Pathophysiology, Diagnosis and Treatment of Fetal CMV, in partnership with Midwestern University and Phoenix Children's Hospital

Presenter: Stephen L Pedron, MD, MBA

- [Maldoone] It's my pleasure to welcome Dr. Stephen Pedron. Today, he'll be presenting pathophysiology, diagnosis and treatment of fetal CMV. I hand the mic over to you, Dr. Pedron.

- Good morning. Thank you so much. I appreciate that and you're right, I'm excited to be here. If you've heard Dr. Maldoone talk about CMV 101, then you've heard it from the best and she's been a great influence on me. Let's make this a conversation much as is possible with a virtual presentation, please. And that is, put your questions in chat or Q and A, however that's working, and interrupt me at will. I have some breaks built into the talk, so we'll have plenty of time for that, I'm sure. These are my disclosures and the main disclosure that I would make is that this conversation, this talk in no way represents the prevailing guidance or opinion and my specialty, I wish it did.

I am board certified in maternal fetal medicine and OBGYN and our subspecialty body, the Society from Maternal Fetal Medicine, and the American College of Obstetrics and Gynecology don't endorse this. We will, they don't endorse my position. They don't endorse some of the conversation that we're gonna have today. And we'll get into this a little bit more later. These are our learning outcomes, and my resources are patients, other professionals, pathologists, immunologists, pediatric infectious disease, obstetrics and gynecology, maternal fetal medicine. And I'm an avid reader. I have references at the end of the talk and I have many, many more references on this subject. If you ever need anything, just reach out to me, would you please, and I'm happy to provide it to you.

Okay. Our objective is to review the pathophysiology diagnosis and treatment of congenital CMV. I'm a clinician and this is a clinical talk. This is a real world issue for us in our practice and in our specialty, and for you as well. Patient asked me last week, "Well, wait a minute, what about all of these, if this is so prevalent, what about all of these people with hearing issues that we've known our whole lives aren't a lot of them

CMV?" And the answer is, you're darn right, they sure are. Pictures of the CMV, the cytomegalovirus inclusion bodies, which are wondrous. They're beautiful to look at. They're terrible in the disease they cause, and this doesn't even come close to some of the pictures that are out there, but I would encourage you to Google CMV inclusion bodies.

They really are beautiful in color. Now, just some terminology for the rest of the conversation, and that is CMV, as you know, is cytomegalovirus. It's a member of the herpes virus family. As such, it shares viral characteristics of all of the other herpes viruses and that can be summarized as once you've got it, you've always got it. There is primary infection, which is the whopper, that's the big infection but then it lays latent. It resides, and it is always at risk for recurrence think or oral HSV and cold sores or genital herpes or varicella, which causes chicken pox if you haven't been immunized or if your immunization has waned or shingles later on in life. And it has a proclivity, it has an affinity for residing in neurons.

IGM is the first responder of immunity. And when white cells surround something and try to get rid of it in our body, the special forces, the special ops, the first Marines that go in, that's IGM, it's a big clunky antibody. And then the hundreds of thousands of troops that are sent in to wipe out the enemy, that's IgG. And the, and IgG endures. One of the characteristics of our immune system is memory and IgG memory to many things endures. And that's why old people like me don't get many cold viruses anymore. I maybe get sick once a year or so, but never as long as I'm wearing a mask in Covid. And that's because I've seen just about everything.

I have immunity and I have memory to it. Avidity is roughly speaking, strength of association, and we'll get into this in a little while. And T cells, for the purposes of our discussion are the type of white blood cell, the part of our immunity, B cells and T cells. Of those two, T cells are the type of white cell that content with viral infections. Any

questions thus far? Okay. There are many fabulous investigators and mentors in this field. One is Dr. Pereira, who's a PhD researcher at UCSF. And the question that she's answering is, well, why does it have such a proclivity for pregnancy? And she finds that her and her team have found that infection and particularly uterine infection, pregnancy is more virulent and that is because there's, immunity is different in pregnancy.

And if you think about this, the pregnancy is half non-self. And a basic component of the immune process is recognition of non-self, that's what we're supposed to get rid of, whether it's pollen or a be sting or a splinter. But the fetal genetics are half non-self. They're half paternal genetics. And so there is an immune setup, an immune balance that occurs in pregnancy where the maternal immune system is tolerating a foreign body, for all intents and purposes. So that's altered and avidity, the tendency for IgG to attack, to attach rises slowly. And it's unpredictable and it's a tolerant environment. The uterus itself is a tolerant environment for CMV infection. Furthermore, T-cells are attracted to the uterus and the placenta.

They like it there. This concentrates CMV infected cells in the uterus. The CMV is there, the T cells like it there. They corral these viral particles and infection is propagated in the uterus. Then the CMV, once it's there, once it's contending, being contended with there, once it's stuck there, it grows into the decidua, the muscular layers of the uterus, the meat, the real stuff in the uterus as opposed to just a superficial infection where the avidity rises even more slowly because it's walled off in there. And it stays in the uterus where avidity continues to languish. And this causes placental abnormalities, fetal growth restriction, even if infection isn't present and can then extend this infection can extend to the intrauterine environment, to the amniotic fluid and to the baby.

