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Case Report

Prolonged SARS-CoV-2 Viral Shedding in Pregnancy and Risk of Extended in-Patient Isolation: A Case Report

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), continues to challenge healthcare systems worldwide, and further investigation is required to determine its effects on the pregnant population. Prolonged viral shedding (>15-33 days), especially without appropriate testing guidelines, can subject admitted patients to unnecessarily long isolation, which influences emotional, physical, and clinical aspects of their antepartum course. We report a young, primigravida Haitian female admitted to the antepartum service at 22 weeks of gestation with preterm premature rupture of membranes (PPROM), who remained admitted in isolation for over 6 weeks due to persistent positive SARS-CoV-2 testing. This case highlights the importance of establishing testing guidelines to prevent unnecessary isolation, which has negative consequences for patient care. There is an urgent need for updated guidelines for the duration of isolation based on the presence of the viable virus.

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Introduction

While there are several on-going investigations into how COVID-19 infections affect pregnant women, there are no published reports of their susceptibility to SARS-CoV-2 and the unique management of asymptomatic patients who remain admitted in isolation. Prolonged contact precautions and isolation have been shown to negatively impact social functioning, sleep, and quality of life [1]. While pregnant, women are at increased risk of infection with severe illness due to other respiratory viruses when compared to non-pregnant patients and therefore, may be particularly vulnerable to an extended hospitalization requiring isolation [2].

Much of the unique impacts of COVID-19 on the pregnant population are yet to be determined. Thus far, a small number of pregnancy complications, such as preterm birth, have been reported in mothers who tested positive for SARS-CoV-2 late in their pregnancies. Nine pregnant patients with COVID-19 in Zhongnan Hospital of Wuhan University were found to have either PPRM, preterm delivery, fetal tachycardia, or fetal distress when the infection occurred in the third trimester of

pregnancy [3]. The analysis of amniotic fluid, cord blood, neonatal throat swab, and breast milk samples available from 6 of the 9 patients in the Wuhan University study found all samples to be negative for SARS-CoV-2. No studies to date have determined whether the virus can be shed vaginally, and it remains unclear what risks COVID-19 poses to maternal and fetal outcomes.

There continue to be many unanswered questions about COVID-19, and the duration of viral shedding is no exception; there is not enough published data to determine exactly how long patients are contagious or how long they should continue to be tested. A large retrospective cohort study of 147 patients with COVID-19 in Changsha, China, found the median viral shedding duration to be 17 days, with a range from 6-47 days [4]. Other supporting studies show median shedding of 22 days for mild cases and 33 days for severe COVID infections and define “prolonged duration” of viral shedding as being greater than 15-33 days [5-7]. As new data become available, guidelines on testing and treatment of patients continue to be updated. No standard of care has been established for real-time polymerase chain reaction (RT-PCR) testing – and especially not in the pregnant population. In this case report, we will describe a primigravida patient infected with SARS-CoV-2 who

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remained in prolonged isolation for over 6 weeks due to persistent positive testing.

Case Presentation

Our patient is a 36-year-old gravida 1 para 0, previously healthy female who was confirmed to have preterm premature rupture of membranes (PPROM) at 19 weeks of gestation. She underwent counseling regarding pre-viable PPRM by the perinatology team at an outside hospital and was provided options of termination versus expectant management at that time. After counseling, she elected for expectant management with plans for admission at 22 weeks and 5 days gestation. Her pregnancy was otherwise complicated by iron-deficiency anemia and being non-English speaking, having emigrated from Haiti two years prior.

Upon admission to our tertiary care center at 22 weeks and 5 days, she only reported complaints of clear leakage of fluid. She denied uterine contractions, vaginal bleeding, or abnormal vaginal discharge. She reported an intermittent dry cough for one month. She did not have associated fever or chills, chest pain, shortness of breath, congestion, gastrointestinal symptoms, anosmia, or ageusia. She had not recently traveled, and she denied any known exposures to people with COVID-19. Due to increased risk for fetal and maternal infection that would require prompt delivery, the patient was counseled about the need for admission until delivery. After a thorough discussion with the patient and her husband, she elected for inpatient admission, latency antibiotic therapy beginning at 22 weeks and 5 days, and antenatal corticosteroids and fetal monitoring starting at 23 weeks of gestation. She was noted to have a normal fetal anatomy ultrasound one week prior to admission.

