this morning. We’re going to talk about screening for genetic disorders in pregnancy, a little bit about the controversies, what’s going on with that particular process and I’ll take you through it sort of step by step through the process.

Our goals and objectives for today would be to understand the basic principles of screening, to get a little idea of the difference between first and second trimester screening and finally to discuss how it is that you would present to your patient the various options they have for screening for other disorders in pregnancy.

It’s important as part of what we discuss that we talk about what it really means to screen versus diagnosis. Drs Cuckle and Wald in 1984 listed for us what they considered this to be and that is identifying within an apparently normal population those people who have a condition that you’re interested in. So you’re interested in finding out for instance whether somebody has a risk for Down’s Syndrome, you’re looking at all the pregnant women trying to identify those and then offer them next steps in terms of what they would have done in the next step of that process.

So we’re going to focus a bit on the traditional quad screening or the mid-trimester screening that is done for Down’s Syndrome as well as for neural tube defects. And most of the conversation this morning will focus really on Down’s Syndrome as it relates to pregnancy as well as trisomy 18 and again will talk a little bit about trisomy 13. But there are four markers that have been identified that help in looking at the possibility that a pregnancy might be at increased risk for Down’s Syndrome.
Alpha-Fetoprotein which has been around for a number of years as a screen for neural tube defects, unconjugated estriol, human chorionic Gonadotropin and inhibin A and each of these has been shown to have some relationship to whether a pregnancy does or does not have Down’s Syndrome.

Now the most important thing in whether a pregnancy does or does not have Down’s Syndrome is the patient’s age as you’re all aware. So if you look at this graph what you will see is that if your are in the 20 age group, the risk of having a live birth with Down’s Syndrome is relatively small but if you’re in the 45 year old group, the incidence becomes much, much higher. And so any testing that you’re doing to screen has to take the age of the patient into account. So you don’t give the same result to a 20 year old that you would also give to a 45 year old.

And so using this particular quote from Dr. Wald and we’ll see changing it slightly, the reason this works is that all of these proteins in the blood are independent of each other and independent of the mother’s age. So his comment is the analytes have to be independent of age and each other and combining the information provided by age and in our case now four markers allows you to use a multivariant analysis and generate a risk review for each individual patient.

So the results are reported as a risk figure and not reported as a yes or a no. So what each individual patient gets is an exact risk based on their age and their level of markers. And in this country as well as in the UK, we have set standard criteria for what we consider to be an increased risk. Where in this country we use the risk we would use for a 35 year old, so that risk turns out to be about 1 in 270.
and in the UK and in some states in the US, 1 in 190 is used as the risk of a 37 year old. So if you come in, you have your blood drawn and your risk turns out to be 1 in 271, you’re considered to be not at risk. If you’re 1 in 269, you’ll be considered at risk for having Down’s Syndrome and the next steps of the process would continue from that point.

But, again, it’s only a risk, if you’re remembering that for a patient that has a 1 in 250 risk, 249 times out of 250 times the result will be normal. So it really is a relatively good screening test but remembering a fairly high quote false positive for the individual patient.

This is some work again from Dr. Wald which you’ll see a number of these types of slides in today’s he’s sort of the guru of screening. But if you just took the patients age and said I’m only going to offer prenatal testing to women above the age of 35 it would detect about 30 percent of all Down’s Syndrome pregnancies. If you use a single marker like AFP, you can raise that to 37 percent, two markers would bring it to 59 but most importantly to use the present quadruple test you will detect about 75 to 80 percent of the Down’s Syndrome pregnancies by a single blood test down in the second trimester of pregnancy.