And I show you this picture because I wanna show you that this is a little bit what an abscess looks like. And that is if you have a superficial infection on your skin, you can generally have some information and clean it off. But the bugaboo of fighting infection

is an abscess and that is a compartment where the infection occurs. And there's no place that has better nutrients, better blood supply, better nutrients, a better environment for a walled off infection that a closed up uterus with a little human passenger in there. Another investigator, Auriti, has gotten into the weeds. Him and others have gotten into the weeds a little more on CMV infection pregnancy. And this gets a little specific and a little more into the area of immunology than we need to be.

But there references for it. And his comment is, quote unquote, a key issue emerged in the last years is the key role of placental impairment in the pathogenesis of congenital CMV infection. I wanna underscore that, the placenta is the key to life. That's the connection between the mother and the baby. That is the organ of oxygen and nutrient exchange. And without proper presentation, there is going to be a complication in the pregnancy. It's either gonna be a fetal complication or a maternal complication, or sometimes a combination of those two. I can't stress strongly enough how important placentation is. Normal implantation, growth and function of the placenta is. Although CMV associated congenital disorders are attributed to direct infection, infection with placenta is a big problem for us.

And it replicates cytotrophoblast. It has a proclivity for the cells that are forming the placenta. It interferes with their differentiation. It prevents normal place presentation, normal invasion. The placenta normally should, like a cancer, invade the maternal circulation on the uterine side of this combination of maternal and fetal circulation and those fetal cells, those cytotrophoblast cells early in pregnancy should invade the uterus and set up a relationship with a maternal vasculature. And that's impeded by this infection. And then this leads to placenta edema and fibrosis and impaired transport and anytime you think of fibrosis, think of scarring and imagine this relationship between the maternal vasculature and the fetal vasculature and a very thin cell layer, which allows this free flow of oxygen and nutrients.

And anytime you put scarring in there, it's going to impede that transfer, isn't it? Now I put this picture up here just to make a point and to compare it in my mind's eye to the picture of the uterus because here's another warm, potentially moist environment where infection can occur. And I'm speculating because I haven't been able to find the literature, which really clearly shows us this pathogenesis. But I'm speculating that it gets up there through saliva, through the back of the mouth and that the CMV gains entrance through the round window, it could be the oval window, could be the round window. I really don't know. I haven't seen anybody else guess at this, but I'm assuming that this is where the infection occurs.

And then, not that this is necessarily a warm, moist environment, but I would like us all just to be thinking about walled off areas where organisms are growing or where a virus is growing, where a bacteria is growing. Now, how does it cause hearing loss? And this is your expertise, not mine. So I'm going to embarrass myself here and I'm confident that you know a lot more about this anatomy than I do. But Zhuang, this investigator, quote unquote, little is known regarding the factors that initiate the inflammatory process and sensory neural hearing loss induced by CMV. They don't know, we really don't know why it causes this damage, but it has to be inflammation and infection of nerves.

And we've already established that CMV loves neurons and they've shown a lot, they've done a lot of bench research, a lot of mirroring research. And that is rodents on how CMV infects the cochlea, but it also infects the spiral ganglion neurons. And those are important. That's what's conveying electrical signals, aren't they? And the culprits are inflammation and apoptosis. Inflammation is just always a problem inside of the body. Inflammation, just think of the redness around a bee sting or around a splinter or a red nose when you've, it's inflamed by mucus coming out, wiping your nose, all of that redness is a response. And if you get that response on a neuron, then that just has to be bad, doesn't it?

And then the other culprit that they cite is apoptosis, which is typically a programmed cell death, this is cell death. Think of the skin between your fingers when you're an embryo that's supposed to dissolve and separate those fingers from one another, that's apoptosis at its finest. But accelerated or abnormal apoptosis is cell death where it shouldn't be occurring. And these are photos of some of the neutrophils. This top, these top are A, B, C and D, I just cut 'em off when I put these pictures in here. But these are mononuclear cells within the cochlea, and these are mononuclear cells within spiral neurons. And these are mononuclear cells or these are T cells that are lit up in these spiral neurons. Any questions thus far about pathogenesis?

- [Christy] Yes, actually we do have a question. This is a two-part question. What is the difference between a primary and secondary CMV infection and how does primary versus secondary CMV infection affect the fetus during pregnancy?

- Great question. We're going to get into that in just a little bit. We'll get into some more depth on that. But the short answer to your question is that a primary infection is your first exposure. It's your first event, your first CMV infection. And a secondary infection is broadly speaking, is another one, there are different variants of CMV, just like there's different variants of a cold virus and there's nothing to say that you might not have had a primary CMV infection in the past, have immunity to that variant of CMV, but then acquire another virus, another variant. Anything else?

- [Christy] Yes, that is interesting. So if I understand you properly, you're saying that it could be like a reactivation of the primary infection or a whole new strain, which is a secondary infection?

