CONGENITAL SYPHILIS

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[video transcript]

00:00:06] So today is today and this is congenital syphilis day at Project ECHO. And this is me, as I said, I work with Margie and Tia at the University of Rochester although I'm over the Golisano Children's. I have no conflicts. And this really Margie and I have been talking about Syphilis for several years now because there's been an uptick in congenital syphilis all over the country, but particularly in New York in the last several years. We had in the statewide, between 2012 and 2015, as probably many of you know, we had at least eight cases including some deaths and stillbirths. We had more in New York City and in retrospect, although it's dangerous to quarterback in retrospect, there were several points of care that were potentially mismanaged that led to these terrible outcomes. That's why, in part, I think I'm so obsessive about treating syphilis if I'm unsure in a baby. And some of these things were missed RPRs in hospitals with whose care protocols weren't being followed or weren't written carefully.

00:01:15] Secondary syphilis rashes, which can be very confusing just as the gentleman spoke of in the other case, of rashes which are misdiagnosed even by obstetricians specialists, by dermatology specialists, or folks who are zipping through pregnancy maybe with lesser prenatal care and not getting a repeat RPR in in high risk pregnancies. We argue back and forth that maybe everybody should get a repeat RPR and a repeat HIV tighter at least twice during pregnancy and I would be all for that. That's not currently the law.

00:01:51] It's a suggestion and I would suggest it for everybody because I hate to be put into possibly in the position of saying who is high risk and who is not high risk. But certainly after you might have a funky rash I could certainly get a RPR.

00:02:06] And so, if you want to look at that data, actually, I know this is probably small on your screen unless you're close-up but the New York state website, and I just clipped this last night, the New York state website has good syphilis data at least by mapping of most recently resulted case surveillance, which here was up through 2014, I think newer data are probably coming. But for my region in Rochester, the map shows you sort of little dots where cases are and what I focus on is the is the bar graph and sort of biometric graph whatever they call those down the left hand corner where it has the blue volume part is the statewide total of primary and secondary syphilis and I believe the gray bars are early Now I'm forgetting our region, so the Rochester region. So wherever you see, the trouble with congenital syphilis is you don't have congenital syphilis unless you have primary and secondary syphilis in women in the population. And so we don't always have good congenital syphilis data on the sites but we know that wherever there's syphilis in the population it will eventually get into a woman of childbearing age who might be pregnant. That having been said, as you can see 85 percent of syphilis cases in New York currently are among men who have sex with men but not all are 100 percent having sex with men. So that can actually lead to congenital syphilis. So congenital syphilis occurs when the T. pallidum them is transmitted from a pregnant woman to her fetus.
And whenever we talk congenital syphilis, we have to remember that a good chunk of it may lead to stillbirth or neonatal death beforehand.

And so you don't realize that the baby has syphilis or you may not realize that the partner, that the mom and her partner or partners, have syphilis. But also in the baby it can cause infant disorders such as deafness, neurologic impairment, bone deformities, actually pneumonia, liver deformities, neurologic deformed, mentioned neurology, and there's a very wide spectrum of severity. And so some of the questions we're asking in our last case well what did the baby look like? what the babies bone x-rays look like? and that, certainly if they're abnormal, that absolutely tips you towards syphilis. If there are norm if they're all normal, as I said sometimes I'm conservative and treat anyway. We do tend to divide lesions in terms of the early lesions in infants less than two years of age, which generally are inflammatory and often have will have life treponemes in them, from the late lesions which tend to be kids to age.

Immunologic more destructive and much more rare to see thankfully in the penicillin and antibiotic era. And I've rarely seen kids like trying to remember, besides reading and books, about kids with true late syphilis, thankfully. It's like I haven't seen rabies either in the flesh and I've always sort of thinking gee it be nice once in my career to see rabies and then I hit myself and say why would you ever wish that not your worst enemy.

I don't want to see rabies ever. So congenital syphilis, there are some weird things about its transmission I don't need to go through all of this in detail but the graph tends to the image, which is an old fashioned image, is trying to point out that there is, you have to think about both the maternal stage of her disease primary, secondary, early, late and late late, and the stage of her pregnancy, which is down the vertical axis first second or third trimester.

And we we over the years we've found that stage of maternal infection at conception is probably one of the biggest determinants of whether the baby's going to get syphilis. This is an old law called Kassowitz's it's a law from probably the 1930s or earlier I think. I don't know if it was the 18 somethings, but that early transmit mothers who have early syphilis are more likely to transmit it to their child than if they have late late or tertiary disease. Now very early in pregnancy for some reason it doesn't seem to transmit even if you're even if you have primary syphilis but in general primary and secondary diseases is more important in transmission than is later late or tertiary disease. And also in the pregnancy except for very early in the pregnancy early transmission sort of late first trimester early mid second trimester can tends to leave more often to fetal demise and stillbirth or early miscarriage whereas late pregnancy the infection is highly transmitted but it might also be highly silent. So that's where we get into why serology is so important. So if you are going to see a congenital, if you're going to
see symptoms of a congenital baby with congenital syphilis, this is the usual list that everybody has and you can notice my references are from 1943 all the way up to 2015 because it's always been the same if you see a symptomatic baby, if it's not a stillborn product, unfortunately, it's a baby you think about with bone lesions, with snuffles, or hemorrhagic rhinitis.

