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PANEL DISCUSSION: SYPHILIS IN PREGNANCY AND CONGENITAL SYPHILIS

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Panel Discussion: Syphilis in Pregnancy and Congenital Syphilis
[video transcript]

00:09
Our three panelists are Dr. Marguerite Urban, she is a Professor of Medicine in the Division of Infectious Diseases at the University of Rochester School of Medicine and Dentistry. Dr. Daniela DiMarco, she is an Assistant Professor of Medicine in the Division of Infectious Diseases at the University of Rochester Medical Center. And lastly, Dr. Geoffrey Weinberg is a Professor at the University of Rochester Medical Center Department of Pediatrics, Pediatric Infectious Disease and Immunology. Pardon me. Thank you for joining us, all of our panelists, and I will turn it over to you now.

00:58
Okay, thanks so much, Melinda. I'm Marguerite Urban and happy to be here. Let me just go through our accreditations. This is accredited for one unit of, one hour of, CME. And no one in the planning committee has any significant disclosures. And of the speakers, Dr. DiMarco and I don't have any disclosures, and Dr. Weinberg has received some research grants and reimbursement for authorship but nothing relevant to today's presentation. We'll go through with attention to screening recommendations for the diagnosis of syphilis in pregnancy, treatment recommendations for the same, and go over the approach to an evaluation of a neonate with possible congenital syphilis.

01:52
So just to give you an idea of how we're going to do it, we had envisioned when we planned this, that because COVID was receding, that the three of us would be in a room conversing together as a panel. But as you know, we can't do that today. So we've structured it that we'll do just about 15 minutes of background information of why this is such an important topic at this moment in time. And then we're going to review cases that have come to us, actual cases, to discuss the management of syphilis in pregnancy and congenital syphilis. And these all have a little bit of a twist. So they were not sort of standard run of the mill, easy cases for us.

02:32
So just as we start to be sure that we're all on the same page, I just wanted to go through the very complex illness of syphilis to be sure that we, at least, are sharing the same vocabulary. So syphilis, as you know, is a contagious infectious disease, and there's an organism known as T pallidum. So when one is exposed, generally through sex, but could be through very close contact, there's a period of incubation that can be up to 90 days. And sometime in that first 90 days, the first clinical manifestation of syphilis occurs, which is the manifestation of an ulcer, known in medicine as a chancre. It's usually genital, but it could be oral or perianal, and that is known as primary syphilis. That generally doesn't have any symptoms. So if one doesn't notice the ulcer, it may disappear on its own without any treatment. And that organism then disseminates in the body through both blood and lymph, and it spreads really entirely throughout the body, and leads to the second stage of syphilis that's known as secondary syphilis. This stage has lots of different manifestations, it's led to various phrasing like 'to know Syphilis is to know medicine' or 'Syphilis is the great imitator.' And that's because the

manifestations in secondary syphilis can pretty much be any kind of itis. So the one we think of most typically is rash, or dermatitis. But you could have iritis, uveitis, meningitis, Hepatitis, nephritis, all sorts of inflammation throughout the body. But again, that resolves spontaneously, even without treatment, and the organism remains in the body, although without any symptoms, and this leads to a stage that's known as latent syphilis. So essentially, you have infection, you have positive blood tests, but you don't have any clinical manifestations. We in the public health world, in the medical world, have divided that period of latency into early latent, and late latent. And early latent is this period within the first year of infection, and the reason we've done that is that those itises of secondary syphilis can recur, and they tend to recur within that first year if the individual is not treated. And some of those recurrences, like primary syphilis, are contagious, so we consider you potentially contagious or infectious through sex for that whole first year with primary syphilis, secondary syphilis, or early latent syphilis. After the period of latency, in the pre antibiotic era, about one out of three individuals who had not been treated yet, effectively treated, which was virtually everyone before antibiotics, would go on and develop late manifestations of syphilis known as tertiary syphilis. And then at the very bottom of the slide here, pertinent to today's topics, you can see that perinatal transmission, transmission to the newborn, can occur really throughout this primary, secondary, or even into latency.

05:54
So what is congenital syphilis? So that's the condition that occurs when the organism known as Treponema Pallidum, is transmitted during pregnancy to the fetus. This may lead to stillbirth, to death after birth, to a neonatal death, or to a number of disorders in the infant, which could include deafness, other neurologic impairment, bone deformities, there's a long list of potential findings. There's a wide spectrum. And really only the very severe cases are clinically apparent at birth. In the pediatric literature, this is divided into sort of early lesions and late lesions, with those occurring in the first two years of life, generally being due to infections. So they're kind of the itises in in the baby or child. And late lesions, tending to be more the immune response, causing problems.

06:51
Here's from a textbook, gives you some idea of kind of the number of abnormalities that can be associated with early congenital syphilis or late congenital syphilis. And you can see there's a wide spectrum from actual itises, rhinitis, osteitis, rash, laboratory anomalies like hemolytic anemia, and you can see a long list, and then these more later findings described here. And we'll go into some of this in more detail later, with some images.