- Yes, to both. And so reactivation is a little bit different than a secondary infection, a secondary infection, technically speaking is a another infection, brand new bug. But

there is also reactivation, and that's one of the characteristics of herpes viruses is that they reactivate and the prototype for that is the cold sore that keeps coming back.

- [Christy] Okay, you may be getting to this in future slides, but how does an audiologist or a healthcare professional working, just working, how do they make sure that they don't get a primary or a secondary CMV infection? How do they keep themselves safe?

- Oh my gosh, that's an amazing question that, yes, we are gonna get into that a little while, but the answer to that is if you are remotely concerned about childbearing, if you are a parent, male or female in a childbearing era in your family, just pretend that everybody that you are associated with is shedding virus. Think the first days of the pandemic when we all were masked up and we were petrified that every surface we touched, had coronavirus on it and that we were vulnerable to infection. Now that didn't turn out to be true, and that isn't true for CMV as extreme as that. But I would ask everybody of childbearing age to never, ever, ever kiss a child on the mouth, kiss your own children on the mouth, share food with them, share secretions with them, don't let them cough in your face, wash your hands all of the time, when you're changing diapers, wash your hands. Never pick up food. Anything that you can do to prevent sharing secretions with somebody else who might have CMV, particularly toddlers, but for my money, everybody is potentially shedding CMV.

- [Christy] That makes a lot of sense.

- Yep.

- [Christy] Okay, well those are all the questions for now. Thank you.

- All right. So right to it, who is harboring and transmitting? And that is everybody, depending upon your group, the prevalence might be anywhere between, and that is people who have had the virus, all of whom might be shedding, that might be anywhere between 35 to 80%. If you are a preschool worker who hasn't been cautious about hand washing, it's a given that you're gonna have CMV. Now this, the transmission is person to person and non typically non-sexual contact and that is coughing, secretions, aerosolized, thinks spooled up secretions. And that is when somebody is coughing out a secretion, it gets aerosolized, it gets minimized, and the droplets are smaller and they get sprayed out. That's how we acquire CMV also but sexual activity, lactation, transfusion, transplantation.

CMV is a big bugaboo in transplantation patients. And this is our, this is who is shedding CMV. This is a cute child, but look at the nose of this kid and all that junk that's coming out of it. From my perspective, and I, don't get me wrong, I love children and that's why I'm one of the reasons I'm in this business and I've got plenty of my own, but they're all petri dishes, all children from the standpoint of transmission of cytomegalovirus, let's just acknowledge that all children are just petri dishes. Forgive me, parents. Now this gets to the question about primary versus other infection. In the US, primary infection is the concern, although most infections are probably recurrent and recurrent infections are less virulent, hanging there with me, you're gonna understand this, I promise.

In other cultures, secondary infection, reinfection are more predominant. Now, if first trimester infection occurs, it's tougher to get it across the uterus. It needs time and it needs a big placenta, it needs blood flow, it needs receptivity, it needs something else to get across. And that's tougher to do. The pregnancy is more compartmentalized in the first trimester, but that's when the action is, in the first trimester is when embryology is occurring. That's when development is happening. That's when the brain is developing. And the consequences of first trimester infection, although the

transmission rate is lower, the consequences are much higher. Yeah, however, if it's in the third trimester, it crosses right across and that's an exaggeration. But it's much more apt to make it across the placenta and affect the pregnancy but the consequences are lower.

Why is that? And that's because everything's pretty well formed. And if you think about this, what's the consequence of a newborn being exposed a week old, month old being exposed to CMV? It's not likely, although, I don't know, this is not my expertise, I'm not a pediatrician, but I'm guessing that it's not as likely or likely to case sensory neural hearing loss. And the same is true a day before that baby's out, it's developed. This kid's ready, doesn't have an immune system that's quite yet primed up, but it's ready to do that. And a week before, but six months before, no, that baby's still developing. So of course there's a continuum between that first trimester, low rate of transmission, but severe consequences and third trimester, high rate of transmission, but less severe consequences. Is that clear?

- [Christy] Yes.

- Good. How common is sero conversion? And that is primary infection, depends on the demographic, and there's literature for this and all pregnancies is about 2%. Daycare, workers at least 8%. And parents of a shedding toddler, about 24%. This is sero conversion, this is, okay, I've developed a primary infection. It's extremely common and 40 to 50% with primary infection transmitted to the fetus, that transmission, as I said, is highest in the third trimester, but the illness is worse earlier in per pregnancy. Overall, there's a 25% risk of symptomatic disease with primary infection, so that's the, in this, in our culture, in our country, that is the bigger problem, primary infection. And that's just to think about primary infection, any herpes virus infection, the first one is the whopper.

When you get genital herpes the first time, it is a miserable disorder, it's a miserable disease. It just hurts like crazy, you have inflammation. It is systemic and it can cause systemic disease, including encephalitis and hepatitis. The first herpes virus infection is a nasty actor, but by the time you're having recurrences of herpes, it's starting to simmer down. And by the time you've had herpes virus, no matter what the virus is for 10 or 20 years, it is much less virulent and you may, if you have genital herpes, you may have a feel yourself having a prodrome, "Hey, I'm getting infected again." and take some valacyclovir and suppresses the infection, you have very little symptoms. And this picture is up here just to show you what is scary about this.

