Lisa Fall, MD: I'm Lisa Fall. I have been with Optum for about 8 years now. When I initially started, I worked in case and disease management and then I moved over to Healthy First Steps. About a year after that. I did my undergrad and medical training at the University of Michigan and then went to the University of Virginia for my OB/GYN residency. I then spent the next 20 years in various practice settings. I've done everything from solo practice to multispecialty group practice involving the education of residents. Most recently, I worked at City Hospital in St. Paul, Minnesota, and had the privilege of teaching residents from the University of Minnesota.

I have no disclosure information, but I would like to thank a few people. Doctors Ryan and Rosterman were key in helping this presentation look a little bit more fun than just straight up slides with information and no pictures. So I want to thank them and also Doctor Ward, because she continually funneled me papers that she thought were interesting and should be included in this discussion. She was a great help in putting together the research for this talk.

Our objectives today are to identify risk factors for severe COVID disease in pregnant women. We'll discuss how COVID affects pregnancy and discuss how COVID vaccination affects both the course of the pregnancy and the neonate.

I wanted to start with a case study. This case is drawn from some of the patients that we've reviewed who've had COVID. This was a 24-year-old at 33 weeks' gestation. She came in complaining of cough, fever, mild shortness of breath, sore throat, malaise, headache, and fever. She had a negative chest X-ray, but a positive COVID-19 test. You can see her vitals there. She was febrile and tachycardic with a respiratory rate ranging up to 30. Her blood pressure was mildly elevated, but her O2 saturations were normal. Unfortunately, shortly after admission, her respiratory status deteriorated, and she required intubation. She underwent an emergency cesarean delivery to assist in maternal stabilization, but her oxygen requirements steadily increased after delivery. Post op day nine: she was transferred to a higher level of care because she had exhausted ventilatory support and required extracorporeal membrane oxygenation. She had ECMO for eight weeks. And during that time, she developed large pneumatoceles and pulmonary fibrosis. These did resolve or the pneumatoceles resolved at the time of discharge. But she had pulmonary fibrosis that persisted. Three months after her initial hospitalization, she was discharged to a long-term care facility. Fortunately, at the time of discharge, her mental status was normal. She had a tracheostomy and had suffered autoamputation of all digits on her left hand and part of one foot due to periods of hypoperfusion.

So maternal physiology poses some unique challenges in the care of a patient with COVID. There are immune changes that can affect the mom's ability to fight off infections. And these changes are necessary to sustain the pregnancy, because, as you know, the fetus represents foreign tissue, and the mom has to have her immune system suppressed in order to be able to not reject the fetus during the pregnancy. But the downside is she has an altered ability to fight infections. There are pulmonary changes that can affect critical care in gravely ill mom. She has an increased tidal volume, but a decreased functional residual capacity. I'm sorry that got cut off in the slide, and for some reason I wasn't able to fix it. She has a decreased ability to clear infections and the hypercoagulability of pregnancy may be synergistic with the increased risk for blood clots that is seen in all COVID-19 patients. There's just a chart for you as a reminder of what functional residual capacity is and—just a fun fact—when you get, "the wind knocked out of you," it is your functional residual capacity that gets knocked out.

And the way that this is relevant in pregnancy is that, during periods of acute decompensation, the mom has less oxygen reserve in which to support her during resuscitative events and even, for example, during administration of general anesthesia in a pregnant patient, she has less reserve to get her from the time of sedation until the time of intubation and ventilatory support. So that, as you can imagine, will pose challenges in caring for these patients.

We now have some data about how COVID affects pregnancy. There was a multinational cohort study that looked at women who were hospitalized with COVID during pregnancy. It was a prospective longitudinal study involving 43 hospitals in 18 different countries. 706 women who were positive for COVID were enrolled. These women were 18 years and older, and there was no specific time during the pregnancy that they had the diagnosis. They were matched to 1400 controls. The diagnosis of COVID was based on either a positive PCR or radiologic findings or the presence of two or more symptoms consistent with COVID. Most infections were in the third trimester. In the women who had COVID, they had higher rates of being “overweight early in pregnancy” and higher rates of previous preterm delivery, still birth, neonatal death, and comorbidities.