Now as you’re all aware most patients prefer to have things that are a much earlier time than a second trimester. So getting your information at 16 to 18 weeks of pregnancy is less interesting to the patient then getting their risk at a much earlier time. And so people have looked at for a number of years the option of doing some sort of screening in the first trimester.
Now interestingly this has been around almost as long as the second trimester screening and I’ll point out in a couple of moments why it didn’t catch on. But it was known from a fairly early time that a protein known as pregnancy associated plasma protein A or PAP A had a very high association with Down’s Syndrome in terms of the fact that its markedly decreased. So relative to a patient who doesn’t have a Down Syndrome pregnancy which would be 1 multiple of the medium this is quite low at .4, so substantial drop off in that point. It also is detectable as early as 8 weeks of pregnancy and it rises throughout pregnancy. Interestingly it comes from the placenta and it appears in all of Down’s Syndrome screening. The markers from the placenta are far better than the markers from the fetus. So in the second trimester inhibin A and hCG are the two best markers, they both come from placenta and it turns out in the first trimester PAP A is also a placenta protein.

And we also use that in association with hCG in the same way that we do in the second trimester so again both of the markers in the first trimester are placenta markers. Again it rises rapidly until about the 10th week of gestation which you can see here and then falls off fairly quickly after that. Again, it’s elevated in Down’s syndrome the opposite of PAP A. So this is about twofold higher in pregnancies with Down’s syndrome versus a pregnancy without and about the opposite for PAP A.

If you just use those two markers alone you can do a pretty reasonable job of detecting Down’s Syndrome, about 63 percent as pointed out by Haddow in 1998. The problem was that that’s no better than the triple screen which we had in 1998 and it did not detect neural tube defects. So it
never caught on as a screen because it wasn’t better than what we had and it also didn’t detect neural tube defects.

At about the same time a number of people are using ultrasound as an option for screening for Down’s Syndrome and found that a very interesting process goes on with the fetus. And that is if you look at this being the head of the fetus and the back of its neck there’s a small collection of fluid here known as a nuchal translucency, I point in this slide also for the benefit of people who do this, the second line here is actually the amnion. In early pregnancy, there’s a separation between the amnion and the chorion and so you see actually two sacs here and one of the common mistakes is actually measuring this as being a nuchal translucency as opposed to these two bright white lines that you see here which are the skin of the fetus and probably the bony structure of the spine that you’re measuring between.

If you look at this picture you can see that it’s markedly increased in this picture of the fetus indicating this fetus has a very high likelihood, it has a chromosome abnormality. I’ll show you the numbers to go with that in a couple of moments.

Now a group out of London, Dr. _____ group has published a number of papers, I’ve chosen just one to show you screening about 96,000 patients using simply the ultrasound maker of the measure of nuchal translucencies and using the risk cutoff of 1 in 300, so very close to the 1 in 270 that we use in the quad screening results and you can see that they were quite good at detecting the 3 major
trisomies about 80 to 82 percent for 21, 13 and 18. That’s very important to keep in mind because the quad screening will only detect trisomy 21 and trisomy 18. The nuchal translucency picks up trisomy 13 so you get a very good pickup. Now you should immediately recognize what the downside is. The false positive rate is nearly 10 percent. So that means for every pregnant lady that we give a result to there are 9 others that have a falsely positive result. So nearly 1 in 10 people of all pregnancies will have a false positive result. So it’s – this is a key to our conversation because in general what this means is that either this is a bad cutoff point or it’s a population that’s much older. If you go back and look at the study you can see that the average age of this population was much older which made for the high false positives, it’s also makes these results look a little better as well.

However, other people tried to repeat this study and were completely unsuccessful. Here’s three studies that were done, this one is done I believe in Scandinavia and only had about a 50 percent detection rate, another European study with a 43 percent rate and a US study, we were by far the worst, had only a 31 percent success rate. And what became very clear in this process is that how you measure that nuchal translucency and the preciseness with which you do that makes all the difference in terms of how good you are at using this as a screening test.