This is what we're concerned about. That is the asymptomatic phenotype, and that is sensory neural hearing loss. It's only here to state, this picture is only here to state the huge, huge personal and public health problem we have. Now, the symptomatic phenotype and prognosis, and this is earlier infection. It isn't subtle, it is really scary to look at, as I tell my sonographers and the team here, you can see it across a room when you're looking at an ultrasound of a baby that's got the symptomatic phenotype. And in the newborn, likewise, it's not a subtle finding at also neurologic signs of seizures, spasms, hemiparesis, abnormal tone, and then really just awful looking brain imaging, MRI imaging of these baby's heads, hepatitis, jaundice, thrombocytopenia, elevated CSF protein.

And this is the not subtle appearance of microcephaly. You do not have to be an expert to see that this baby's head size is small. And this is a baby with microcephaly. Likewise, this is almost what anencephaly, complete absence of the top of the head looks like. And this is the so-called blueberry muffin rash of a thrombocytopenic severely ill newborn with the phenotype for congenital CMV. Now, recurrent or non-primary infection causes a less severe phenotype, but it's still a very common cause of hearing loss. And since it occurs more often, the numbers add up. And this is why in other cultures, the recurrent or non-primary infection is a much more prevalent

problem because you have a lot of people and a lot of it, and it's causing a lot of sensory neural hearing loss. Any questions about the phenotype type?

- [Christy] Yes, a couple questions. So if you are a woman who gets cold sores, which would then mean that you have the herpes virus, are you gonna give your baby CMV when you get pregnant?

- No, because the CMV is a different virus in the viral family of herpes viruses. Good question but there are HSV one and HSV two, which cause oral and genital herpes. And there used to be some differentiation, but they're both the same, pretty much, either one can cause oral or genital herpes. That's what causes cold sore.

- [Christy] Okay, so if you have genital herpes, you're not gonna give your baby CMV during childbirth.

- You, you are not, you might give your baby general herpes, you might give him HSV one or HSV two during childbirth and there are strategies in place to prevent that from happening, which is viral suppression with valacyclovir in the third, from 36 weeks on in pregnancy but no, you are not going to transmit CMV because there's, you may or may not, but there's no evidence that you have it. And I'm willing to say that just because you have one end the other, it increases your risk of either, but CMV is a completely different herpes virus, just like Epstein Barr virus, which causes mononucleosis just like varicella, which causes chicken pox and shingles and there are several others in that viral family as well.

- [Christy] Great. That makes a lot of sense. Can you speak just for a minute about the CMV titer test? If there is someone who's planning to get pregnant and they take the CMV titer tests and it shows the presence of the proteins in their system, what does that mean as far as contracting CMV?

- That's this, that's coming up right now. We're going to get in there.

- [Christy] Oh. Okay, well, thank you, that's all the questions for now.

- You bet. Let's get to it. The, now let's discuss maternal diagnosis. How is that diagnosis made? And these are exactly the titers that you just asked about, and those are IgG and IgM and we've already discussed what the difference is between these two. And these may come and go with CMV, depending upon when your infection was, where your immune system is. You may have IgG or IGM for the rest of your life, or they may come and go, wax and wane so to speak. But a new infection will have a very specific profile for IgG and IgM. Technically, you, once you suspect a new infection, you want those titers done with a week or two of your suspicion of a new infection.

And then you need to see what's the profile, what's the result of those IgG and IGM titers. Now let's think this through, since the IGM is the first responder, that's going to be the first CMV antibody that you're going to detect with your titers. And the level of that titer is not really that important. Even though there have been some investigators who've said that the IGM index, quote unquote, the extent of the elevation is important and really not a big factor, the main thing is presence or absence. Now, after two to three weeks, your IgG is coming online. Now you're sending in the troops to contend with this virus, and you'll have an elevation of your IgG.

So an IgM to CMV might be a primary infection, but before you have IgG, now you can see you're starting to be able to time this a little bit. And now two weeks later, first you had IgM with your first set of titers, but two weeks later you do your titers again, and now you've got IgG. Now you're pretty well locked in and there are lots of exceptions to this, but you're pretty well locked in with the primary infection. Now, you may have forever, you may have IgG and IgM, and that's quite likely that you're going to, but it's

the new of these titers responses, titers presence or absence that we use to start to zero in on, have you had an infection when that might be.

Some people say that the elevation of the IgG, it was a low level to begin with, and your second set of titers, it's a higher level that that might be informative. It may or may not be, but the real test is avidity, and we're gonna get to that in just a minute. So let's have that conversation about what avidity is and the difference between affinity and avidity. And I would ask you just not to consider there to be a difference between the two. Avidity is going to be a part of our conversation. It's an extremely important concept in the diagnosis of management of this problem. And think of it as the strength of association of your antibody with the antigen, that unique surface marker for whatever it is that our immune system is fighting.