In the women who had COVID, they had higher rates of pregnancy-induced hypertension and higher rates of infections requiring antibiotics. There were more ICU admissions and a higher rate of preterm birth. There were 11 deaths, and overweight women appeared to be at the highest risk. There were four deaths from hypertensive disorders, five from respiratory failure, antenatally, and 2 from respiratory failure postpartum. The deaths tended to be clustered in countries that had less sophisticated medical care. There was a cohort of asymptomatic women with positive tests, and they appeared only to be at risk for pregnancy-induced hypertension. Out of the preterm births, 88% were medically indicated. One woman in the cohort group died from a pre-existing cancer.

Of the children born to these women, there was no increased positivity rate seen in moms who breastfed. There was a higher rate of preterm delivery and a lower weight at birth. Twelve percent of the infants with COVID-positive moms at delivery also tested positive, so there did appear to be a low rate of vertical transmission. The COVID-positive infants tended to have longer ICU stays and increased morbidity, and these adverse events persisted even after adjustment for gestational age at birth. There were some big limitations to this study. For example, COVID-negative women did not have negative COVID tests that they just lacked the presence of a positive test or symptoms consistent with a diagnosis of COVID. So there is the possibility that there were asymptomatic infections in the control group.

The next study I wanted to look at was some CDC data on stillbirths. Looking at the timeframe from March 2020 through September 2021. The CDC pulled information from 1.2 million deliveries at 736 hospitals across the country. This data is abstracted from a large hospital-based administrative database. Out of the 1.2 million deliveries, there were 8000 stillbirths affecting 0.64% and 1.26% of deliveries without COVID and with COVID, respectively. So that equates to a relative risk of still birth in a COVID-positive mom to be 1.9. The relative risk increased dramatically to 4.04 during the Delta wave, which was from July to September of 2021. In moms who delivered with COVID, there was a higher incidence of chronic hypertension, multiple-gestation, adverse cardiac events, placental abruption, sepsis, shock, acute respiratory distress, mechanical ventilation, and ICU admission, all of which were associated with a higher prevalence of stillbirth. The limitations of this data abstraction are that the data is based on diagnosis codes, and it's unknown whether patients had active COVID at the time of delivery or how many had asymptomatic infections that were detected on screening at the time of admission. So

these may have been patients who didn't know that they had COVID prior to their screening at the time of admission. The vaccination status of these patients is unknown.

A second series abstracted from CDC data is looking at women with COVID during pregnancy in the state of Mississippi. Out of 1600 cases, there were 15 deaths defined as death during pregnancy or within 90 days of the end of the pregnancy. All 15 were admitted to the ICU, 14 had invasive mechanical ventilation, seven emergency cesarean deliveries, three died during pregnancy, and two died after their births. This equates to 9 deaths per 1000 infections, and, just for comparison's sake, during a similar period, deaths in reproductive age women were 2.5 per 1000, so there was a substantial increase in pregnant patients.

These women frequently had underlying medical conditions, including obesity, hypertension, diabetes, cancer, and one patient with HIV with pneumocystis pneumonia. Out of these 15 patients, there were no patients that were fully vaccinated. There was one that was partially vaccinated and 14 that were unvaccinated.

So I wanted to turn now to just general information about COVID and pregnancy. This is abstracted from lots of published data and summarized in UpToDate. Infections in pregnant women are more likely to be asymptomatic. They are often milder, although the types of infections are similar. COVID can cause transaminitis, which may be confused with HELLP syndrome during pregnancy, although acute hypertension is not seen with COVID, and that should help determine whether or not transaminitis is related to the pregnancy itself, as opposed to COVID. There's an increased risk of ventilatory support and death compared with nonpregnant women, although there are studies out there that have found no difference in the rates of ventilatory support and death.

Risk factors for severe disease are age, obesity, preexisting comorbidities (especially diabetes and hypertension), unvaccinated status, late second and third trimester at the time of active disease, and women from minority groups. So in in women who had laboratory-confirmed COVID infections, they had a higher rate of ICU admissions, invasive ventilation, ECMO, and death.

