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EVIDENCE TO ACTION (E2A) WEBINAR:

COVID-19 AND ITS IMPACT ON PREGNANCY AND POTENTIAL MOTHER-TO-CHILD SARS-COV-2 VIRAL TRANSMISSION

PRESENTED BY THE ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION - APRIL 15, 2020

WELCOME – DR. ANJA GIPHART

Hi everybody. Welcome to this webinar. Thank you for joining and good morning, good afternoon, wherever everybody is. My name is Anya Giphart. I'm the Executive Vice President for Medical and Scientific affairs at the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF).

This webinar is one in a series of webinars that we host at EGPAF. For those of you who do not know us very well, our mission is to eliminate HIV and AIDS in children, youth, and families, and we do this through program implementation, innovation and research programs, advocacy, and technical assistance and capacity building efforts. We have activities in 19 countries, mostly in Sub-Saharan Africa.

In this edition of the Evidence to Action, featuring COVID-19 and its impact on pregnancy and potential mother to child SARS-CoV-2 viral transmission, our Senior HIV Technical Research Advisor, Dr Lynne Mofenson will present the latest data on vertical transmission of SARS-CoV-2. For many, Dr. Mofenson doesn't need introduction, but for those of you who don't know her, she has been with EGPAF since 2014, and previously led the maternal and pediatric infectious disease branch at NICHD at the NIH.

So without any further ado now, I would like to hand over to Dr. Lynne Mofenson for her presentation. Lynne, go ahead.

COVID-19 AND ITS IMPACT ON PREGNANCY AND POTENTIAL MOTHER-TO-CHILD SARS-COV-2 VIRAL – PRESENTED BY DR. LYNNE MOFENSON

INTRODUCTION

Hi. Good morning everybody. Good morning, good afternoon, good evening. So I'm going to talk about COVID-19 and pregnancy. And I want to start out by noting that data are extremely limited. They are very preliminary. Some are of very poor quality. And the data change almost daily.



WHAT IS CORONAVIRUS? (3:53, SLIDE 5)

I want to start out with some basic information on SARS-CoV-2. So what is a Coronavirus? Corona viruses are single-stranded RNA viruses that are named because of the projections, or spike proteins, on the envelope that resembles a crown. They're classified into four different genera based on genomic structure; can infect different hosts and have different tissue tropism. The Gamma and Delta CoVs infect birds, fishes, and a few mammals. Alpha and Beta CoVs are the important ones. They infect only mammals, including humans, and have repeatedly crossed species barriers, with bats and rodents being the primary gene sources.

There are seven human CoVs known to date, four of them cause mild disease and three cause severe disease. SARS-CoV-1, MERS, and SARS-CoV-2, as shown on the screen.

Comment on terminology: SARS-CoV-2, or a Serious Acute Respiratory Syndrome Coronavirus 2, refers to the virus itself, whereas COVID-19, or Coronavirus Disease 2019, is the disease caused by the virus, and was named by the World Health Organization in February. This terminology is similar to HIV, which is the virus that causes the disease called AIDS.

HOW DOES SARS-COV-2 CAUSE INFECTION? (5:35, SLIDE 7)

The human receptor for this virus is Angiotensin-Converting Enzyme 2, or ACE2. This enzyme is involved in the regulation of blood pressure through catalyzing cleavage of angiotensin II, which is a vasoconstrictor peptide, into angiotensin, which is a vasodilator peptide. It is expressed by many cells in the body, but its principle target cell is in the lung.

SARS-CoV-2 binds to the ACE2 through the spike proteins as shown in this little figure. And it also subsequently down-regulates ACE2 expression, which could have a negative effect clinically because you're basically enhancing vasoconstriction.

This shows you a simplified replication cycle for the virus, and it's pretty simplified. We start with fusion. So the spike protein binds to ACE2 and is fused into an endosome and brought into the cell. The genetic material of the virus, the RNA, is released, and then that begins to be translated by the host ribosomes into polyproteins. These polyproteins are then cleaved by a viral specific protease, and some of them form a transcription replication transcription complex, which enables the viral RNA to be replicated with viral RNA dependent RNA polymerase. All of these proteins and the RNA enter the Golgi apparatus where the viral envelope is assembled from their constituent proteins. The viral RNA binds to the end protein to form the ribonucleoprotein complex, and it buds out to form an intracellular vesicle, and then finally is released into the general area.