And the amount of it, think of the affinity, the strength of the association, and how many of those antigen sites are, have IgG attached to it. Good so far, stop me if we're not. And divinity is helpful for timing the infection. So we've already created enough confusion by saying, well, wait a minute, I've had a past infection. I may have IgM, I may have IgG, I probably have both. And how do you tell them if I have a primary infection or not? I've never been tested. I'm around kids all the time, I've never been tested. Now my doctor says they want to test me in pregnancy just for grins, and I come up with IgG and IgM.

How do I tell if it's an acute infection? And the answer is avidity. And that avidity can roughly speaking, tell you whether it's a recent or a distant infection. There are some metrics for this, depending upon the percent of avidity for how long the infection is. But suffice to say that with high avidity, the risk of this being a new infection or a virulent recurrent infection is quite low. Any questions on avidity?

- [Christy] This is kind of a general question, but it's about avidity also. How do you know, since we know that CMV is so common, how do you know when to ask your provider for this sort of test so that you would know?

- In this country, you just do it, in this country, that's why we're talking, because you want to know, that's my personal opinion. And this is where I differ from ACOG, from the society, from Internal Field Medicine, from the CDC, they do not recommend it.

- [Christy] So what exactly would you ask for? What would you ask your physician for?

- I would say, test me for CMV. And if your provider, your OB provider pushes back on that, then you can insist. If they don't know how to do it, you can ask 'em for a referral to a maternal fetal medicine specialist. But I think that this is what education is about. I think our childbearing people should be digging in on this and asking to be screened. And I think if you are, and I don't think I know for a fact that if you're in France, they have this discussion with you and every single one of your prenatal visits, and it's just a, it's de rigor, it's just a way things are done there. That's true in France, it's true in Italy, it's true in Israel, it's true in other places, but in this country, we're just not there yet.

- [Christy] Okay, we do have another question. I don't know if you're gonna get to this in the future, I'm just gonna read it now. What is the physiological significance of testing within three weeks after birth for CCMV.

- After birth, I don't know, not my area of expertise, because I'm a perinatologist, not a neonatologist, not a pediatrician, so my patients are pregnant, however, I'm gonna speculate that if you're worried about infection, newborn infection, you want to test, you wanna road test that newborn's immune system, the moment that baby's out, the immune system is present, but really hasn't been exposed to much of anything except

for maybe CMV in utero. But the immune system really isn't ramped up yet. It's not mature, it's not online, it's not active, but it is after a couple, two or three weeks. And so if that's what somebody is suggesting is the timeline for newborn CMV screening, then I'm speculating it's probably time. That's the time interval that it takes for the immune system to come online.

- [Christy] Yeah, that makes sense. And I've heard and read also that, you know, if you test a baby after three weeks, then you don't know if it's an acquired CMV infection or if it's a congenital CMV affection infection because like for the first three weeks also, babies aren't out and about, you know, as much, they're with their parents kind of sheltered. So what you said about the immune system makes sense.

- Yes and I'm way over my skis here. I think that's a really good point and I would guess that this is being sorted out, that this is one of the questions that's being asked as far as newborn screening programs and in addition to what do we screen, do we screen saliva? Do we screen blood? How is this done? How do we interpret it? But I think that's an excellent point, well, wait a minute. If you're waiting two or three weeks, how can you tell if it's something that I acquired in utero or if it happened to me after birth? Maybe that doesn't matter because everybody's gonna get screened but I would, I think that's a really good question to ask and I just don't know the answer.

- [Christy] Yeah, and if you look at the American Academy of Audiology position statement on CCMV, they say 21 days. I mean, everyone where you look or every place you look, 21 days is the cutoff. So, I'm not quite sure why, but that is what it is.

- Well, if that's the cutoff, then you are highly likely to be, if positive before that cutoff, it's highly likely to have been inquired in utero. Think about this. If it takes two to three weeks for the immune system to fully contend with the production of IgM and IgG, then really by rights, if you test a week afterwards, it's congenital. If you test 10 days

afterwards, it's congenital, two weeks, probably still congenital, but it probably isn't that three weeks is the optimal time. It probably, as you said, is the cutoff time where you don't wanna do it any later than that if you're trying to ascertain is this a congenital infection?

- [Christy] That makes a lot of sense.

- It does, thinking it through right now, I think that is the thing that makes sense.

- [Christy] Okay.

- Keep going?

- [Christy] Keep going. Yes.

- Okay, there is a calculator for this and the link works as far as I know, you'll have these slides and I won't take the time to go through it. But this is a ballpark figure calculator for the tendency to have congenital infection after a maternal primary infection. And it has to do with the socioeconomic group, with this IGM index that I mentioned with a lower avidity, and then the presence of maternal CMV PCR and that is, now I'm concerned about a infection. Now I'm gonna asay the mother's serum and find out how much of this virus does she have circulating in her serum. Now let's just go through some of the ultrasound findings of CMV, as I said, it's not subtle, I just saw a patient here this morning that has got a lot of brain findings that I think is highly likely to be CMV, we're testing her, this is actually an abdominal film, an abdominal picture of an ultrasound of a baby with ascites.