And so there are now ways to be accredited to do the nuchal translucency measurements. To different accrediting agencies in the US, the maternal fetal medicine society does accrediting and also the group in London, the Fetal Medicine Foundation also does accrediting. This is information
from the Fetal Medicine Foundation accrediting process and you can see that it has to be at a very precise gestation between 11 and 14 weeks essentially, a mid sagittal view which you see here with the fetus taking up essentially three quarters of the picture and then away from the amnion which you see here and measuring at least three measurements and taking the largest one and then the Fetal Medicine Foundation, they’re using the calipers on to on here from that point. You can see that there’s the didactic course that’s part of it, 50 scans that are reviewed, videotapes, everything to be sure that people are quite consistent in their measurements. If you do this process then you find that the results will be far more effective.

So if you look at first trimester screening in its current version where it involves again screening between the 11th and the 14th week, it’s screening for Down’s Syndrome and trisomy 18 but again you will pick up a reasonable number of trisomy 13s, the ultrasound not only does the screening but it also dates the pregnancy so it’s quite accurate from a dating perspectives, it measures the nuchal translucency and then the mother has blood work done to look at PAP A and hCG. All plugged into computer and risk generated in the same way that the second trimester is done.

Here’s some modeling data again from Dr. Wald to point out what could be expected when you put this test together and I’ll show you what the real life version looks like. But you can see that if you use just the serum, you get about 60 percent detection and if you use the neural nuchal translucency again about 60 percent out of 5 percent false positive. But the two together should reach about 85 percent. So this is all mathematically done to say if you put the test together and did it this way, this
is the expectation.

So now comparing you can see that if you put this beside the quad screening, you should in fact have a much better test for the first trimester, then a second trimester screen with about a tenfold or 10 percent difference in the results.

And here are four studies that have been done to identify how good it is, the BUN study done in the US, FASTER in the US and both of these were in the UK. You can see now about 104 thousand patients that were done with an 84 percent detection rate, almost identical to what Dr. Wald had anticipated, you can see there’s some variation between the studies, the smaller study that there is, you can see the confidence limits were quite large here. But when you add in all four studies you have a very precise, about 84 percent. A very good screening test in the first trimester.

Now once you get one test people begin to look at what are the options for beginning to combine these tests? Well one option is to say why not do both a first and second trimester test as part of what you’re doing. And there is a test described as the integrated test which takes both the first and the second trimester biochemistry and adds the ultrasound from the first trimester and generates a risk factor based on both of those.

Now again we’re using Dr. Wald’s study for this purpose and you will see that what he did was he looked up all the previous published studies to come up with his anticipated numbers. So what you
do now is you take the nuchal translucency in the PAP-A from the first trimester and then add the four from your quad screen. So notice you’re not using the hCG that you would normally use in a first trimester screen because obviously they can’t be independent if you’re using the same test twice. So remember our first our second slides said the markers must be independent of each other. So to do this test then you take out the hCG in the first and do it in the second trimester, it will generate a single risk figure at the end. So do your first testing at around the 11th week, your second testing around the 15th or 16th week and generate only one risk figure at the end.

Again, here’s some modeling data along with some real life data, the red dots are the real life data from the Suruss study, these are the anticipated numbers based on modeling and you can see in the slide that he modeled and expected that he would get about 85 percent with the first trimester screening, it came just under that, you saw the 83 percent number a few moments ago. The quad screen actually performed a bit better, slightly above the 76 that was anticipated and again, his integrated screen using all the factors we just talked about will raise up in the range of about 94 percent and came out exactly as expected. So again you see, you pick up about another 5 to 7 percent, increased detection, you get the benefit of both the first and second trimester screening in that process.

So what are its advantages? Well it’s obviously the most effective way to do it. It’s also the most – the safest method to do it because it decreases the number of amniocentesis. You’re getting a much lower false positive rate therefore to get a 90 percent detection rate, you’re only having to do 5
percent of all the population. You don’t confuse patients with multiple test results, you still get your AFP screening for neural tube defects. But your big disadvantage is timing and this period of waiting for the patient. And when you put in the waiting for the patient, two things happen. One, they get anxious and two they fail to come back. And what happened to Dr. Wald is more than a third of the patients didn’t come back for part two of the screening. So when you have the patient not showing up, now you have an inefficient first trimester screening because you took the hCG out and you have less information for her to give her for that result. So it absolutely requires that the patient come back.