07:27
Transmission is not uniform throughout pregnancy, and that's for a couple of reasons. So the risk of acquiring congenital syphilis is somewhat dependent on when in pregnancy infection happens and what type of syphilis, what is the stage of syphilis. So infection is transmitted through the placenta. And since the placenta really grows during pregnancy and is not really present early in the pregnancy, transmission is less very, very early in pregnancy, the placenta fully develops by 20 weeks. It is true, though, that any stage of disease, of syphilitic disease, can lead to transmission. And it's also true that the effect in the fetus tends to be worse if Syphilis is transmitted after 20 weeks. There is a higher risk of actually acquiring congenital

syphilis if the stage is early, particularly primary or secondary. But as I mentioned earlier, any stage, including latent syphilis, can lead to transmission to the neonate. There is a bit of increased risk if infection is late in pregnancy. And certainly, and this is where we can intervene, there's increased risk if there's a failure to adequately test and treat for the infection during pregnancy. With that testing and treatment, you can avoid transmission.

08:59
So the reason we're talking about this now with some degree of urgency is that syphilis in the United States has changed. And you can see here on this slide, the black and green lines are syphilis in men. This is sex acquired at birth, as reported to CDC. And syphilis in women. And you can see they were fairly equal and actually quite high in the early 90s. Syphilis declined, and that particular outbreak of syphilis really was eliminated in the mid to late 90s, and we had relatively low rates. When around the year 2000, rates took off in men, and this was really almost exclusively among the men who have sex with men population. About half of those infections, and that continues to be true, were acquired in men who were already living with HIV. However, syphilis in women was relatively low, and this corresponded to low rates of congenital syphilis, until about 2015, when this again began to rise. And some of this rise here, in the green line of men after 2015, was a corresponding rise in syphilis in men who have sex with women.

10:21
This is a CDC slide looking at syphilis in women, with darker colors being higher rates. And you can see back in 2010, it was really limited to a relatively few number of states, though did include New York. And by 2019, had spread to most of the country, so had spread geographically. And the darker the colors show higher rates, so we were having higher rates and more widespread infection among women. And that has correlated with a rise in cases of congenital syphilis to a projected high of 2100 for 2020. The formal final numbers are not out yet.

11:04
CDC did an analysis of cases between 2015 and 2019, and this is kind of a complicated slide. So let me walk you through it. So they were looking at, really every case of congenital syphilis is really a failure to diagnose and treat during pregnancy. And it looked like the the greatest proportion of cases nationally was no adequate treatment of the pregnant individual, despite a timely diagnosis. So people were being tested and diagnosed but not being treated appropriately. The second highest reason was no timely prenatal care, so there was no testing and therefore no diagnosis and treatment. And far fewer were syphilis actually acquired during the pregnancy, later in pregnancy, or no testing despite prenatal care. And finally, fortunately, the lowest was progression to congenital syphilis, despite adequate treatment. This is not randomly distributed among women, and there are a number of case reports. And what we're seeing locally in our area in Monroe County in New York, is that syphilis in women is disproportionately affecting those who have some connection to drug use, and particularly injection drug use. And these are data in the MMWR, again a complicated slide, but if you just follow my marker here. So this looks at rates in women who had primary and secondary syphilis who also reported use of methamphetamines, and that increased between 2013 and 2017. A similar increase among men who had sex with women diagnosed with primary and secondary

syphilis, but relatively flat use of methamphetamines among men who had sex with men in that same timeframe. Similarly, reporting sex with an individual who injects drugs in the prior year, among women with primary and secondary syphilis went up 2013 to 2017. Same for those men who have sex with women, but much flatter for men who have sex with men. So this rise in the heterosexual population that's occurring has disproportionately impacted those who have some connection to drug use, at least a sexual network who use uses drugs, even if the individual with syphilis themselves is not using drugs.

13:33
This is a graphic from New York State, fairly recent, and I'll just call your attention to this what seems like good news of a decline in early syphilis that's present for less than one year. But if you look into the details, you see that despite that overall decline, there was an increase among women. And it's presumed that some of this decline is related to COVID, and a lack of testing. And this increase among women was associated with a 20% increase in congenital syphilis. This led to a health alert that came out, a health advisory, about congenital syphilis increasing in New York State. And essentially, a more than doubling of cases of those reported 2015 to 2017, compared to the 2018 to 2020 period. And I know from sort of off the record conversations, that this has continued to rise, actually, since 2020. And the state has put together a very similar graphic to that, that I showed you, nationally. And really, we see a different picture in the state, at least really across years, and especially in the recent years where the greatest reason that congenital syphilis occurs is the late identification of syphilis acquired during pregnancy. So someone who didn't have syphilis early in pregnancy, and does by the end of pregnancy and transmits. The second biggest reason was no timely prenatal care and therefore no screening. And then much lower was lack of testing despite prenatal care or inadequate treatment. And fortunately, the lowest was progression despite treatment. But we have this big proportion of people who are acquiring syphilis mid pregnancy and therefore being missed by some of the routine screening that's done early in pregnancy.