But they have, they can be very subtle signs, but for the very sick baby, they can be very severe signs of echogenicity, calcification, growth restriction, big placenta, big

liver and spleen in the baby, ascites, which is what I've shown you here, microcephaly, which we've seen some pictures of. And the diagnosis is amniocentesis and so, we're screening a lot of babies for CMV with amniocentesis. And that's really the only way to tell is it in there? Is it in the baby's compartment? It might be, the mother might have it, it might be in the uterus, but she may not be transmitting for whatever reason, she just dodged a bullet. But if you wanna find out that if it's in the fetal compartment, this is how it's done.

And so we do a lot of this. Any questions about diagnosis thus far? Okay, let's keep going then. Now, how do we decrease it? One is prevention, screening, newborn screening is coming online, that is gonna be happening. Prenatal screening is done in other countries, it just, we're not there yet in this country and as I said, this is just my opinion, if somebody asked me, we have a group in one of our community hospitals, in our region, we have a group of family medicine physicians who, they've decided to screen. So we're receiving a lot of patients from them with CMV screening results to be sorted out. Why is that? That's just because they're screening and they're finding a lot.

Valaciclovir, we're gonna talk about in just a moment. And then there's some novel therapies out there, including, we're really hopeful about this mRNA vaccine that's on the horizon. Just some definitions though, there is primary prevention, which is prevented in the first place. Secondary prevention is, well, now I've got it, how do I prevent it from getting to the baby? And then tertiary prevention is newborn interventions, Primary prevention, we've talked about this and that is just, be aggressive with it and don't get it. Just do everything possible to avoid it. And there are fabulous handouts for primary prevention. This is a CDC handout and this is another one from Idaho, which are just really good and straightforward and should be distributed with every single prenatal visit.

But they are not, they're out there, they're available for you but they're, unfortunately, the OBGYN providers in this country have just decided to put their head in the sand about this issue. And that, there is, there are multiple experts in this field who will unabashedly come out and just say, it's just an under recognition and inattention to the problem. And these are our groups. These are some of the groups who say, don't screen. I've already mentioned CDC, ACOG and the Society from Internal Fetal of Medicine. There are investigators who assert that there's no proven treatment for it, that it, people get frightened and they terminate their pregnancy, which is true, without experience and without expertise in discussing and interpreting those results.

This for sure is true, and they're not wrong. Investigators are not wrong in saying we should be emphasizing hygiene. We definitely should be emphasizing hygiene. But across the board, the rationale for ignoring it is that there's no known treatment. And we're gonna talk about that next because there is, this is the CDCs position on screening, and I'm not gonna beat a dead horse here. Pardon the expression. And this is the current state of play as far as treatment. This is just good old fashioned Valtrex. And again, I won't take up too much time with going through the details of these studies, but dating back since at least 2016, before 2016, the nature of the treatment, the guidance was IVIG was cytogam, which was a concentrated CMV hyperimmune globulin.

And there had been some quasi evidence in the past that hyperimmune globulin was effective until a really good study came out in 2021 by Hughes and others in the New England Journal of Medicine, which just put it to rest that, no, I hyperimmune globulin hasn't been shown to work, but investigators have been looking at viral suppression and viral treatment with Valtrex for natural reasons. It treats, it's very effective at treating herpes viruses. So they've been doing these studies for a while now, and I have references for all of these. And there's, this investigator, Shahar-Nissan in 2020

published an excellent randomized perspective, double-blinded trial. And that's the best of the best, with a randomized perspective, double-blinded trial.

You take a group of patients and you give them the treatment and you take a group of patients and you give them a placebo and you don't tell the investigators or the patients which is which, and you do the treatment, you run the study, and then you finally, when all is said and done in the data is an analyzed, then you break the code and you tell the investigators who was who. And they're very tedious and expensive and difficult to do from the perspective of ethics and review boards. But this is a superb study which demonstrated that Valtrex, Valacyclovir decreases transmission. And there's another, and this group, Shahar Nissen is in Tel Aviv, and this group, Faure Bardon is in Paris.

And likewise, they did their study a little bit differently. This is a case control study, which is not statistically as strong as a perspective randomized double blinded trial, but it's still a very good study and these are highly legitimate investigators. And they've also published results which show that Valacyclovir does decrease transmission and phenotype. And then there have been some other investigators, Adler's been a big name in this area for quite some time in this country. But their investigators have to some extent suggested that maternal CMV, once you've got a patient that you've identified as having a primary infection with maternal titers, with amniocentesis, whatever your tools have been, once you start treating those patients, you might be able to assess the efficacy of your treatment noninvasively by following maternal CMV DNA.

And that makes sense, well, if I'm really suppressing it and if it's going, if by suppressing the maternal viral load, that's gonna decrease what's getting to the fetus, which by rights, it should, then it might be reasonable to follow CMV DNAemia and we do in our patients. And what about outcomes with this treatment? Depends upon the

timing of sero conversion and fetal infection. If you've got an early sero conversion in a baby that is already severely affected, then it is not going to be an effective treatment. But if you have somebody who has early seroconversion, and by early I mean days or weeks, then you can absolutely suppress that virus with some valacyclovir and prevented from getting to the fetus in the first place.