EPIDEMIOLOGY (7:51, SLIDE 9)

A pneumonia of unknown cause was detected in Wuhan and Hubei Province in China and reported to the World Health Organization China Country Office on December 31st, 2019. It was rapidly linked to exposure to the Wuhan Seafood Market.



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The epidemic doubled in size every 7.4 days with transmission among close contacts rapidly becoming evident. If you look at the graph, in blue you see linked to the market, and in orange you see cases not linked to the market. By January, the vast majority of cases were no longer linked to that seafood market.

There was then rapid spread out of Hunan to the rest of China, increasing from five cases on December 29th to 51,000 cases by February 16th, a 10,000 fold increase in less than two months. Then it rapidly spread outside of China to the current global pandemic. And in orange you can see the cases outside of China in the graph. The figure shows you the current epidemic as of yesterday, over 1.8 million confirmed cases, over a hundred thousand deaths.

WHY IS THERE SUCH RAPID GLOBAL SPREAD OF THIS VIRUS? (SLIDE 10)

The first is the **ease of transmission**. It is spread through respiratory droplets and also touching contaminated surfaces and bringing those contaminated surface materials to your mucous membrane. It has a high attack rate because its infectious before symptoms, with viral shedding one to three days before symptoms occur, and prolonged shedding after symptoms, a median duration of 17 days, and with more severe disease you have a higher viral load and a higher duration of shedding. And you can have transmission from asymptomatic persons, which was recognized only relatively recently.

Also there's a **population lack of immunity**. It's a novel virus, there's no herd immunity globally, so everyone is susceptible. And then finally, **global travel leads to ease of importation of cases of a highly infectious disease**.

This figure shows you COVID-19 Disease. What I want to emphasize is that both the virus and the host immune response to the virus play a part here. And the symptoms here are based on the first 72,000 cases in China that were reported by Zhang in JAMA.

STAGES OF VIRAL REPLICATION

The **first stage is the stage of viral replication**. Clinical symptoms are mild constitutional syndrome symptoms: low grade fever, dry cough, headache, sometimes diarrhea, and loss of taste and smell, and some mild clinical signs including lymphopenia. In these China cases no symptoms were reported in 1%, mild symptoms in 81%. You **then** begin to get a host immune response and get moderate to severe disease with shortness of breath, dyspnea, hypoxia, and you begin to get abnormal chest imaging findings. And then **finally**, you can get a cytokine storm, where the host immune response takes over. You get acute respiratory distress syndrome, a systemic inflammatory response shock, cardiac failure, elevated inflammatory markers. And you can see the difference in the chest x-ray between moderate and critical. The mortality is currently estimated between 1-3.8% with factors being older age, male sex, and co-morbidity.

So just to emphasize that *the majority of cases end right here in the viral response phase, the mild phase*.

Just wanted to point out that the virus can affect organs other than the respiratory tract. These are some things that have been more recently reported: neurologic manifestations including cerebrovascular disease and impaired



consciousness, skeletal muscle injury, and cardiac injury has been reported, including two cases of COVID-related cardiomyopathy in pregnancy. Diarrhea has been reported in a minority of cases. Conjunctivitis has been reported, and then finally the loss of taste and smell.

This slide shows you risk factors for severe disease and poor outcome. The first showing you patient characteristics, and then abnormal vital signs, and finally abnormal laboratory. And as you've heard, the primary characteristic for severe disease is a history of some kind of chronic disease.

COVID-19 AND HIV (13:10, SLIDE 14)

But I want to just point out for HIV, there are only two case reports I could find in the literature, as of yesterday, of COVID-19 in HIV. So there's really a minimal amount of information that's known. It's hypothesized that if you're on treatment, you have a high CD4, that COVID-19 disease would not be different than for those without HIV infection, but COVID-19 Disease has been reported in low prevalence countries (China, US, Europe) and not yet in areas with high HIV prevalence. So we really don't know. However, we're now beginning to see COVID-19 in Africa, and it's going to be critical to monitor its impact in the HIV population.

COMMENTS ON TESTING FOR SARS-COV-2

The test that's been primarily used is a Real-Time Nucleic Acid Amplification Test, or rtPCR, that detects the SARS-CoV-2 RNA. And that can be used for a variety of different fluids, as well as tissues. It detects current infection with SARS-CoV-2, however, it doesn't detect whether that is infectious or not; it just is detecting the RNA. It can be used to inform the individual of their infection status so that they can know that they're sick and take actions to prevent transmission, it can be used in the facility to inform patient management and actions needed to prevent transmission, and then finally, it can be used for public health purposes to inform actions to prevent transmission.