[00:07:45] I'll show you that in a second. Baby with jaundice, hepatosplenomegaly, and but it can be and skin lesions but they can be very subtle and very variable and the late congenital syphilis is where you have the classic board question type lesions which thankfully we don't see now the saddle nose the destruction of the nose cartilage the frontal bossing the Hutchinson's triad which is abnormal incisors, eighth nerve deafness, interstitial keratitis of the eye, and then, if it really goes on without treatment, these kids have bad joints, sternoclavicular thickening, Saber shins, flaring scapulars and the whole works that we've known about for 100 years in syphilis.

[00:08:31] So the trouble with congenital syphilis is the pictures you find in the book can be quite flagrant. So I don't think anybody would say if you saw a newborn infant with this type of stuff in the middle picture with sort of a hemorrhagic snotty nose and mucous membranes that you would say that's abnormal, or if you saw this wet lesion, which probably is teeming with treponemes, if you had a dark field scope which I certainly don't have except maybe doctor Urban, then I mean that's what you get, but the baby on the left is just kind of looks like a post dates baby with peely skin.

[00:09:09] So sometimes the symptoms can be very very subtle. More lesions of congenital syphilis, well if you start getting sort of white mucus patches or a peeling of the feet or hands I think we would all wonder what they are but we would know they're not just normal creamy skin. A baby with big time hepatosplenomegaly, you can see somebody has has marked out the liver and the spleen in this child and also although this isn't a video.

[00:09:42] This is a pseudo paralyzed left arm that's from the osteitis of syphilis which is an old finding called pseudo-paralysis of Parrot, and I see this maybe once a year once every other probably once every other year now, but I've seen a couple of babies with it because they're osteitis hurts. They have osteitis and osteochondritis from the syphilis and it can mimic what we think of as an erb's palsy, delivery palsy from somebody you know yanking the baby out a little bit energetically.

[00:10:12] But if you see it with hepatosplenomegaly you have to think of yourself, "Gee could this be syphilis?". So you see periosteal elevation, there's sort of a moth eaten Olma there at the edges of the bone. These are the things we look for in the radiograph of the early child. Later on if you had a child over two years of age and the osteitis can be quite severe. I believe this is called Limburger sign where you have the looks like big bites taken out of the shins taken out of the proximal tibia, there. Lots of
bony remodeling in the radiograph on the right, the notched incisors, the Hutchinson's teeth and it's hard to tell if they have Mulberry mollers or not but, certainly the incisors are enough abnormal for a physician, not a dentist, who is me, a physicist not a dentist to tell, and interstitial keratitis is what this eye shows.

[00:11:14] So if it's variable clinical findings, and we're all a twitter as to how to really make the diagnosis, it everything comes back down to serology which is how we started the hour and the non-treponemal tests, as you know well are the RPR, the rapid plasma reagin, the older but sometimes used venereal disease research laboratory test the VDRL, a trust test which I personally don't know if I've ever seen but Dr. Urban just told me about one the other day or today. So some laboratories may use that. These are all the ones that look for the non-treponemal, and we've argued for years whether it's a piece of the treponeme or whether it's tissue damage that starts that cardio life in response. But, there anti-cardiolipin antibodies, I think it's now we think it's more detecting tissue damage than any sort of antigen mimicry, antigen from the treponeme. And then the treonemal test, FTA absorbed which is the one we said

[00:12:16] is sort of operator dependent because like everything else under a fluorescent microscope you're trying to figure out whether you're seeing background fluorescence or little light green fluorescence. The TPPA, the treponemal pallidum particle agglutination, the new enzyme immunoassays and Chemiluminescence assays which are essentially enzyme immunoassays, and the BioPlex which we use in our hospital but isn't gannets a fancified, you can think of it as a fancified enzyme assay, and we really do like both types even in 2017.

[00:12:48] We like to have both types of test to make an accurate diagnosis but we know that even the fancy tests have variable sensitivity and specificity by stage of disease and, hopefully not by phase of the moon, but sometimes we wonder. And again these newer tests we think they're good.

[00:13:08] They're really being pushed because they're cheaper and more mechanized and that's not always the way medicine should be but when you have to do so many thousands of these tests that's what the lab has to consider.