On physical examination, the patient was afebrile and normotensive, with a normal respiratory rate and normal oxygen saturations (>95% on room air). Her cardiac exam was unremarkable, and lung auscultation was clear throughout all lung fields. Her cervix was visually assessed and noted to have clear normal fluid leakage from the cervical os, and it did not appear dilated. On admission, a bedside ultrasound revealed that estimated fetal growth was appropriate for gestational age (estimated fetal weight 506 g, at the 39th percentile). The fetus was in cephalic presentation with oligohydramnios (maximum vertical pocket 0.59 cm), as expected with PPRM.

Due to departmental policy regarding SARS-CoV-2 testing for all admitted patients and given her reported history of cough, a Roche SARS-CoV-2-RNA rapid test was performed on a collected nasopharyngeal swab and resulted positive. In response, the patient was transferred to a negative pressure room on our obstetric care unit (OBCU), placed on telemetry, and reflexive testing was performed including a chest X-ray (CXR), complete blood count (CBC), lactate dehydrogenase (LDH), ferritin, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and cardiac troponins. Though her lab reports were normal, her CXR demonstrated "mild hazy opacities at both lung bases without consolidation."

The patient was closely monitored for the development of a fever, oxygen desaturations, and increased work of breathing. Her negative pressure room included a video monitor to minimize direct contact. Antepartum management, as outlined above, included latency antibiotics

for seven days, antenatal corticosteroids, and daily fetal monitoring with the fetal non-stress test (NST). She had a resolution of her dry cough on day 3 of admission. On day 6, the patient had intermittent desaturations (92-93%) overnight during sleep and required 1 liter/min of supplemental oxygen to achieve oxygen saturation of >95%. She was able to come off supplemental oxygen later that day and saturated well on room air for the remainder of her admission.

The patient was tested for SARS-CoV-2 every 7 days following admission, per our hospital's infection control guidelines. On the third week of testing, the patient expressed frustration and sadness that she must go through the discomfort and pain of swabbing when she is asymptomatic. There were concerns that her mood, engagement, and even appetite was being affected due to prolonged isolation. During her admission, she had a detailed antenatal ultrasound demonstrating compromised fetal lung development (small chest and increased cardiothoracic ratio). During the interdisciplinary meeting, there was an extensive discussion to educate the patient regarding pulmonary hypoplasia and the poor neonatal prognosis involved with this diagnosis. Ultimately, the patient decided to continue expectant management of PPRM until 34 weeks of gestation, at which time delivery would be recommended with Neonatal Intensive Care Unit (NICU) present to resuscitate as indicated.

The patient had positive SARS-CoV-2 RNA tests for six consecutive weeks despite the resolution of mild symptoms during her first week of admission. After multiple discussions with the infectious disease medical team, the decision was made to remove enhanced contact and droplet precautions after 42 days of hospitalization without symptoms, with no plans for further testing. The patient developed preterm labor at 29 weeks and 5 days gestation and underwent an uncomplicated vaginal delivery.

Our patient gave birth to a female with Apgar scores of 8 & 8, at one and five minutes, respectively. Birth weight was 1450 g, and weight to age percentile was 75%. Neonatal testing for SARS-CoV-2 was negative at 24 and 48 hours, making the neonate no longer a person under investigation for COVID-19. The neonate has been admitted to the NICU for over 6 weeks, while our patient was discharged on postpartum day one. The neonate's admission has been complicated by septic ileus, feeding intolerance with bilious gastric output, high-frequency jet ventilation in the setting of increased work of breathing, and pneumothorax requiring bilateral chest tube placement, and continued failure to wean from supplemental oxygen. The patient continues to advocate for her daughter to receive all possible interventions to prolong life. She is able to visit the neonate in the NICU a few times per week, and otherwise, she remains at home in self-isolation. The neonate will be transferred to a hospital closer to her parents' home in the coming days, where she will continue to require intensive care.

Discussion

I COVID-19 and Prolonged Isolation

Our case calls into question whether the risk of prolonged viral shedding outweighs the risk of prolonged isolation. In the case of our patient, it is important to consider the effect of isolation on patient well-being.