Now one other option that people have talked about is well, you know, if you can’t get patients to agree to this process of doing it in two steps, why not just offer them both tests. That is, do the first trimester screening give them the results from that, let them act on that and then if the results are negative come back and repeat the screen. Now I’ve already pointed out one factor for you that’s a problem. The first factor is the hCGs are not independent. So by definition the test will become less efficient because you’re using two markers that are not independent. The second one that most people don’t think about is that if you prescreen the population and as you’ve taken out all the people who had an increased risk in the first trimester then your age risk is no longer reliable. So if you’re 30 years old and you had a screening that said your risk based on first trimester is 1 in 2000, now look like a 15 year old not a 30 year old. But the second trimester test doesn’t know that. And so it takes you back again and makes you 30 again and so what you can immediately understand from that is your likelihood of getting a falsely positive test goes way up. Because you’ve been
prescreened but the computer doesn’t know that.

And so when you look at the real numbers, you see yes, it’s very effective at detecting Down’s Syndrome but again almost a 10 percent false positive rate because of the factors that we just talked about. So to make it even more confusing there is a way to get around this and it has two names as you read the literature, one is called contingency screening and the other is called sequential stepwise or stepwise sequential screening. So rather than doing them sequentially you’re doing in a stepwise fashion and what that simply means is that you take the first trimester screen and if you have a relatively high risk, you at on that. That patient goes to appropriate prenatal testing which would be CVS in the first trimester. So notice a very high risk 1 in 30. If you have a really low risk 1 in 1500 you’re done. There’s no further testing, you’re complete, move on with your pregnancy. If you’re in between those two results you get your quad screen and then you can either be positive or negative for that and if you’re positive you have the option of amniocentesis. So multiple steps along the process. But each of steps designed to take out the problems that the sequential had and hopefully take out some of the problems of the integrated because again you’re giving those people at high risk their information at appropriate times. A reasonable number of people don’t have to come back. It’s only this group that’s borderline that you have to try to get back into the system.

Here’s a look at one study that – looks at that, you can see that the detection rate was pretty good, about 91 percent, very similar to the integrated result. The overall false positive was again right around the 5 percent we’d like it to be. Interestingly, 60 percent of the positive pregnancies were
picked up in the first trimester screening part of this and only about 1 percent were falsely positive in that first initial round. And of all the patients you screened, only about a quarter had to come back for something more. So overall a pretty good test, the problem is when you look at this at a population level, trying to get back that 25 percent of people who are borderline is where your logistic problem comes in.

So to close out this component of the discussion, you can see that as of 2011 there’s really no consensus as to the best screening method. Each institution tends to make its decision about what it seems to feel is best for its local institution. What you can say is the first trimester yields the best screening if you’re comparing first and second trimester. Integrated is probably the most efficient as we talked about before but the most logistically difficult to do. No place for sequential screening at all but a reasonable possibility for putting in some kind of stepwise sequential or contingent screening as an alternative to integrated but again similar logistic difficulties in getting patients back for the second blood test.

Now, the organization that does most of the work in this as it relates to OBGYN is the American College of Obstetrics and Gynecology. They’ve given some guidelines in terms of what we should be doing and their guidelines are that if we see somebody for their prenatal visit before fourteen weeks they should get a first trimester screening or some combined screening such as the integrated or stepwise sequential. So they really set the standard for us to say, we should not be waiting for quad screens for patients who present early. If they present later obviously quad screen is what
should be done. What they’ve created though is a second part to the statement, it is logistically very
difficult for the practicing physician to do and that is not to use a set cutoff because earlier in the
discussion about the 1 in 270 cutoff point, well they’re saying we shouldn’t actually use a cutoff
like that, we should talk to each patient individually about their risk relative to their age risk which is
great for patient autonomy but very difficult to practically do in an office situation, to talk to every
single pregnant patient and explain to them what you and I have just one over and in a 20 to 25
minute conversation. So although this is a very good process technically I think will be very
difficult to introduce.