Turning to the transplacental passage of antibodies to the fetus, there is not a whole lot of data yet available regarding this topic. There is a research paper, a letter, that was published at *JAMA* in early February, looking at 77 women who received vaccinations sometime between 21 and 32 weeks of gestation, and 12 women who were infected from 25 to 32 weeks gestation. The study participants had maternal and cord blood drawn at the time of delivery, and analysis showed higher levels of antibodies in infants born to vaccinated moms. And this difference persisted at six months of life, although only 28 of the vaccinated and 12 of the unvaccinated babies were actually tested at six months.

So, COVID has some interesting effects on the placenta. The placenta usually acts as a barrier to transmission of viruses to the fetus, but viral particles for COVID have been found on the fetal surface of the placenta as well as within the placenta itself.

The placental pathology is very similar to changes seen in pregnancies that are complicated by eclampsia and preeclampsia. Placentas from women with active COVID at the time of delivery show inflammation and areas of infarction.

So, turning to newborn outcomes. The Delta wave was definitely associated with more severe disease in moms. The risk of vertical transmission remains unclear. There actually is some speculation that

hematogenous spread is the most common, although ascending infection from mom to baby is also possible. So far, the accumulated data shows no increased risk of miscarriage or congenital anomalies, and the data on preterm birth and cesarean birth are somewhat unclear and may be limited to patients with severe disease and/or comorbidities. So the average pregnant patient who gets COVID would not necessarily be expected to have a higher rate of preterm birth. And then as we saw in some of the earlier data, there's an increased rate of hypertensive disorders of pregnancy.

The data on stillbirth does appear to be unclear and has not been verified across multiple studies, although the preliminary data does suggest an increased risk, especially with the delta variant, as we saw earlier. What we do know is that maternal infection later in pregnancy increases the risk for adverse outcomes.

Looking at newborn outcomes, over 95% of infants born to positive moms are uninfected.

Neonatal morbidity is largely related to the effects of medically induced preterm birth. There does not appear to be an increased risk of early neonatal death. And there's some very preliminary data that suggests that maternal inflammation from COVID may increase the risk of neuropsychiatric disorders in children.

So turning to care of the pregnant patient with COVID. Care of the asymptomatic patient is pretty self-explanatory. It's basically self-monitoring for the development of symptoms. They can continue routine care, and the presence of the viral infection itself without symptoms should not impact delivery indications.

For the symptomatic infected patient, we need to assess for risk factors such as the presence of obesity, diabetes, or hypertension. And the general guidelines for hospitalization would include hypoxemia on room air, respiratory rate greater than 30, and lung infiltrates greater than 50%. And as a reminder, chest X-ray and CT are safe in pregnancy as most patients will have their belly shielded during these tests.

For hospitalized patients, the goals are to maintain oxygen saturation above 95%. This is higher than in the general population just to promote oxygen transport across the placenta. The recommended prone position can be difficult, obviously, for advanced pregnancies. So mom should be semi-prone whenever possible. The uterus should be displaced off aorta to promote venous return to the heart. The use of antiviral medications, monoclonal antibodies, should be considered in appropriate patients. There's limited pregnancy data regarding these, but the indications currently are for treatment based on basically the same indications that we would use for nonpregnant patients. Venous thromboembolic prophylaxis should be given as you would in a nonpregnant patient, and then the fetus and the uterus should be monitored as you would for any critically ill patient. Delivery should be considered if the mom's condition deteriorates, especially if the pregnancy is beyond 32 weeks' gestation, and the fetus has a good chance of intact survival.

There is no contraindication to intubation and mechanical ventilation and, as we saw in our case presentation, ECMO can be used if needed, although most patients will have undergone delivery if they deteriorate to that degree.

For home care of the symptomatic infected patient, the guidelines are very similar to the nonpregnant patient. Unlike nonpregnant patients, the use of NSAIDs should be limited of limited duration and

COVID-specific treatment should be considered, especially in moms who are at higher risk for progression to severe disease, such as those with comorbidities.