[00:13:23] So you end up with these complicated algorithms in pediatrics. This is the algorithm for the AAP red book, the American Academy of Pediatrics red book. Similar to what the CDC has, although the CDC STD guidelines tend to say this all in words, and the AAP tried to put it in pictures and both of them I have to read every time because it's very difficult to memorize five pages of words. And this picture doesn't really stick in my head either.
But for the purposes of this basically we're starting with such as the first case, a woman who has a reactive treponeme, a nontreponemal titer like an RPR, and you're trying to decide OK if the non if they have a non-reactive treponemal test then you say the RPR is a false positive and you don't need to consider syphilis. In the case Margie, Dr. Urban presented, we had a Margie, hey you, to my right presented, we have a reactive maternal treponemal test. Now granted it was weakly reactive but we don't know.

So then you start to look at the algorithm closer and you say well the easiest thing is if mom was treated adequately in pregnancy before a month before delivery so that we think there was enough transplacental transfer of the antibiotic and enough antibiotic activity in mom and fetus both to prevent syphilis, then you're down that center line and things get easier you check the babies RPR and if it's not larger than the mom, suggesting that there might be continued infection, then you come down to either no evaluation or treatment option two, as I'll get into in a minute, is when we're really unsure of follow up and we're not precisely sure of the treatment, You can give a shot of benzathine penicillin. The most troubling one is when you add that's I'm sorry on the on the right side is the one where you have adequate mom treatment, baby's fine bang-o. No treatment. Go home. Bless you. The middle one is where you're not quite sure or there's some abnormality in the physical exam of the baby.

And then you have to try to sort out whether we're going to treat with one shot of benzathine penicillin or 10 days of full penicillin. And the most difficult, to some extent, is exactly like the case Margie presented. That's the big box in the center. So mom has a positive RPR.

You can argue whether she does or she doesn't. But for the case of discussion we think she has a positive treponemal tests. She doesn't tell you she's ever been treated for syphilis. She doesn't know she has syphilis but she certainly has no documentation of treatment. So then you really have to evaluate the baby.

And just as some of the callers sent in, the evaluation includes a physical examination, long bone radiographs, serum RPR, I do not like cord blood RPR they're known to have false positives with cord blood. False positives and false negatives, in fact. Although many hospitals, including ours, used to do cord bloods all the time. CBC and different platelets liver function tests. Often we really should do a CSF although we know that lumbar punctures sometimes lead to bloody fluid from a bit of trauma during the testing and that's hard to interpret. And I tend to go ahead and get long bone films. Whether we do an ophthalmologic exam and placental histology every time I must say I haven't always they're harder to get, especially when you're outside of the medical center, but you try and get as much information of the babies as you can. If anything is abnormal, or if the baby's titters are greater than the then the moms, you really have to treat that child. And if everything is normal we still end up usually treating.
So that's why I was so conservative with the first one. And of course the treatment we have for certain or probable syphilis, I'm talking about 10 days of I.V. penicillin. I know Benzathine has been in shortage it's been difficult to get aqueous crystalline penicillin has also been in nationwide shortage.

But I think it's more available now.

There's always still the sub line here that you give procaine penicillin IM daily for ten days. I have never used that. It hurts. It's like in a developing country or somewhere or let's say we were in Puerto Rico and we had real trouble with our electricity and our our hospitals still, then that might be an option that you could give intramuscular penicillin for ten days. But this is where you really have to remember the differences, this is what residents don't understand anymore, the differences between the three types of penicillin and where we really have to keep telling them oh this isn't pharyngitis I'm talking about.

This is crippling syphilis. For possible syphilis it's the 10 day one or maybe a 50,000 unit per kilo dose IM of Benzathine. For unlikely, oftentimes I'm the one who likes to use Benzathine penicillin because it worked for 50 years in the, you know, in the last half of the last century. It may not get into the CSF well but it seemed to work. But if you really can exclude syphilis then you don't need any therapy. So we end up talking about two algorithms these days. I'm glad Margie didn't bring me a reverse sequence algorithm to confuse you even more. But I'm going to talk about it anyway because many of our hospitals, including our medical center, have moved to the reverse sequence. So traditionally, in the way the case was written today or the way the case happened today, elsewhere, was a quantitative RPR came back it was positive a treponemal specific test was sent to confirm it. And the problem is we're not sure about the last part but if we knew that the treponemal specific test was positive you'd say "Okay that's syphilis" either past or present. And if it was negative for sure you'd say "Well it's probably not syphilis" and the trouble with the first case is we were in between still. It's become a little more complicated with a few more boxes in the reverse sequence era. The reverse sequence era, again, is doing an enzyme immunoassay, or one of the mechanized assays, to push through put and ease workload and reduce cost to both patients and labs both. And they're very sensitive. And they but even they are not totally specific.