More recently, there's been SARS-CoV-2 antibody detection, virus specific IgG and IgM. This shows past exposure to SARS-CoV-2 and can be used to detect people who are susceptible, meaning antibody negative, and those who are supposedly immune, previously infected antibody-positive, to identify those who can be returned to work. It can be used to identify individuals with neutralizing antibody, and some treatments are using that, and to facilitate contact tracing and surveillance.

CLINICAL TRIALS (15:32, SLIDE 16)

There are no proven treatments for SARS-CoV-2, but there are many under study. As of yesterday, there were 461 studies in ClinicalTrials.gov. And these experimental treatment strategies attempt to interfere at different steps in the replication cycle. So for example, monoclonal antibodies, a neutralizing antibody, can prevent viral binding and getting into the cell. Camostat mesylate is a serine protease inhibitor and it inhibits a receptor called TMPRSS2.



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And for entry of the virus through the non-endosomal pathway, which I didn't discuss in the prior slide, it cleaves the spike protein to activate it. And this particular drug inhibits that trypsin enzyme.

Chloroquine and hydroxy chloroquine decrease acidity in the endosome, so would interfere with the virus being able to get un-coded. Cell culture studies suggest that you need high doses for this. Lopinavir-retonavir and other protease inhibitors, notably atazanavir and darunavir, can inhibit the protease inhibitor, that protease enzyme. And Remdesivir and favipiravir inhibit the viral RNA polymerase. And then finally we have immune response modulators that are used to modulate the cytokine storm, and these are primarily monoclonal antibodies that are used for treatment of other diseases like rheumatoid arthritis.

This shows you the 461 clinical trials as of yesterday. The vast majority are in China, in Europe, and the US. And I just want to comment that the more things change, the more they stay the same. All of these trials generally exclude pregnant and breastfeeding women and children. We'll have good information about the effectiveness in adult men.

Randomized trials are needed to discern efficacy and safety and the scientific data really rapidly change every day. March 18th we had a trial of Lopinavir-Ritonavir in adults with severe COVID that showed absolutely no benefit. April 4th there was a trial, a comparative study looking at hydroxychloroquine in hospitalized patients that showed no benefits and actually an increased need for respiratory support. There was another paper on April 11th looking at a higher dose of chloroquine finding no benefit and that the higher dose was harmful. And then finally on April 10th there was finally some encouraging data, looking at compassionate use of Remdesivir and finding that it had the suggestion of some clinical benefit and there are a number of randomized trials that are ongoing.

That's the basics. I want to now talk about a COVID-19 in pregnancy.

COVID-19 IN PREGNANCY (18:53, SLIDE 19)

Data are limited, they're preliminary, and also potentially duplicative. There have been three to four reviews and meta-analyses, but only small numbers: 23 patients, 38 patients- I think the largest was less than a 100. And so I did a rapid review in PubMed, MedRxiv and Science Direct to identify reports in pregnant women and their infants, including case reports using the terms COVID-19, SARS-CoV-2, novel coronavirus, and pregnancy or newborn. These are data published as of yesterday: 37 patients were identified including 475 pregnant women with COVID-19. 28 of these patients, including 82% of the patients come from China. These papers are generally relatively poor quality, and an unclear amount of duplicative reporting- 15 of the patients, including 259 women, come from overlapping institutions and overlapping time periods, so you really can't tell whether they're duplicative cases or not. There are now four reports from the US on 80 patients, 16%, and then one case report each from Korea, Turkey, Spain, Honduras, and Sweden.

This (slide 21) shows you the characteristics of pregnant women with COVID-19 and these tables will all show you the characteristics, the number of patients, and then the number over the total sample and percentage. Of 475 pregnant women, 87% of those are rtPCR confirmed and 13%, or 64 women, are clinical diagnosis. These come from China and a clinical diagnosis is defined as a suspect patient with a



typical chest CAT scan but a negative rtPCR test or no rtPCR test. Maternal age was 22 to 42 years. Gestational age at presentation of symptoms was six to 41 weeks. But if we look at trimester of infection, the vast majority are third trimester, 91%, while 8% were in the second trimester. There were four reported in the first trimester, but they all had induced abortion so pregnancy outcome there is not known. 413 of the 475, or 87%, had a pregnancy outcome reported including four abortions and one stillbirth. And 13%, or 62 women, were still pregnant at the time of the papers.