Now, what about termination? Yes, termination is an option for patients with early onset CMV. That's a conversation to have with them. What's the efficacy and the wisdom of treatment. If you have somebody who is 16 to 20 weeks and they have, everything lines up that that patient has a primary infection and that fetus is obviously severely affected already. The baby has calcifications, echogenicity and ascites, hydrops, the baby's obviously sick and the mother's serology lines up that the pregnancy is affected by CMV or you have an amniocentesis, which shows amniotic fluid, PCR to CMV, then termination is a very reasonable, not stating this as any particular position on termination, that's irrelevant here, but it's a very reasonable decision and many patients will take it.

And then there are novel treatments, and we'll just go over these briefly and then we'll take time for questions. And if you wanna talk about a case, we can talk about a case here in just a minute. But there are other viral targeted therapies out there. There's some great literature on this and review literature, which summarizes some of these. Then some of the research is cutting its teeth and patient, immunosuppressed patients and that's a really vulnerable group to CMV infection. And there is probably some crossover and intersection, so to speak, between the immune status of an immunosuppressed patient, an HIV patient who's insufficiently treated as of yet, and a pregnant patient. And that is this immune modulation that occurs to tolerate the fetal paternal antigens.

And then vaccination monoclonal antibodies. We'll get to vaccination in a minute, but monoclonal antibodies are being investigated by these teams and monoclonal antibodies, which really started to get a lot of conversation during Covid, just like mRNA vaccines did. They're changing the landscape of medicine, I, you cannot imagine the ways that monoclonal antibodies are changing the lives of patients with lupus, rheumatoid arthritis, Crohn's disease. They're just hugely effective and the cutting edge of medicine as far as treatment of immune disorders. And the CMV vaccine, I've, there are two separate vaccine trials underway, and I'm really not as clear on the Merck, Sharp and Dome trial, I know it's out there, but I really can't nail down the information on this.

But the Moderna vaccine is close and there are some thought leaders in this country. If you are in Europe, there are many thought leaders on this subject, but the clearly the thought leader on, at least from a pediatric perspective, on congenital CMV is the University of Alabama. And of course they're involved in both of these studies. Therefore, to summarize, prevention is extremely effective. That is just don't get it. Serum diagnosis is not necessarily complex. It just takes suspicion and some learning, you have to understand it a little bit and our OB providers in this country just haven't gone the distance on this yet. And they haven't gone the distance because they colleges are telling 'em don't bother.

There is absolutely effective sonographic and invasive diagnosis. And the invasive diagnosis is amniocentesis, of course. And the treatment, though it's off-label, it's not the standard of care, it's reasonable, it's tolerable and it is quite plausibly effective, right now, the evidence says that yes, it is effective in decreasing viral transmission and the CMV phenotype in babies. And as I mentioned, there's hope on the horizon for an MRAA vaccine. I think we're real close and I think that other novel therapies, as these investigators ramp up, as they continue, I should say, I think that we'll get there. And

that is it for now. I'll take some questions and then, if we have a few extra minutes, we can talk about a real world patient that I saw last week.

- [Christy] Thank you. That was fabulous, Dr. Pedron. We have a question from Pamela and she's wondering, does CMV cause other neural tube defects including spina, she says bifocals, but I think she meant bifida and hydrocephaly?

- No. Yes. No, it does not cause spina bifida, not that I am aware of. I suppose I could make a case for a severe infection at four weeks, when the neural tube is forming, causing a neural tube defect, so-called spina bifida. But that association, if it's there, I'm sure you could find a case report, but if it's there, it's not a strong one, no. However, yes, absolutely causes hydrocephalus and the pathogenesis of hydrocephalus with CMV is quite different from that of spina bifida. Spina bifida also causes hydrocephalus, but that's because the opening in the spine causes some backward displacement of the brain and it plugs the frame and magnum the hole that leads outta the back of the skull down into the spinal cord and the CSF backs up.

But for babies with CMV, with hydrocephalus, with CMV, that's generally down to brain destruction. And if you destroy, brain fluid will fill the space. That's true anywhere in the body. If you destroy tissue or fail to have it develop normally, fluid's going to fill that space. Other questions?

- [Christy] That was the last question. So I would love to hear your case study. I think everyone else would too.

- Okay, let's do that then. This is a patient that I saw on Friday, actually, a 29 year old gravida 2 para 1, who is eight weeks. Her first pregnancy is healthy. She has a one and a half year old toddler. The patient, and as you know, anybody who has kids will tell you everybody's sick around the house all the time, you just, you send your kid off to

preschool, daycare and they're just bringing home colds all the time. And for the first couple of years with your first couple of kids, they're just viruses going around the house all the time. That's just normal. For some reason, over the past four weeks or so, this toddler's actually been healthy, but the mother had a severe bronchitis or pneumonia about four weeks ago and it probably was Covid with a super infection to pneumonia.