15:37
So how do we prevent and diagnose congenital syphilis? Clearly, the best way is to identify syphilis during pregnancy. So you have to do the screening, and even in the setting of syphilis being acquired during pregnancy, have a high index of suspicion to look for diagnosis outside of screening. Make sure the treatment is appropriate. We'll go into that in a minute, but really in pregnancy treatment is limited to penicillin. You want to make sure you look at at-risk neonates, to be sure you're not missing the diagnosis. Because as I said, only the most severe are clinically apparent at birth. So you want to be sure you're looking at the neonates who are at risk, and provide adequate treatment and follow up for those neonates. I did, because of time, I pulled out another slide, but there is a recent MMWR report about syphilis diagnosed after birth, greater than one month after birth. And there were more than 60 cases in this MMWR report, so you really do have to be vigilant.

16:41
So just to end here, this sort of introduction, what are the screening recommendations? So these are the national recommendations by CDC, screen all pregnant individuals in the first trimester. And based on risk and prevalence in your area, third trimester screening at 28 weeks,

and then again at delivery. And they've expanded the risk factors to include this association with drug use. So the risk factors are what you might expect, multiple partners, sex with drug use, transactional sex for money or drugs or housing, etc., late or no prenatal care, history of incarceration in the patient or the partner has been associated epidemiologically, and unstable housing also associated. If you're watching us from outside of New York State, you can find your state specific screenings on the CDC website. But within New York State, essentially, New York State statewide guidelines mirror what I just said for the CDC. So first trimester, delivery, and strongly recommended especially with risk in the third trimester. New York City has slightly different recommendations where they mandate first trimester, third trimester and delivery for all pregnant New Yorkers.

18:08
So with that, I'm going to switch to going into some cases. Through the CEI program, we do have this what we call a warm line for clinical consultation. And we're going to present with some modifications to shield identity, some cases that have come to us through that warm line.

18:29
So the first one is a 27 year old cis female who presented for a first prenatal visit during her first pregnancy. She did have a history of injection drug use in the past, some years prior. She feels entirely well. Her exam is unremarkable, and her estimated gestational age of the pregnancy is nine weeks. She has routine prenatal visit with routine testing. And it turns out her HIV test is nonreactive, her gonorrhea and chlamydia tests are non reactive, but she has a reactive syphilis ELISA and a reactive RPR with a titer of 1:32.

19:07
So just before I throw it out to the panelists, just to review the testing. There are two types of serologic tests for syphilis. The first is the nonspecific, non treponemal antibody almost universally in RPR in the United States. It results as a titer, such as 1:32, or 1:256. And importantly, it can be nonreactive very early in disease, even when there is an ulcer. This is really an anticardiolipin antibody, it's a human antibody. So it goes up with inflammation, particularly inflammation with syphilis. Because it's not specific, you have to confirm it with a specific antibody test, and here in this litany, this long listing of initials, there's many, many specific antibody tests. These differ a little bit in that they're qualitative so they're positive or negative with no number They don't distinguish past or present infection, even past treated infection. So they may be positive for life. And they tend to turn positive a little bit earlier, and you do have to have both kinds of tests to really make an accurate assessment.

20:15
So the patient was called and advised to come back for penicillin treatment, but told the nurse on the phone that she had a history of a penicillin allergy, just one year prior. So as a result, the OB referred this patient to the local STI clinic to address the syphilis. And she arrived five days after her RPR of 1:32. Unfortunately, it was one o'clock in the afternoon, and tomorrow was the start of a three day holiday weekend. So I'll throw it out to you, Dr. DeMarco, what do you want to know about this patient?

20:49
Great question. So the first thing is probably I would want more details about the allergy history. When it happened, the severity, more details about what actually was the reaction, and if any similar or even the same medications have been taken since then. And then also some other general history, because we will want to stage the patient. So we'll want a little bit more about sexual history, potential syphilis exposures, partner information. And then also necessary for staging is just the exam and any findings that might be consistent with syphilis.

21:30
Okay. So that's sort of what I anticipated. So this patient has a single lifetime partner of nine years. But the partner, the patient knows the partner has other partners, and has had active injection drug use on and off over several years. Patient herself feels well and no complaints, and her physical exam is confirmed to match that seen by the OB, essentially a normal nine week pregnancy. And the allergy turned out was an urticarial rash with amoxicillin that was about one year ago, and she's not had any penicillin since then. So sort of, as you said, you kind of need to address staging and treatment. So these are the questions that I thought we might might want to address. And I'll start with what's the stage of syphilis? So either of you, Daniela or Jeff, want to just jump in and say what you think?