SYMPTOM IN PREGNANT WOMEN (SLIDE 22)

This looks at **timing of symptom onset** in the pregnant women. Antepartum onset was reported in 78% starting one to 10 days prior to admission, intrapartum onset of the first symptom was described in 2%, postpartum onset of their first symptoms in 8% one to three days postpartum, and no symptoms in 12%. Although the majority presented with symptoms while still pregnant, 10% didn't have symptoms until they were admitted in labor or after delivery. Additionally, 12% had no symptoms at any time, but screened positive by rtPCR and they were screened either because they had known exposure or in New York City, they're doing universal screening.

And I'll present you this data. This was published two days ago in the New England Journal and this is from New York Presbyterian and Columbia University Hospital in New York City reporting on 215 pregnant women who delivered and they're universal nasal pharyngeal rtPCR testing in labor. Four of the 215 women or 2% had symptoms. All were found to be positive. 29 of the 210 who were tested who had no symptoms were also positive: 14%. Thus 29 of the 33, or 88% who were positive by PCR, had no symptoms at admission. And fever developed postpartum in three of the 29, or 10%, of those who initially didn't have symptoms. We haven't really done surveillance screening in the US yet to know the numbers that are asymptomatic and we also don't know whether if you're asymptomatic and you've got PCR, whether you are infectious or not.

This slide (24) looks at the type of symptoms in pregnant women with COVID-19. Antepartum fever was the most common in 44%, postpartum fever in 37%, cough and 33%, myalgia 22%, fatigue 15%, shortness of breath and dyspnea 14%, sore throat 11%, gastrointestinal, primarily diarrhea in 9%, chills in 7% and as we talked about, no symptoms in 12%. And you'll notice that the number of papers that actually report symptoms are many less than the 37 papers that were published.

Now this (slide 25) compares COVID-19 symptoms in non-pregnant adults to pregnant women. These are over 55,000 adults with lab confirmed COVID-19 and these are the women from the survey that I did. Blue is fever, orange is cough, gray is fatigue, yellow dyspnea, blue sore throat, green myalgia, dark blue chills and brown is GI. You can see 88% of adults had fever, but 45% of this was early. And in pregnant women, 81% had fever, 37% antepartum early and 44% late. And then if you look at these curves, you can see **pregnant women with COVID-19 do not appear to have major differences in symptoms**, maybe slightly less cough and fatigue compared to non-pregnant individuals.



These are laboratory findings in the pregnant women and again, the number of studies is relatively small. Low or normal white cell count in almost 70%, lymphopenia in 42%, increased C-reactive protein 60%, increased transaminases in 8%. In terms of radiology in China, their preferred radiology test was a chest CT, so very few chest x-ray were reported. The reports on chest x-rays primarily come from the US. And 88 to 100% who had an x-ray, had abnormal findings.

Again, we're going to compare adults with COVID-19 to pregnant women with COVID-19 and blue is low normal white count, orange is lymphopenia, gray is CRP, yellow LFT and green is abnormal CAT scan. And again, you can see pregnant women with COVID-19 lab findings are basically similar to that in non-pregnant individuals and lymphopenia and elevated CRP both in non-pregnant and pregnant women appear to be important markers and most people have abnormal radiologic findings. But of course these data are skewed towards evaluating symptomatic individuals.

DISEASE SEVERITY IN PREGNANT WOMEN WITH COVID-19 (28:02, SLIDE 28)

This looks at disease severity in pregnant women with COVID-19 and this is really difficult to get from the papers. 16 papers talked about oxygen support. 48% of people in these papers required oxygen support. Mechanical ventilation was rare, 2%, nine women, but three of those nine had not resolved at the time of publication. And there were no deaths. The majority of pregnant women had mild to moderate disease, 52% requiring only supportive care without the need for oxygen. A significant minority, 2%, had severe disease requiring intubation and although there were no deaths, three of these, that should be nine patients, requiring ventilation were still receiving ventilation at the time of a paper publication, including one getting ECMO. Women, pregnant women can get severe disease, but it doesn't appear to be elevated.