I’d like to switch gears at this point and talk about things that we also talk about with our patients as
it relates to screening in their pregnancy and that is screening for risk of this genetic disorder or
carrier screening is the old term that we’ve used for years. All of the obstetricians in the audience in
listening would know that we already have in place a very standard process for cystic fibrosis. We
already have a relatively standard process in place where we ask the patient their ethnic background
and then make decisions about whether or not additional testing should be done. If you come from
an Ashkenazy Jewish background we’ll talk to you about Tay-Sachs disease and some other
conditions, if you happen to have Mediterranean ancestry like Italian or Greek we’ll talk about
Thalassemia or if you’re from an African-American background we’ll talk about Sickle Cell
screening and Alpha thalassemia screening as part of that. So these are standard, have been in the
OB offices for a number of years.
I’ll go over briefly the cystic fibrosis discussion to point out why it’s become a standard part of OB practices at that point and that is that if we look at certain populations the carrier frequency of a gene for cystic fibrosis is relatively high so in people of Caucasian backgrounds about 1 in 29 of us carry the gene for cystic fibrosis as do people of Askanazy Jewish. As you go up the scale here you can see Hispanics at 1 in 46, African Americans at 1 in 65 and Asian Americans at 1 in 90. So it becomes far less likely someone who comes from an Asian background will have a child with cystic fibrosis and I’ll give you the exact numbers in a couple of moments. Clearly this is the relatively high risk group here.

You can see if you were to screen all these populations you do a very good job of finding the cases of cystic fibrosis in people who are non-Hispanic Caucasians. About 1 in every 3500 pregnancies have cystic fibrosis. Askanazy Jewish about 1 in 2800 and notice when you get to Asian Americans you’d have to screen an incredibly large number of couples to find the one case of cystic fibrosis. And so there’s quite a bit of controversy about whether or not we should limit the screening to these two groups only or whether it should be offered and available to all populations. The problem in the United States is that we’re all not from a simple ethnic background, most of us have some mixed heritage and it’s difficult to know exactly where we fall into these categories. But the difficulty is in screening this population the likelihood of a true positive becomes less likely when you’re talking about population with a very low incidence.

Now, switch gears a little bit and talk about the Askanazy Jewish population, we talked earlier about
the fact that we have traditionally for years screened for Tay Sachs disease but it turns out if you look in the population you will see that because of the number of diseases that are carried within the population that has an incidence ranging from as low as 1 in 900 to as high as 1 in 40,000, the likelihood that if you’re Askanazy Jewish that you’ll be a carrier of one of the disorders, between 1 in 4 and 1 in 5. So it’s very appropriate to have a conversation with a couple about their ethnic background and if they’re Askanazy Jewish to talk about the various screening modalities that are there. The reason for this is again something we call the founder effect that if you are descending from a limited population, their ancestries are fairly limited, but that also means the testing is much easier because the known mutations will become much, much smaller. As most of you are aware if you screening for cystic fibrosis in Caucasians, you’re talking about well over a thousand different mutations as opposed to looking for a disease in someone with an Askanazy Jewish background where you’re talking about a very small number of mutations.

So if we’re looking at what ACOG recommends for people of Askanazy Jewish background which they first published in 2004, it’s cystic fibrosis, Canavan’s disease, familial dysautonomia and Tay Sachs disease, all with similar frequencies of being a carrier, somewhere in the ballpark of 1 in 25 to 1 in 50. And so ACOG is taking the stand that this is the rate that we would consider to be appropriate for screening for Askanazy Jewish ancestry.