Additionally, contact isolation is associated with shorter and fewer interactions with healthcare workers, more depressive symptoms, prolonged hospital stay, and lower standards of care [8]. A case-controlled study investigating the effect of isolation on patients with multi-drug resistant infections demonstrated that adopting contact precautions and isolation can further negatively impact social functioning, sleep, and quality of life [8]. Clearly, isolation can have repercussions for patients, and we would argue that, in order to provide the most quality care, patients should be taken off strict isolation as soon as it is medically safe to do so without putting patients or healthcare providers at risk for spreading the virus.

II Pregnancy and Immune System Compromise

Regarding the prolonged viral detection in this patient, it is widely known and accepted that pregnancy compromises the immune system [9, 10]. There are many examples of viral infections that pregnant individuals are more likely to be susceptible to or more likely to develop severe complications compared to non-pregnant individuals, including herpes simplex virus (HSV), influenza, smallpox, Lassa fever, Ebola, and SARS. HSV is one of the most common sexually transmitted viral diseases worldwide, but it becomes a serious health risk for pregnant women compared to their non-pregnant counterparts. Pregnant women with a primary HSV infection are more likely to develop disseminated skin lesions associated with visceral involvement such as hepatitis, encephalitis, thrombocytopenia, leukopenia, and coagulopathy with a mortality rate approaching 50 percent [11].

A similar phenomenon is seen in pregnant women diagnosed with influenza. Pregnant women are at increased risk for influenza-related severe illness resulting in hospitalization and death. During the 2009 H1N1 pandemic, pregnant patients accounted for 1% of patients infected with influenza A subtype H1N1 virus, but they accounted for 5% of all H1N1-related deaths [12]. Some hypothesize that pulmonary viruses are likely to be more severe in pregnant women, especially in the third trimester, when decreased maternal lung capacity might increase the risk for severe disease from viruses that target the lower pulmonary lobe [12, 13]. Another theory of immune response changes during pregnancy is the idea of generalized immune suppression to reduce the likelihood of an antigen-specific response against the semi-allogenic fetus [13].

III SARS-CoV-2 and Prolonged Viral Shedding

While it seems plausible from both physiologic and immunologic perspectives that pregnancy may prolong viral shedding, the longest known SARS-CoV-2 shedding to date was about 60 days in a non-pregnant 71-year-old woman who recovered from the mild disease [14]. Several studies have begun to look at the duration of viral shedding and risk factors for prolonged shedding [5-6]. A study of 49 people with COVID-19 of varying severity found an estimated time to loss of nasopharyngeal shedding of up to 45.6 days, with a longer median shedding duration in severely ill patients, although the sample size was small [6]. Risk factors for prolonged viral shedding were also studied in a retrospective cohort of 113 patients, where prolonged shedding >15 days was more likely in men with severe disease and those treated with corticosteroids, although the study did not mention the pregnancy status of women or stratify participants based on this [7].

Previous studies looking at both influenza virus and community-acquired human coronavirus demonstrated that viral loads in asymptomatic carriers are relatively low [15]. In contrast, a study looking at patients in a skilled nursing facility in Washington State showed that approximately half of all residents with positive test results were entirely asymptomatic, and there was no significant difference in the quantity of viral RNA in symptomatic versus asymptomatic patients – both had large quantities of viral RNA [16]. Despite being largely asymptomatic, our patient continued to have at least six weeks of consecutive positive RT-PCR SARS-CoV-2 results. In the environment of a novel coronavirus, it is possible that our patient will more closely follow trends of asymptomatic patients in China and Washington State studies rather than studies that investigate influenza and previous coronaviruses. Because of this possibility for asymptomatic patients to have large quantities of viral RNA, it is prudent to isolate patients with positive RT-PCR tests regardless of the presence or absence of symptoms. Additional studies on the natural history of COVID-19 and viral shedding in pregnancy are urgently needed to provide the best guidelines for isolation and to improve patient care.