And again, comparing adults with pregnant women, blue is no symptoms, orange is mild, gray is moderate to severe, yellow is critical and green shows you mortality. And just to comment that in the pregnant women you couldn't really differentiate mild from moderate to severe. This is put together and so this is compared to moderate, severe and mild put together. And you can see from this, the pregnant women do not appear to have more severe disease than non-pregnant adults. A higher percent [of women] look asymptomatic, but this is because some sites are doing universal testing regardless of symptoms. And there's no increase in mortality- no mortality in the pregnant women, and in individuals age to 20 to 44 the mortality's only 0.2%.

PREGNANCY OUTCOMES (28:54, SLIDE 30)

This looks at pregnancy outcome in the women. And I just want to note that of the papers in whom we could discern what trimester it was, you really had most in the third trimester 91%, a few in the second trimester. The effect of infection in the first trimester and early pregnancy is really not determined yet. We don't have any reports on that. In these women, 15% had fetal distress, 11% premature rupture of



membranes. There was one stillbirth which gives a rate of 0.4%. The vast majority were born by Cesarean section, but that's because in China COVID-19 is viewed as an indication for Cesarean section. There were 380 births, including six twin sets. 24% were preterm, 9% were low birth weight.

This looks at outcomes of the newborns. Neonatal asphyxia and neonatal death were very rare. There was only one death and this was in a preterm 34-week gestation infant with multiple organ failure DIC shock that died at nine days. No rtPCR was done, but it was a pretty premature infant. Neonatal symptoms were reported in 20%. These were very vague: fever in 29%, respiratory distress 45%, GI 26%. Notice that very few papers really reported on what the symptoms were. In the 120 that had an x-ray, 23% had an abnormal chest x-ray, but chest x-rays were generally performed in infants who had respiratory symptoms, not asymptomatic symptoms.

Disruption

IS THERE MOTHER TO CHILD TRANSMISSION? (SLIDE 33)

What are requirements for in-utero infection? (31:54, slide 34) In-utero infection requires the pathogen to cross the placenta, and I was asking, is there a receptor in the placenta? Is there a receptor in the fetus?

This is the placenta and this is immunohistochemical localization of mRNA for ACE-2. The brown shows you the mRNA and ACE-2 was found in the placenta localized to the decidua and the chorion and in the intervillous spaces. And it's also found not just early in gestation, but also late term. These are from later term and you can see again in the decidua and placenta.

And ACE-2 enzyme can be found in the fetal lung. Again, looking at imminent immunohistochemical localization with the brown showing you ACE-2. It's found as early as 12 weeks gestation with an increase over gestation and postnatal development.

WHAT ABOUT INTRAPARTUM TRANSMISSION? (32:57, SLIDE 36)

This requires fetal exposure to infectious virus. The question is, is SARS-CoV-2 found in vaginal fluids? Minimal data. There's one study of 10 post-menopausal women with severe COVID-19 that had testing in their vaginal fluids with rtPCR 17 to 40 days after diagnosis while still in the ICU. All samples were negative. We have data from six pregnant women at delivery to date and all six were negative for virus. But just to point out that potential exposure to the virus after birth in the delivery room is possible, but that's really postnatal and not intrapartum infection.



What about breast milk transmission? SARS-CoV-2 PCR was evaluated in 14 breast milk samples. All tested negative for virus and postnatally transmission looks like it's more likely through close contact with the infected mother of the infant than through breast milk. (see more info in Q&A)

IMMUNOLOGIC EVIDENCE FOR MTCT OF SARS-COV-2 (34:04, SLIDE 38)

So what's the immunologic evidence? There have been reports of seven neonates with SARS-CoV-2, IgG and/or IgM, but negative rtPCR results. I'm just going to briefly go through the cases.

Infant one was 38 weeks, born by C-section, negative pressure room. The mother supposedly wore a mask, infant had no contact with the mother. The mother had high IgG and IgM in their serum. The infant was asymptomatic but had both IgG and IgM at age two hours as well as elevated cytokine levels and leukocytosis. Five nasopharyngeal swabs taken from two hours to 16 days of age were all negative, as was breast milk. So no virus found. And at day 24, the IgG had significantly decreased and IgM was almost gone. Normal is less than 10.

Infants two through seven come from one report from China. These are six infants, again, born by C-section, negative pressure room, mothers wearing masks, separated immediately after birth. Two of the infants had elevated IgG and IgM and both mothers had elevated G and M. Three infants had elevated IgG, but not IgM. All of these mothers had elevated IgG and one infant had elevated IL-6 only. All of them had negative rtPCR on nasal swabs and no symptoms.