However, the American College of Medical Genetics a sister organization has come out with a totally separate statement and as you can see they have increased that number to 9 different disorders
stopping here you can see the four here but adding Fanconi’s, Neumann Pick, Bloom syndrome, mucolipidosis IV and Gaucher’s disease. Now Duchene’s disease has a very high carrier frequency but it’s also in many families a very mild disorder, very treatable disorder so ACOG has decided that this should not be among its screening and for the reason that these are relatively rare occurrences and said that we don’t agree with this statement that the American College of Medical Genetics has put out. But as a practicing physician you have to deal with the fact that these competing guidelines and what your local genetics community may be saying to your patients as opposed to what the ACOG statements said.

And so part of the explanation for why ACOG has said this is, if things like Tay Sachs disease occur commonly, mucolipidosis IV occurred uncommonly as does Fanconi’s anemia and so over time we’ll resolved those issues but for now it’s felt that this is a better location to stay in terms of screening for disorders.

So we’re not supporting them as a member of ACOG but as a practicing physician certainly have the option to say, I’m going to offer a broader screen to my patients along the lines of what the American College of Medical Genetics does.

And the last issue I’d like to talk about is a current issue in terms of quite a bit of controversy about the screening for spinal muscular atrophy. For geneticists a well known common disease, for
obstetrician gynecologists, family practitioners, probably not a disease that most people are familiar with. You have a carrier frequency that is relatively high in what appears to be all populations, there’s not a lot of good data yet to confirm that. But it appears that the carrier frequency is relatively high and it’s across all populations, there are three types, the infantile version, a later childhood version and an adult version. The most severe one is Type I or the infantile presentation and the screening is really focused on trying to find those particular individuals. As you can see from the slide about 95 percent of individuals have, are homozygous for a deletion in this gene known as SMN 1 gene. Now what’s very interesting about this disorder and makes it complicated is whether you have a severe disease or not appears to depend on how many copies you have of a second gene known as SMN 2. The more copies you have of SMN 2 the more likely you will be in this category as opposed to this category but its not necessarily a one to one correlation that makes the counseling, when you find these individuals, a bit more complicated in terms of expectations.

So there are very different recommendations by the two organizations at this point. And that is that the American College of Medical Genetics is now recommending that all patients who are pregnant or considering pregnancy should be offered SMA screening. That’s a very major change in how the practicing physician should be doing. ACOG on the other hand recommends that screening only those people who have a positive family history or somebody expressing an interest in being screened. And those expressing an interest should have a genetic counseling session as part of that. So not a routine screen for everyone but a directed screen based on either family history or interest with a full counseling session and understanding the risks and benefits of the screening from that
point. This is still to be worked out. ACOG has put their statement out, the American College of Medical Genetics has put their statement out and I suspect over time that as more data is available it may be that these two come much closer together in terms of recommendations and SMA may be the next cystic fibrosis for the practicing physician.

What’s on the horizon? I think there are two other things of importance for the practicing physician to keep in mind. The first one is that there are likely to be screening tools for the Fragile X syndrome, a very common, the most common form of inherited mental retardation that will be on the horizon as a screening tool for patients who are thinking about pregnancy or are already pregnant. And as many of you know in your own communities there are now genetics testing panels that look a number of different genetic diseases. It’s very complicated because many of the things on those panels are ethnic related. And so if you happen to have a couple and that you’re screening them using one of these panels and the patient is Jewish and you find that she has Canavan’s disease but her spouse is not Jewish then screening and looking for mutations in that individual is going to be much more complicated and the counseling becomes much more complicated in whether or not you can truly predict if their pregnancy will be affected or not affected from that point. So these are things to keep in mind as we’re going through this.

The remaining fourth lines of this talk are really the references for people who want to go back and delve in more deeply into these but this will end the discussion for this morning of the sort of controversies currently present in screening for disorders in pregnancy. Thank you very much for
your attention.