22:34
Yeah, so I think we're starting with she's got higher titers, she has no symptoms, and we may not have enough information yet to say. So this is a scenario where you could say it's latent, and it may be early latent or late latent. You would probably want some details, if they're available, on past syphilis testing. Or you could also say stage pending while you do some investigation, for example, testing the partner or examining the partner.

23:09
Okay. So as you say, she's latent by definition, no signs or symptoms, but it matters if she's early or late. And you could look and see if she's ever had syphilis, which she denies, and by public health records it turned out there was none. Could check the partner status. So it turned out in this case, in that intervening five days, the health department had been involved and realized that the partner was a recent diagnosis was secondary syphilis. So it's very likely that this patient acquired syphilis from this partner, who she says is her only partner. And when she arrived five days later, although this didn't come back until the next day, it turned out her RPR was much higher, it had gone from 32 to 128. So it was a four fold rise in five days. So how would you feel about that then for her stage?

24:06
Yeah, that helps put her into the early latent stage, if you have that four fold rise over a minimum two week period.

24:15
Okay, so she was diagnosed with early latent syphilis. So what would be the recommended treatment for early latent syphilis? Well, I'll just tell you, I'm sure you know. It's penicillin. So if syphilis is fairly recent, it's 2.4 million units IM as a single dose. In a pen-allergic patient who's

not pregnant, you could use doxycycline for 14 days. And just as sort of a kind of footnote in the guidelines by CDC, they do say some authorities use two doses of benzathine penicillin one week apart. And there's also a comment that there's limited data about using doxycycline in those living with HIV, which this patient doesn't have. If she had something, just of note, if you have any syphilis present for less than one year, primary, secondary or early latent, it's the same recommendations, penicillin times one dose or doxycycline for two weeks. If your latent syphilis was present for more than one year, you want more penicillin, so it's weekly times three, or four weeks of doxycycline. But again, not in pregnancy. If you have neurologic involvement, you actually need IV penicillin. And partner management, there's no expedited partner therapy, which can be used for gonorrhea, chlamydia, or Trich. But partners of contagious cases of syphilis would be offered therapy.

25:47
Can I just mention something here? Thanks for having me in from the pediatric perspective. From the baby's perspective, it's not just that doxycycline doesn't work for mom in pregnancy, or you know there's way old literature about not giving tetracycline to pregnant women because of their liver, this, that, and the other. It's really specifically because we don't know of any drug, except penicillin G, which effectively treats the fetus when the mom's pregnant. So this not in pregnancy, to me that would be in bold, but it's not because of mom's safety. It's because when we get to the other end of the pregnancy, it's not going to have successfully treated the baby. Yeah, just want to make that clear. Yeah, that's my vote in all of this. Thank you.

26:38
All right. Well, actually, this is for you. Can we can we use an alternate drug like doxycycline since it's before 12 weeks?

26:46
Yeah and I'd say no, I mean, no is the short answer. Because there is the business that below nine weeks, you know, you're probably less likely to transmit syphilis, you don't have a full placenta. But there have been babies who have had syphilis transmitted, there have been stillborns or miscarriages at nine or 10 weeks that have had been shown to be treponemic. So these rules are kind of made to be fluffy as most rules are. And so I would still be worried that even a mom this early could transmit, and therefore needs penicillin to cure it. And yeah, it's probably too early for tooth bud development, but who cares? The overriding sentence is the first one, or is the second one here, is that there's no data about anything else successfully preventing congenital syphilis except penicillin G. Okay. Yeah. So, I subsume all those other tooth questions and placental questions, and just say, I'm sorry you need penicillin.

28:02
Okay. So then we're left with it's one o'clock before this holiday weekend, big, big holiday weekend. And can we use penicillin with this allergy history of an urticarial rash about one year ago in a pregnant woman, the day before most settings will be closed? I think that's kind of a leading question.

28:34

Yeah, that's a great question. At our medical center, we have a very sort of active allergy division, and they have some internal recommendations for us. And if the person was not pregnant and needed a penicillin type antibiotic or something. Rash, you know, if it was over one year ago, would be a time you could potentially challenge someone with an oral equivalent. But CDC in pregnancy with syphilis, I believe recommends that you would send for skin testing.

29:13
Yes, yes. So that's correct. So in general, even urticarial rash, you might want to give an oral amoxicillin challenge, but in pregnancy the recommendation is that anyone even just with a simple rash would have a skin test. And if that were negative in oral challenge, and if importantly, if the skin test is positive, the patient would need to be desensitized, because as Dr. Weinberg said, really your only choice for treatment is penicillin and desensitization during pregnancy generally results in an ICU admission. As you gathered, this was before a recent holiday and even the idea of going to the ICU which was filled with COVID patients, you wanted to avoid that if possible. So what can we do? We've got like four hours to do something. It's the holiday weekend. Is there a risk to delay? I think I'll throw this to you, Geoff. So given that it's nine weeks, would you just admit this patient?