Comments on these cases: IgM antibodies are too large to cross the placenta, so detecting it in the newborn could be assumed to reflect fetal production following in utero infection. Evidence for transmission is based only on elevated IgM antibodies in blood drawn following births. Elevated levels of IgG and IL-6 may be from transplacental passage from the mother. However, IgM assays can be prone to false-positive and false-negative results along with cross-reactivity and testing challenges, and none of the infants had a positive virologic test, so there's not virologic evidence to support the serologic suggestion of in utero transmission. And the decline in IgM in one case in 14 days is very unusual kinetics for IgM- with congenital zika or rubella IgM antibodies usually persist for a year or more, so serologic cases are not definitive proof of in utero transmission. (See further discussion in the Q&A)

VIROLOGIC EVIDENCE FOR MTCT OF SARS-COV-2 (36:51 SLIDE 41)

So this is the data of virologic testing by rtPCR: 32 neonates had swabs, 11 of them were positive for a transmission rate of 4%. Amniotic fluid, placenta, cord blood, gastric aspirate, maternal breast milk and vaginal swabs, all negative. Of 44 infant stools, five were positive for 11%.

So I want to briefly go over the cases with the viral positive results.

1. (slide 43) The first infant, 38 weeks gestation, born by C-section due to severe pre-eclampsia. The mother was not diagnosed until five days postpartum. Infant had initial respiratory distress



resolved on its own, transferred to the mother and breastfed until they realized the mother was infected. At that time, the infant was asymptomatic and had a negative nasopharyngeal aspirate, but two days later had a positive aspirate. Had minimal symptoms, but had an abnormal chest X-Ray. Symptoms resolved within 24 hours. Child asymptomatic, but the aspirate was still positive at day 13.

2. Infant two, another C-section, another mother wearing a mask and an infant isolated. Again, the mother's PCR returned late at day three and the infant had a swab at 36 hours, which was positive. The infant had no clinical symptoms but a chest X-Ray "consistent with pulmonary infection," at 53 hours, which resolved. There's a lot of chest X-rays with "Mild infection," that they never described what it really is. This child had negative tests at four, eight and 15 days.
3. The third infant, similar, 39 weeks, born to a mother, rt positive 36 hours. No real symptoms but an abnormal chest X-ray and then turned negative. Infant four was a 40 week infant born to a mother with a fever, abnormal chest X-ray, wore a mask, mother found to be positive. Infant was swapped at age 36 hours. Asymptomatic again, but having some abnormal chest CTs, which improved, and the next swab of the infant was negative at day 14 and all other samples were negative. Infant five, again, a similar report. A brief period of nondescript symptoms. Normal lab results. Chest X-ray with quote, "Pneumonia." Positive tests at age two and four days, negative at day six.
4. The next two infants, again, very similar. Immediately after birth, separated from mother, mild symptoms. Chest X-ray abnormal, positive at day two and four, negative at day six.
5. Infant seven was a premature baby who had symptoms that were probably due to prematurity and sepsis with Enterobacter: had NP and anal swabs positive at two and four days and negative at seven.
6. Infants eight and nine, two infants with swabs collected post C-section after birth had positive tests. One had, again, pneumonia on chest X-ray, the other asymptomatic and no other tests.
7. And the last two had nasopharyngeal swabs collected at age 30 hours and another at four days. Similar, born by C-section, isolated. One had mild symptoms of shortness of breath. The other was asymptomatic but supposedly had abnormal CT scans, and repeat swabs were negative prior to discharge. They also reported on infants with anal swabs but no one knows what that really means.

Comments on these cases: The first case from Spain is likely horizontal transmission as there was breastfeeding from infected mother for three days prior to the test. Eight of the 10 remaining cases report operative delivery and separation from the mothers. Aside from the preterm infant we talked about with RDS, all the infants had minimal symptoms but some poorly described radiologic findings which resolved quickly. Five of the 10 had a single positive test followed rapidly by multiple negative



tests within two to 14 days and no virus was detected in any other fluid except stool. So it's possible in-utero infection, but also possible false positive tests.