In looking at the pregnant patient who is sitting at home with symptoms; she needs to call her provider if her shortness of breath worsens, [she has] a respiratory greater than 24 or heart rate that's persistently above 100, if she has an unremitting fever, or [if she] cannot tolerate oral intake. She should call her physician if she has persistent pleuritic chest pain and then, obviously, confusion and the usual obstetrical indications such as contractions, bleeding, or decreased fetal movement.

During labor, care is typically unchanged. Delivery should occur for obstetrical indications unless mom's condition deteriorates. Most people are recommending, given the hypercoagulable state that persists even after delivery, that these patients should have VTE prophylaxis until at least postpartum day 10. Breastfeeding: it's still unclear whether it's a mode of transmission, although that risk does not appear to be high, so I think most doctors are using usual considerations for breastfeeding.

And now turning to vaccination and pregnancy, does vaccination during pregnancy adversely affect the pregnancy? And this is obviously of course what most pregnant moms want to know immediately. There was an Ontario-based study that enrolled almost 100,000 women and looked at outcomes such as postpartum hemorrhage, chorioamnionitis, cesarean delivery, admission to NICU for the babies, or low Apgar scores. And so these were in women who did not have COVID but just were vaccinated. Out of the 97,000 women enrolled, 23% received at least one dose during pregnancy (most of those were in the third trimester) as compared with 44,000 who are vaccinated after pregnancy and 30,000 unvaccinated patients. Vaccinated women tended to be older and more affluent, and the most important part of this is that there were no differences in adverse outcomes amongst any of the groups.

So then then the next question is, does vaccination provide a benefit and the statistic comes from the CDC data from February 2002 and looked at the incidence of babies that were hospitalized at less than six months of age and looked retrospectively at maternal vaccination rates. Data was obtained from 20 pediatric hospitals from July of 2021 through January of 2022, and 379 hospitalized infants less than six months of age were identified. Out of those infants, 176 had COVID or COVID symptoms and a positive PCR. In these 176 patients, 16% of the moms had been vaccinated. There were 203 with negative PCRs and, of those patients, 32% of the moms had been vaccinated. Now, of note, there were 21% of these babies with comorbidities, 22% had been born prematurely, and those rates were similar between the two groups. The other thing to note is that mothers were considered vaccinated if they received a second dose during pregnancy, but greater than 14 days prior to delivery, and most of these moms had proof of vaccination, although some did not.

Of these 300 hospitalized infants, 15% went to the ICU, and, of that cohort of infants, the maternal vaccination rate was 12%. These infants were more likely to be Black or Hispanic, and the physicians conducting the study concluded that vaccination later in pregnancy seemed to be more effective than vaccination earlier in pregnancy. But, they noted, this was a small sample size, vaccination status was based on recollection for several moms, and there was no information regarding maternal comorbidities or behaviors during pregnancy.

So, moving on to just general maternal vaccination information, we do know that vaccination decreases the risk of infection. It decreases the risk of perinatal death. It decreases the risk of hospitalization for babies up to six months of age.

And looking at adverse events reported to the CDC, there doesn't appear to be any effect on pregnancy overall from the vaccine, and no increased incidence of adverse effects just due to the vaccine itself, not necessarily related to the pregnancy. There is no increase in miscarriage rates. Early vaccination provides the most maternal benefit, but later vaccination provides more benefit for the baby, and that primarily has to do with antibody levels in mom and the timing at which antibodies are transmitted through the across the placenta. Vaccination before pregnancy does not appear to have an effect on fertility.

And then I wanted to just give a couple words of caution for some data that has recently come out regarding vaccinations. There is some data that has come out of Sweden. This was a meta-analysis looking at all of the patients that were included in the drug company approval studies. What the analysis found is that the mRNA vaccines had no impact on all-cause mortality. So in essence, what this means is that although the vaccines decreased the risk of death from COVID-19, [they] increased the risk of death from other causes. The adeno-vector vaccines, which are the Johnson & Johnson and the AstraZeneca, which is in Britain, actually had a significant reduction in all all-cause mortality by a relative risk factor of 0.37. We don't have any long term-data and, unfortunately, we will not have long-term data looking at all-cause mortality because, once these studies were released, most of the study participants went ahead and got vaccinated.