30:23
I think in a normal non pandemic world where we had open beds, I might have, if I had been that worried. But I think there's not a giant risk, as long as she understands and comes back to you right after the holidays. I mean, to be honest, her syphilis was probably not acquired yesterday or today, because she just had a big titer rise. So she's probably had syphilis for a while. So acting today versus tomorrow, or the third day, is not really changing the baby's exposure. And it's so early that it's hard to know what the baby's exposure is anyway. So I think the only risk is if, heaven forbid, she is lost to medical follow up, then we got to go find her. But if she understands the importance of this and can come back, and we can do it right after the weekend, I think that's medically appropriate and it doesn't add risk to the baby.

31:27
So you're sort of alluding to what I mentioned earlier, so the likelihood is progression is affected by stage and stage of pregnancy. So by stage, maybe a tie, but time in pregnancy might be low. So this is what happened. We were able to successfully get the patient from one o'clock into an allergist that very afternoon, get skin tested, and an oral challenge of amoxicillin which she tolerated, where she had to wait in the office to be sure nothing happened. But by that point, it was so late in the day, the allergist was unable to get any benzathine penicillin, and it was too late to come back to the original clinic that had benzathine penicillin, so she returned for treatment three days later. For follow up, the CDC would recommend follow up eight weeks later, which in her case would be 17-18 weeks of pregnancy, and then again at the third trimester and again at delivery. But the obstetrician was concerned with the history that the patient was very clear about, that the partner had multiple partners and also active drug use, so concern about a network where syphilis was quite prevalent, so opted to do a monthly repeat RPR.

32:48

So this is just putting up on the slide exactly what the CDC says. And they say for follow up in pregnancy, reinfection or treatment failure definition is a four fold rise. So you would want to go two dilutions up, so 16 to 64. And that has to be sustained for two weeks because the RPR can kind of bounce around in pregnancy. So you would want to be sure that that rise was persistent. So the CDC says eight weeks after treatment, unless new signs or symptoms, and again, you want that rise, which is shown here as an example of 4 to 16 to be confirmed two weeks later. So if you repeated that 16 two weeks later and it was 1:4, you would just continue to follow. Whereas if it was still 1:16, you would repeat treatment, and maybe even do an LP for treatment failure if the patient hadn't been re-exposed.

33:51
So I'm going to switch to case two. This is another interesting case, 33 year old cis female G2P1. Initial syphilis screen at 12 weeks, a syphilis EIA, one of those specific antibody tests was nonreactive. The patient had a second test done as highly recommended in New York State, but had changed OBs by that point, and that OB, the new OB, went to a different lab. So they did a different syphilis test, and they started with an RPR that was 1:4. However, that defaults then to a specific antibody and that was nonreactive. So nothing further was done. The patient then delivered at 39 weeks and at delivery had a titer, and that was 1:16. And now the syphilis specific antibody, a chemiluminescence immunoassay, was reactive. So what do you want to know, what are the next steps? So this involves both the adult and pediatric ID people.

35:04
Yeah, for me, I would want to know more about her potential syphilis exposure or risk. Because you're trying to decide if she really has syphilis, when it was acquired, and any issues with the test integrity. And so I guess the next thing for the adult portion would be signs or symptoms.

35:30
Okay. And how about you, Geoff?

35:32
I mean, really from my end, this really raises my alarm bells. And you could say, well, did she have, you know we all know we're in the midst of this major transitional shift of thinking of going from the traditional non treponemal RPR first and then confirming with a treponemal antibody, or many of our hospitals, including ours, are going to a treponemal antibody screen first and then an RPR, but then also confirming the treponemal antibody screen with a different treponemal test. So I didn't see on this one, the different treponemal test, and I would like to know that. And as Dr. DeMarco said, I would like to know, is this with a partner who had syphilis or is it a socioeconomic situation like the last patient case? But basically, if you just showed me this, and this was, what do you do right now, Doctor? I would evaluate this baby for syphilis with a pretty full panel.

36:38
Okay, so let's start with the adult side. So the patient says only a single partner for several years, no outside contact, no history of STIs. Asks about COVID, could my vaccine have caused this test to change? Had a vaccine months earlier, but no booster. Mom and baby have

unremarkable exams. And as you said, the pediatric people involved with this case did go ahead to evaluate the baby. Maybe you want to just address that.