PROPOSED DEFINITION OF IN-UTERO INFECTION (41:43, SLIDE 49)

So I thought that this was very helpful. Looking at what can we use to define whether there's in-utero infection, and this comes from a recently published article and she accounts for both maternal testing, whether there are symptoms in the infant, whether there's detection of the virus, including the type and timing of the sample, with blood and amniotic fluid being more important than the placenta or nasopharyngeal swabs, and whether there was antibody. So she starts out if the infant has clinical features of infection and you know that it was born to a mother with SARS-CoV-2, confirmed infection requires detection of the virus in blood or amniotic fluid at birth.

A probable infection is detection by NP swab at birth and having a placental sample positive. Possible infection is no detection in an NP swab at birth, but having IgM antibodies in the cord or blood. Unlikely is no virus by PCR in the nasal swab and no antibody testing. Not infected, you can see [No virus detection by PCR in NP swab at and no SARS-CoV-2 IgM in umbilical cord or neonatal blood]. If the infant has no clinical findings of infection, again, detection of the virus in blood at birth is required for confirmed, detection and amniotic fluid is probable, detection of IgM in cord blood is possible, and onward. For intrapartum infection, if the infant has clinical features to be confirmed you have to have virus in NP swab at birth and age 24 to 48 hours. Probable is at birth but not at 24 to 48 hours. Possible is no NP swab, but detection in other samples, et cetera. And then they go to infant with no clinical features. Confirmed is detection at NP swab at birth and age 24 to 48 hours. Here we have at birth for possible.

And lastly is the definition of postpartum infection that she says the infant has to have clinical features and a parent with infection or symptoms but not tested. And here a detection of the virus in the NP or rectal swab at greater than 48 hours of birth in an infant who tested negative at birth. Probable is detection of virus at greater than 48 hours of birth in an infant who was not tested at birth. So if we look at the cases that I described to you, we see the cases here, the mother's test, the infant's symptoms, birth samples, type of sample, timing of samples, and later tests.

HOW WELL DO DESCRIBED POSSIBLE MTCT CASES FIT DEFINITIONS? (44:24, SLIDE 52)

So of those with the positive virologic test, none of them meet the definition of confirmed or probable intrauterine infection as none of them had birth blood or placental samples or an antibody test done.

Two of them met the definition of possible intrapartum because they had a test at 24 hours with no second test in an infant who had minimal or no symptoms, and you see for most of these kids you can't tell what symptoms they had. And then nine may meet the definition of probable postnatal infection if you view 30 to 36 hours as equal to 48 hours and a probable postnatal was detection in NP in the



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neonate, not tested at birth. The immunologic cases meet the definition of possible in utero infection. They all had IgM in cord blood and negative detection of virus in blood.

So what can we say? **The serologic data are not definitive but are suggestive (slide 53)**. We do know that there are ACE2 receptors on the placenta and in the fetal lung suggesting it's possible for in-utero transmission. The viral data are suggestive, but there were no birth testing and rapid conversion from positive to negative within a few days, which is concerning regarding the potential for false positive tests. So is it possible? We can say yes. Do we have definitive proof? I would say not at this time.

MANAGEMENT OF SUSPECTED PREGNANT WOMAN WITH SUSPECTED COVID-19 DISEASE

(46:13, SLIDE 54)

And I wanted to end with what I thought was a nice description of the management of suspected women with COVID-19. You start out with the mother who's got suspect symptoms including some of those infrequent symptoms and you do nasopharyngeal and oral swabs. If the mother tests positive she should get a mask for source containment. If severe symptoms, ICU support. You minimize the number of providers in the delivery and operating room to reduce the exposure risks, and neonatal providers in particular should have personal protective equipment for airborne precautions should they have to intubate. The infant should be isolated post-delivery and cared for in a single room pending their test result with NP and throat swabs at birth, 24 and 48 hours. If the infant tests negative, which most infants appear to do, they're discharged to a caregiver pending a negative test and symptom resolution in the mother. If the infant tests positive and they have no symptoms, and most infants who test positive have minimal symptoms, they can be discharged and potentially quarantined at home, avoiding care by elderly or those with comorbidity. If they have symptoms, they go to the NICU.

In terms of infant feeding, both the WHO and CDC say that healthy caregivers can feed expressed breast milk using a dedicated pump and strict hand hygiene, but if the mother and infant are not separated, breastfeeding while wearing a mask and after hand hygiene may be considered. And I just want to bring to people's attention that the Perinatal Guidelines Panel has issued interim guidance. Actually, the Adult Perinatal and Pediatric Panel have issued interim guidance for persons with HIV and COVID-19 that include issues related to pregnant women and children as showing here.

And that's it. Thank you.