In Changsha, China, prolonged duration of viral shedding was found to be associated with patients who had the highest temperatures (38.3 °C) on admission ($p = 0.028$), the longest time from symptom onset to admission ($p < 0.001$), and longest hospital length of stay ($p < 0.001$) [4]. Another study conducted in Qingdao, China, defined the communicable period as the duration from the first positive RT-PCR COVID-19 test to the first successive negative detection and found the median duration to be 14 days. Longer communicable periods in this study were associated with older age and chest tightness [17]. As is the case in older patients, pregnant women might also experience longer periods of viral shedding, as both patient populations experience immune system compromise.

IV Diagnostic Testing for SARS-CoV-2

Knowledge of diagnostic tests for SARS-CoV-2 is still evolving and understanding how to interpret the findings of these tests is crucial. Thus far, the most reliable test being used is the RT-PCR test performed using nasopharyngeal swabs or other upper respiratory tract specimens, and this was the test used for our patient [18]. Of note, a positive PCR result does not necessarily mean that a viable virus is present; it only reflects the detection of viral RNA [18]. There have been reports that viral RNA has been detected by RT-PCR beyond six weeks of the first positive test, but studies have shown that the SARS-CoV-2 cannot be isolated in culture beyond day 8 of illness onset, which correlates with the decline in infectivity beyond the first week [18].

This supports the “symptom-based strategy” of isolating patients for at least ten days after symptoms first appear – the Centers for Disease Control and Prevention (CDC) recommends this strategy to prevent contagious individuals from spreading the virus. Some published studies suggest that patients should not be discharged or taken off isolation until they have two consecutive negative RT-PCR tests within 24 hours, though these studies do not investigate the use of cultures to determine the presence of the viable virus [19]. Because asymptomatic patients have been reported to spread COVID-19, it is appropriate, based on our current understanding of the virus, to isolate patients who are testing

positive in order to prevent the spread of a virus that has caused worldwide devastation.

V Proposed Guidelines for SARS-CoV-2 Testing in Pregnant Patients

Longer hospital stays put patients at higher risk for nosocomial infection, and isolation has significant negative impacts on mental health, so it would be in the best interest of patients to limit isolation to only what is absolutely necessary to prevent viral spread. Continuing to re-test asymptomatic patients, like ours, with RT-PCR seems unnecessary if positive testing does not necessarily indicate viable virus [18]. Perhaps a modified approach to isolating patients using a combination of RT-PCR results and follow up cultures to determine the presence of viable virus should be investigated to prevent unnecessary re-testing and isolation. Ultimately, we should be treating the patient and not the lab result, but with a risk of asymptomatic viral shedding, we do not want to perpetuate the pandemic by avoiding isolation for patients who need it.

There continue to be many unanswered questions about COVID-19, and the duration of viral shedding is no exception. Though there is not enough published data to determine exactly how long patients are contagious or how long we should continue to test them, there is significant evidence for the potential of asymptomatic viral shedding [20]. As new data becomes available, guidelines on testing and treatment of patients continue to be updated. Though no standard of care has been established for RT-PCR testing – and especially not in the pregnant population, some hospital policies require patients to have two consecutive negative tests within 24 hours before they can be discharged [19]. In our case, in collaboration with the division of Infectious Diseases at our institution, SARS-CoV-2 weekly re-testing was discontinued after 42 days without symptoms, given the unavailability of any standard guidelines for re-testing in pregnancy. The patient's status was de-escalated from a negative pressure room to contact and droplet precautions, which continued to provide a degree of protection without as many limitations to the day to day care of the patient.

Certainly, we would not advocate for policies that put other patients or health providers at risk for spreading COVID-19, and we promote isolation for patients testing positive for SARS-CoV-2 based on the understanding of the virus that we have at this time. However, if the viral cultures that follow up persistently positive RT-PCR testing indicate that no viable virus is present, it may be reasonable to take patients off strict negative pressure isolation to improve patient mood, recovery, and the quality of care that they receive. Further studies are necessary to understand the effect of SARS-CoV-2 on the viral shedding of pregnant patients and to develop guidelines for RT-PCR re-testing in pregnant patients who test positive and may be at risk for prolonged isolation. As we continue to learn more about the virus, we are hopeful that there will be clarification on how long patients need to remain isolated to prevent viral spread. We are optimistic that we can prevent the viral spread and protect patients as well as health care providers, while also advocating for the removal of strict isolation precautions as soon as it is medically safe.

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Conflicts of Interest

None.

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