37:13
Yeah, I think it's really hard. I mean, this is a mom who has, despite the histories and partner histories, are only as good as your partner wants to tell you. So you know, that is a mom who had a fourfold rise in titer and a conversion from negative to positive of her treponemal test. So I would have been worried enough to go ahead and do a careful physical exam on the baby. We like to repeat RPRs and serum from the baby. And there's an old teaching and I've seen it a couple of times, it's hard to figure out what the biophysical mechanisms are, but cord blood and Wharton's jelly can sometimes interfere with antibody testing, especially RPRs. So I really, really, really advise people to actually poke the baby. Unfortunately, you have to do a phlebotomy on the baby, or at least a heel stick on the baby, not trust the cord blood. And then to look at the baby's CVC, LFTs, to do a lumbar puncture. Remember, in the lumbar puncture, for various weird immunological reasons, we have to do a CSF VDRL, not a CSF RPR. So it's still a non treponemal test, a different serologic method. Long bone films, eye exam. And when we can get it, I like to see if the placenta looks abnormal. I put plus minus because these days, it's hard to get the placental histology back quickly if ever, and usually I've made treatment decisions before then. Yeah, some of the signs or symptoms you might look at, Dr. Urban rightfully said that many babies are asymptomatic when they're first born even if they have congenital syphilis, it said about two thirds are asymptomatic. But in the third who become symptomatic quickly or who might be symptomatic at birth, this weird rhinitis, one of her itises, which I tend to call Snuffles, it's the old name for it. That sort of chronic goopy rhinitis of children, flat condyloma sometimes, a rash. The pseudo paralysis of parrot, where syphilitic osteitis, in the humerus for example, causes you not to want to move your arm as a baby, which can be misdiagnosed as an Erb's palsy or a delivery trauma. Hepatosplenomegaly. And then on the lab side, we're looking for abnormal platelet counts, abnormal white or red blood cell counts, and the CSF abnormalities mentioned, and any periostitis in the long bone films. And there is a Snuffly baby on the left, I mean, babies often are congested, but they're usually not goopy like this. An example of some rash, some odd rashes on the face, condyloma or dry pili rashes on the hands and feet. And hepatosplenomegaly has been drawn out of this file picture. And children I've seen with periostitis, who have, it's hard to tell sometimes, but can have a periosteal long bone accentuation, new bone formation, some celery stocking if there's osteolysis in the shaft. And those are the types of things we'd be looking for in this child.

40:58
Okay, so this is what happens. So all of those things were done, and the baby's RPR came back at 1:1, the CBC is normal. The baby has an LP that's mostly normal with the exception of an elevated total protein, and the X rays are normal.

41:16
And this is constantly a source of consternation, because those of you with pediatric experience know that it's said that preemies, even full term, but young neonates in the first month of life, can have a higher cell count and a higher protein count than an older infant. And as well, it's often hard to get a crystal clear champagne tap, so to speak, with no cells, because sometimes

there's a little capillary trauma as you do the LP. So here's a child where the cell count is clearly normal. And normal, I would probably in a newborn, I might accept up to 20 white blood cells, five is certainly normal. It said that 95% of children, even at birth, have a protein under 120. So here you're really getting into sort of a questionable abnormal range. So this is nerve racking in this child, it is nice that the RPR is less than the moms RPR, but that doesn't exclude syphilis, it just doesn't diagnose for sure syphilis.

42:28
So this is what happened. So their reasoning was exactly as yours, that the baby started IV penicillin. Mom was referred after discharge to get treated at a local sexual health clinic, and she got a single dose of benzathine penicillin, with the reasoning being she had seroconverted for syphilis, and therefore it must be recent. And they ordered repeat serology but because they couldn't do it at the clinic, she went the next morning, and then her repeat was 1:4, and now the CIA is nonreactive. Her regular partner came in and was tested at a different lab, and his test was also nonreactive. So you're kind of left with did mom actually have syphilis? If not, what could have affected the test results? And should this baby have received treatment? So I've put out sort of the tests along the way here. So at 12 weeks, you know, the test is negative, so clearly no syphilis. At 28 weeks, Daniela, what do you think? 1:4 with a nonreactive?

43:44
Yeah, it's interesting. You mentioned earlier, the specific tests are generally positive earlier than the nonspecific tests, though, in some cases it can can occur the other way around, and does not follow the textbook. But you could certainly call that a false positive, given the risk factors and the story. But then, as you saw there, at 39 weeks you got two positives, and you're certainly hard pressed to call two tests falsely positive. So I think a complicating factor here is the recent COVID vaccination, although I don't know how recent it was, but you know, we had a recent FDA alert about how that can influence the RPR. Might be interesting to consider how that played a role here.

44:41
Right. So would other testing be helpful? So maybe, as Dr. Weinberg alluded to, that there is an algorithm where if you start with, particularly some sort of enzyme immunoassay, like an EIA or a CIA, and that's reactive and the RPR is nonreactive, you default to another kind of test. And so that's one thing we suggested when we got this call was to do that other kinds of test, which is typically a TPPA. So what could have affected mom's test results? You alluded to a false positive. So these are the causes. Pregnancy is a big one, and really all sorts of things that cause a lot of antibodies. And you alluded to this recent health alert that came out December 17th. And if you go into the weeds of this, it was a few page long health alert from the FDA, they are reporting particularly on a BioRad assay, but note that this is likely an antibody produced by COVID vaccination or potentially even COVID. So it wouldn't be surprising to see it with other assays or maybe even natural infection. We've gotten that question several times. So this is the first formal report that there is false positivity with COVID vaccination, and it was particularly with BioRad. They false positive specific antibody tests are a little less common. But pregnancy is also on there, and particularly has been reported with a CIA test. So it is very possible that

these were false positive results. But should the baby have received treatment? So you've kind of given us your view.