So again, if you get a negative EIA, we think that that's the same meaning and maybe even more predictive negative in a negative predictive sense of having no syphilis. If you get a positive EIA you could still have a false positive so you still have to fall back on the RPR, which again, is quantitative not just a qualitative yes no as these other tests are, and if the RPR is positive in somebody who the enzyme assay has called you as seropositive, then you're considered to have syphilis past or present. If your RPR
is negative, you go on to sort of break the tie of one negative test one positive test. In our hospital that's done with a TPPA.

[00:21:09] You could still use an FTA-ABS if you wanted. And there you if the tiebreaker is negative, syphilis is unlikely. If the tiebreaker positive, syphilis is likely because now you’re saying even though the RPR is negative you have 2 positive treponemal specific tests and you hope that that extra specificity has helped you. The problem,

[00:21:31] the reason I have more syphilis question mark, explanation mark, is this is where it really hurts me, not hurts me, but confuses me in the labor deck because these patients are ones who may have had perfectly adequately treated syphilis and what we think about the enzyme assay, just as we do with the TPPA, is those are probably lifetime titers.

[00:21:57] So it’s not inconceivable to me that a mother could have had syphilis, been treated perfectly fine, and either forgotten it decided she doesn't want to tell me about it, or had a rather what's the word? Not patronizing but whatever it is, paternalistic physician who didn't tell her syphilis because of some other socio economic prob socio-eco bio-psycho-social issue that they felt this was not worth bringing up. They just want to treat it and have everything well. Hopefully that doesn't happen in this day and age but certainly when we have patients who give you their history, as in the first case, when you come from other cultures and other countries, we know that this sort of, kind of a 1950s paternalistic doctor of the US that we don't have anymore, still goes on in other cultures. And so it’s certainly conceivable that a mother may not have been told she had syphilis. So we end up with this place where when you're in the STD clinic and you can say and you can retest them or you can wait a week or wait a couple weeks and see if the RPR is coming up. That may be OK if you have good follow up. When you’re on the Labor Deck and you have to, here’s the newborn baby, they're going to go home in 48 hours if you say nothing or if you want them treated you better go now. It gives us a lot of problem because we don't always have the luxury of waiting. So the scenarios we get out of these algorithms again the easy one are the traditional algorithm, everybody's positive OK that's syphilis go ahead and treat them.

[00:23:46] Everybody's negative, RPR's negative well in those days we said it wasn't syphilis. The RPR positive, TPP negative, we usually called them biologic false positives. Now with the EIA's in the reverse sequence algorithm, we get into the first row is fine, everybody all three antibodies are positive; consider that syphilitic. The second one, if it's negative, fine. That's even more so not syphilis because we think the EIA turns earlier than the RPR. The real problems are those ones in yellow where the CIA is or EIA is positive. Have negative RPR, negative TPA. Well, then we think those are probably false biologic false positive EIA's even though it's supposed to be a specific assay. And the last one where we have discordance, and it might represent old treated early primary syphilis or late late therapy, that's where I
usually end up saying let's treat this baby and treat the mom. So just in closing syphilis and the pregnant woman. Remember all women should be screened serologically for syphilis early in pregnancy. And actually I would like it was a third bullet. I would like to say also it should be performed in the third trimester too. And I’d throw an HIV assay in there, as well. In populations in which, certainly in populations where prenatal care is not optimal, screening and treatment should really be performed again. Any woman who delivers a stillborn infant after 20 weeks is actually supposed to be tested for syphilis certainly by medical regulation. I can't remember if that's a state rank as well. It may actually be in some states

[00:25:38] I think that's written in somewhere, it's an old fashioned state rank. But it's certainly my medical experience and the CDC regular CDC STD guidelines and American academy pediatrics guideline. And I always tell the residents no infant should ever leave the hospital without somebody looking themselves at the maternal serologic status at least once during pregnancy. I don't want to hear "Yeah I heard from the Labor Deck that this woman was fine". I want to hear "I looked at the computer and I saw a negative titer". And what is treatment? Well this is where I turn around and call the health department because they keep such marvelous records especially in Monroe County of past treatment of women who have been treated men who've been treated and I can find out. Oh yeah they forgot or they didn't want to tell me they were treated for syphilis but indeed they were already treated. Treatment to me means only and approved penicillin regimen. It means more than four weeks before the woman’s delivery. It means even if you’re treated three months ago. But your RPR is on the way back up. That's not adequate treatment. That's reinfection or a failure of first treatment. And for people this is one of the very few times in medicine where I wouldn't trust anything except penicillin. And if she told me "Mom told me she was allergic", then I'd say fine I have a friendly allergist here who would love to skin test you, desensitize you, and then allow our penicillin treatment. There's no effective alternative proven. Many of us believe deep in our hearts.

[00:27:16] Ceftriaxone probably works but we have just no, again, we have since 1940s evidence for penicillin and we don't have any other evidence much for anybody else.

[end]