We really don't know because she wasn't tested for that. And it probably wasn't CMV because it doesn't cause that degree of illness in an adult. An adult who's infected with CMV, you probably don't notice it at all. And your kids just got the sniffles, just got a, you know, snotty nose like this beautiful little baby we showed you earlier, child toddler we showed you earlier. But her family medicine provider does screening and screened her for CMV and sure enough, she has IgM. With negative IgG, this was done two weeks ago, so at about six weeks, just shy of six weeks of pregnancy, as a routine for their prenatal visit, this team, this entire team of providers at this rural hospital have decided to screen.

She came up positive for IgG, IgM and negative for IgG two weeks ago. Really by rights, that's a primary infection. Her history isn't actually characteristic for a primary CMV infection. Maybe just a mild, you know, cold, maybe mild cold symptoms would be more characteristic. But who knows, maybe her immunity was compromised, not just by the pregnancy, but by having a co-infection with Covid or some other bacterial infection, we don't know. And really doesn't matter much whether her toddler was symptomatic or not because her toddler is highly likely to have CMV just because that baby goes to daycare and is shedding anyway, at any rate, we met on Friday and that, we said, well, this was two weeks ago, it's time to repeat your titers Wednesday, which is today.

She's having them repeated, let's see what happens with the titers. And the patient asked the question, "Well why wait? This looks like a primary infection, why are you waiting for my second set of titers to verify this infection? Don't you think we should just start Valtrex? I've taken Valtrex before, I have genital herpes. I've taken it before, it's well tolerated." When you take it for genital herpes, it's a gram or two a day, and the treatment for CMV is eight grams a day. And so the Valacyclovir sits on your gut like a rock. And it's a little bit of a chore to take it, but generally it's well tolerated and it isn't dangerous for the mother to take it.

There have been some side effects, but they're very unusual. And so I said, "I don't know if it sounds like a good idea to me, but I don't know for sure." And so what I did is what I usually do, and I phoned a friend and what I usually do when I have no friends in my area, I will reach out to the experts that are doing the work and these experts are across the pond, of course. And so I reached out to Dr. Shahar in Tel Aviv and I did it on Friday night, and it must have been right about Saturday morning because I think it was Shabbat in Israel and he didn't get back to me 'til, kid you not, 12:01 AM Sunday morning, I got an email back from Dr.

Shahar and he said, "Yes. Absolutely, jump on it and treat her." So we did. I picked up the phone and called the family medicine provider and said, "Go for it." And we'd had this discussion before, we were all prepped up to do this as soon as we got a green light from these investigators. And we started this patient on eight grams a day of Valacyclovir Saturday night. Meanwhile, I reached out to Dr. Veal, and this is another group of investigators in Paris. And so full transparency, Dr. Veal got back to me Sunday afternoon, I heard back from Shahar Sunday morning, I heard back from Veal Sunday afternoon and Veal said, "Nah, I deposited by GM alone as meaningless, you gotta wait for her second set of titers."

By then, we'd already started the patient on treatment already, so no sweat but I wanted to, I wanna make several points here, first, don't hesitate to ask. We are creating protocols in this country because we just don't have colleagues and guidance. And so I'll ask anybody anytime. There's another team up at the University of Minnesota, Mark Slice, who's a pediatric infectious disease fellow, and Jessica Niholm, who's a maternal fetal medicine specialist, they'll treat CMV and they're wonderful resources. So I've had multiple communications with them about how to handle this issue. And then the other thing that I would say is there are different opinions on this and there are no clear guidelines on this, it's still a research issue, but there are some amazing world-class people who always answer the phone, so to speak.

They always answer the call. They're available to us, to guide us on how to handle these things and there's some different opinions. We'll see what happens with their second set of titers here today. Any questions on that?

- [Christy] Yes, actually we are, we have two questions and we are out of time. So let me ask you these questions. That was a fascinating case study. You need to get back with the group and let us know what happens. But first one is from Janelle and it's a comment. She says, thank you. Spouse is MFM MD and concurs with universal screening. And the other question is, this is from Kathleen and she says, I apologize. What is the promising off-label treatment for maternal primary infection?

- Valacyclovir.

- [Christy] Okay.

- Yeah, valacyclovir. As far as I know. Let me go back and see if I had something else buried in this slide that I glossed over. I think we are probably talking about Valacyclovir. Valacyclovir is absolutely promising. It is off label, there, as I alluded, there

are some really good summary papers on what is on the horizon for the treatment of this disorder. And so might, could be that we're, I'm missing something else. Haven't mentioned something else that's out there on the horizon. Probably in the category of hyperimmune globulin or concentrated IVIG or monoclonal antibodies. And love the fact that there's another MFM out there who's team for screening, probably ought to hook us up because I don't know, I don't have anybody who I would consider a peer group on this in my specialty, if there's somebody out there, try and connect them with me, would you please, just so we can have a conversation, get to know one another?

- [Maldoone] Yes, absolutely, Dr. Pedron, we will definitely forward any comments or questions that come our way once the webinar closes. And I wanted to thank you again for your time and your expertise.

- It's my pleasure to do so, thank you.