46:31
Yeah, I think 10 out of 10 times I would have sent this baby to treat.

46:39
Right, it's hard to ignore, particularly in these short hospitalizations. Yeah, so the baby had actually gotten six days of IV penicillin by the time all this information came back. And the medical team did send those additional specific antibody tests, which were still pending. And by that point, it was actually the seventh day they decided to just finish out 10 days, just in case there were any possibility that this baby could have disease, they didn't want to find that out after the fact. So they opted to treat.

47:15
I think my bottom line is treatment for syphilis is always an investment in the child's health for the next, you know, 90, 100 plus years. It's not a good thing to avoid. And this was a tough situation. Maybe in retrospect, this may have been a false positive. Boy in prospect, it was really, really hard to guess that.

47:38
Yeah. So I've put up here what the CDC breaks down as the four possible scenarios when you're confronted with a situation at birth. And we'll go through these in a little bit more detail with another case, but this scenario was sort of possible congenital syphilis with a neonate with a normal exam, a serum RPR that was equal or lower than the maternal level, who had an evaluation and then was treated with the recommended regimen of IV penicillin. They do give you an option of using a shorter course, a single dose of penicillin, but certainly the IV penicillin for 10 days is one of the recommendations.

48:26
I'm going to try to get one more case in, so this is case three. So this is a 32 year old female who again comes in, in first trimester with a new pregnancy, and has an abnormal exam with a genital ulcer. So that obstetrician does full testing, looks for herpes, gonorrhea, chlamydia, HIV and syphilis. The syphilis test comes back positive 1:64 with another reactive specific antibody test known as the FTA ABS, all the other tests were negative. Gets treated as appropriate, as is recommended for what is thought to be primary syphilis with this genital ulcer. The partner is negative, so presumably this patient acquired syphilis from from a different partner sometime in the prior 90 days. Just to show you some examples from various atlases of the genital ulcer, which is generally well demarcated, has a indurated edge so you can see a bit of a thickened edge there. Much harder to see either when it's internal or oral or perianal. So this case was followed along and had repeat serology 20 weeks later at 32 weeks, and now the titer had gone from 1:64 down to 1:16. So what do you think?

49:54

Yeah, I think it's a nice decline in the RPR. Maybe this was pre-guideline update where they were repeating in the third trimester pre-delivery. Now you do repeat at eight weeks there. Yep.

50:13
Yeah. So this is what's new in the CDC guidelines. If you were treated before 24 weeks, eight weeks later. You're treated after 24 weeks, repeat at delivery, and also obtain a fetal ultrasound. I don't know if you want to comment on that?

50:31
I tried to look up the data, because this is a fairly new recommendation, or maybe an older recommendation for the ultrasound, but I I just wasn't that aware of the primary data. There are some within the last 10 years data from high syphilis areas in Texas, that fetal ultrasonography detected a lot of fetal hepatosplenomegaly and some ascites sometimes. And hopefully it would detect hydrops, but hopefully not many of the kids have hydrops. But it's hard for me to know whether that made much treatment. If you had a hydropic baby, it would mean a lot of different treatment for the obstetrician or the family physician with care towards delivery and care towards hour of zero care for the baby. A lot of these, the ultrasound was powerful in showing it, it wasn't clear in my mind that it changed what they did much. And newborn ultrasonography is always better than fetal ultrasonography as well.

51:44
And CDC I think says, if you did find abnormalities, this might be a setting where you add that second dose of benzathine penicillin, although would be sort of after the fact if you already have abnormalities. So ultimately, the patient delivered and the RPR was even lower at 1:8. The baby had a cord blood of 1:16. So what would you do now?

52:10
Well, let's not a four fold, it's a two fold. And RPRs can be variable, and it's not unexpected that the mom's FTA absorb is going to stay positive, possibly for life, for a long time. So it still sounds like mom has had successful therapy. So I would, you know, examine the baby, I probably wouldn't do lots of extra tests. But if I had any uncertainty in my mind, this is one of the ones I would give benzathine penicillin 50,000 units per kilogram times one to the baby.

52:50
I think a serum for the baby, rather than cord blood.

52:54
Oh, yeah, I'm sorry.

52:56
Based on what you said earlier.

52:58
Yes, I really like to see serum and to see it in this case.

53:03
So with the CDC four choices. So this is a mom with syphilis that was treated, and a baby with likely a lower titer. So this falls into congenital syphilis less likely, so mom treated during pregnancy. Treatment appropriate, and before one month prior to delivery, and no evidence of reinfection or relapse by her lower titer. And so as you said, the baby would get a single dose of benzathine penicillin 50,000 units per kilo. If someone was reluctant to do that, it would be important to be sure that baby had follow up to make sure that the titer goes away, right?