Their second study that I wanted to just point out is that there's a study that's come out of Israel that looked at calls to emergency…like 911 calls or the Israeli equivalent…that were related to acute coronary events in the general population from the age of about 18 to 40. So, basically any calls to emergency centers that could be related to either cardiac arrest or acute coronary syndrome. And they looked at three time periods, they looked at a time period of pre-COVID, early COVID, which was essentially before the vaccine, and then later COVID which was during the vaccine rollout and the third wave of COVID. The reason that they actually wanted to look at this data was because of the reported risk of myocarditis, especially in young men who had received the vaccines.

And what they found, this is kind of a busy slide, but you can actually see pretty clearly when you look at the information right here. What you can see… This purple line indicates when people got their first vaccine dose, roughly, the second line is the second vaccine dose, and then this red line indicates an increased rate in call center calls for acute coronary syndrome and cardiac arrest. So it suggests that there may be a correlation in cardiac events, particularly related to the second dose in a younger population. The study was interesting. They split it out, men vs women and looked at compared with pre-COVID, the increase was about 20% and was closer to 25% in women.

So finally, looking at all the data together, as we go forward in time, now that the pandemic has really moved into an endemic phase, there are just some things to think about for the pregnant woman who may not have already been vaccinated. As you probably all know with this most recent Omicron wave, this is a variant that was highly infectious, and there are estimates that somewhere between 75% and higher of US citizens have probably at this point either been infected or vaccinated. So as we move forward in the pandemic, some things to think about. Maybe, you know, do you have risk factors for severe disease such as obesity, diabetes, or hypertension? Consider antibody testing prior to vaccination, and then maybe consider selective vaccination for those [with] risk factors who have not, or patients who have not been infected as seen by antibody levels. And all of this in consideration of the

fact that the variants that we have seen most recently and will probably see in the future will continue to be more mild variants that have less risk for severe disease.

So the first question is which of the following statements about COVID and pregnancy is true? Pregnant women are more likely to have asymptomatic infections. B. Maternal vaccination is most effective in transferring protection to the infant when given as early as possible. C. New mothers with COVID should not breastfeed, and D. Vaccination should not be administered in the first trimester.

So A is the correct answer. Pregnant women are more likely to have asymptomatic infections. As we talked about, maternal vaccination is most effective in protecting the infant when it's given later in pregnancy, but it is most effective in protecting mom if it's given earlier in pregnancy and, at this point, we feel the benefits to the mom out outweigh the slight decreased protection to the infant. New mothers with COVID at this point are still…The recommendation is still to breastfeed. We don't have enough information to say that breastfeeding is a significant vector of transmission to the to the infant. And then vaccine can be administered in any trimester.

And are we ready to move to the next one?

So the following are risk factors for severe disease and pregnant women: A. Obesity, B. Hypertension, C. Hypothyroidism, and D. Both A and B.

And the answer is D, both A and B. The main risk factors are obesity, hypertension, and diabetes. Obviously, there are less common risk factors such as pre-existing cardiac conditions, but those are the top three.

And then question #3. Hospitalization should be considered for the symptomatic patient who A. Has a positive test, B. Has mild shortness of breath that is not worsening, C. Has an unremitting fever, and D. Has infected family members.

And the answer is C: Unremitting fever.

So as we talked about, most patients who are symptomatic with mild disease can be managed at home, and mild shortness of breath that is stable is fine at home. The status of family members should not be an indication for hospitalization. The primary indications for hospitalization would be unremitting fever, inability to tolerate oral intake, worsening shortness of breath, tachycardia, and hypoxemia, obviously. And so those are the main ones to consider when you're trying to consider whether someone should be hospitalized during the pregnancy.

And then finally, #4 ECMO. It isn't just for babies anymore, true or false?

And this is true, as we saw in our case presentation. ECMO can and has been used successfully to treat moms with severe disease.

There's still a lot we don't know about COVID and pregnancy, but we are learning more every day.

Thank you very much everyone. I really appreciate your attendance.