53:51
I mean, honestly, we usually ask people to get follow up serologies on the babies every couple of months. And with today's visit schedule, something like two months and four months, or to watch that no increase in RPR is developed. So whether I give a child 50,000 units per kilo or not, I'd like to see a follow up in a couple months, that that RPR has disappeared. And it may take a tad longer for the FTA or for TPPA to disappear, because those are IgG antibodies and they're more sensitive tests, but the recommendation still stands for the pediatric end to repeat these tests, to follow them in nfancy.

54:39
Okay, so I have one more case, but it's four of. So are there any questions in there?

54:46
We do have two questions.

54:48
Okay. Maybe I'll just advance to just some other resources to finish. So if you're interested, syphilis is something that you master over a lifetime, if one ever masters it. And so I'm continually surprised and learning. So we did put together through CEI, a mastering syphilis learning pathway with these four one hour presentations. That's available on our website, CEItraining.org. There's also a really helpful a monograph, which is essentially about a 100 page, sort of magazine, type of literature about the diagnosis and management of syphilis. It is being updated to reflect current guidelines. However, even without the update, it's still very, very helpful. There's lots of photographs in there, and you can download a digital copy at this website. You can have a copy of the slides, or if you look up Syphilis Monograph New York City PTC it pops up on a Google search. This is a very helpful algorithm that doesn't go through the specific antibody testing route, or the nonspecific antibody testing route, but just starts out at screen all women for first prenatal visit. And then once you have your results, down here, you sort of walk down the path, this is from Up To Date. So I found this to be sort of a helpful little chart, if you're not really immersed in syphilis, it really helps you walk through it. And finally, we are going to be printing the new STI treatment cards that are available to go on your lanyards, which you could get at CEItraining.org or emailing Cory here. And we are also launching a podcast, Conversations with CEI, that will start for for the Sexual Health Center in March. And finally, before we take those couple of questions, you can call and you'll reach one of us at this line if you have questions about syphilis, or really any STIs. And in the next several weeks, we are adding a dedicated line to congenital syphilis in the neonate, where you would have access to a pediatric ID specialist, which often will be Dr. Weinberg, but we'll get you to a pediatric

specialist specifically without kind of being hung up by going through the adult specialist first. So with that, how about we'll take those questions.

57:29
Okay, I think we've got three. So are the screening recommendations in New York State very clear as to what type of testing should be done, for example TP versus RPR?

57:42
No, they're not. They're not mandating a particular approach, although in an earlier health alert that came out, they did prefer that it starts with a specific antibody test, because traditionally that is positive maybe 7 to 10 days sooner, so you might be more likely to pick up very recent syphilis. And given the experience that most of the cases of congenital syphilis in the state, at least outside of the City, are due to syphilis acquired during pregnancy, there's a lot of very recent syphilis. So there is a preference to start with that, but it's not a law, not a mandate.

58:24
Great, thank you. Since there's been an increase, and this came up during your epidemiology section, since there's been an increase should there be testing in the second trimester?

58:38
That's a great question. I think that the idea is to try to catch people by the third trimester. And there's been a lot of communication between ACOG, the American College of OB/GYN, and various health departments at the state or federal level, and what would be feasible in sort of the routine follow up of pregnancy. So that's how they got to the first and third trimester. I must say that in my personal practice, when we have had very high risk individuals, particularly individuals who might be engaged in like commercial sex trade, or have a partner who's high risk, particularly in the setting of kind of rapid rises of cases, as we are seeing here, I've done monthly screenings with cooperation of the individual. So that's the way I've gone rather than first, second and third trimester, in particular settings.

59:46
Great. Thank you. And this last question, and thank you for bearing with us. I know we're a couple minutes over. This so sent to Dr. Weinberg, when an infant is followed after treatment, do we need a negative treponemal and non-treponemal test, or just one of those tests?

1:00:03
That's an excellent question, and just as we haven't mandated which one we're supposed to do for screening, I'm not sure I've mandated which one we do for follow up. But I would say, traditionally the RPR, and the RPR has tended to, I would probably say the RPR, because I'm worried that the treponemal test, the technology to detect treponemal specific antibody is much more sensitive. And in that situation, where I think I've already treated the baby, but I'm looking for disappearance of a sensitive test, that's going to take a long time, and I think it's going to make people more nervous. So I usually say follow an RPR, if it's one or the other. It is an ordering problem, because for example, at our Medical Center here at the University of Rochester, you can't order an RPR, you will get a treponemal test first. So theoretically, I would

say do the RPR. Practically speaking, I would say get whatever, just getting a serology of any type for me is a good thing to see. And then you know, if you get a screening enzymatic test first and they default to an RPR, and the screening enzyme test is positive and the RPR's still negative, then I'd stop. Because in this case, I'm using the RPR as my traditional guide. But you know sometimes what we say then when it is not what you can do when you translate it out into the field, because I'm sitting here in the ivory tower.

1:01:52
All very good points. Thanks, Dr. Weinberg. Thanks, Dr. Urban.

[End]