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False-negative testing for severe acute respiratory syndrome coronavirus 2: consideration in obstetrical care

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Because the obstetrical population seems to have a high proportion of asymptomatic patients who are carriers of severe acute respiratory syndrome coronavirus 2, universal testing has been proposed as a strategy to risk-stratify all obstetrical admissions and guide infection prevention protocols. Here, we describe a case of a critically ill obstetrical patient with all the clinical symptoms of coronavirus disease 2019 and 3 false-negative results of nasopharyngeal swabs for molecular testing. We review and discuss the uncertain clinical characteristics of current severe acute respiratory syndrome coronavirus 2 molecular testing and the implications of false-negative results in the obstetrical population.

Key words: coronavirus, COVID-19, diagnostic test sensitivity, pregnancy, SARS-CoV-2

Introduction

Real-time reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal (NP) swabs for severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) is the most commonly used test for the diagnosis of coronavirus disease 2019 (COVID-19); however, there is limited information regarding the characteristics of the diagnostic test including negative and positive predictive values, especially in pregnancy.

Case

A primiparous woman at 33 weeks' gestation presented to the obstetrical triage unit complaining of contractions, emesis, and cough for 2 days. She had fever, tachycardia, tachypnea, lymphopenia, and mild elevation of liver enzymes. The fetus had reassuring testing, and her cervix was closed. Her body mass index was 37.1 kg/m^2, with no other comorbidities. A chest radiograph showed subsegmental atelectasis without consolidation. Blood cultures, a respiratory virus panel, and a PCR of an NP swab for SARS-CoV-2 were sent to a laboratory for testing. Empirical antibiotic therapy was initiated.

It was noted that her admission NP PCR test for SARS-CoV-2 obtained on day 3 of symptoms was inadvertently sent out to a national reference laboratory, and thus, a second test was performed in the hospital on day 4 of symptoms for more timely results. Both tests returned negative on the same day. Chest computed tomography revealed bilateral areas of consolidation and ground-glass opacification (Figure). All other infectious test results were negative. In case the previous 2 tests obtained by the obstetrical staff were limited by inadequate sampling, a third NP PCR test for SARS-CoV-2 was obtained by the intensive care unit (ICU) staff on day 4 of symptoms. The third test returned negative the next day. During hospitalization, the patient's cardiopulmonary status worsened, and she was intubated. Given persistent maternal tachycardia at 150–160 bpm, high fever requiring increasing amounts of vasopressor support, and fetal heart tracing with minimal variability, the team proceeded with primary cesarean delivery. The neonate had Apgar scores of 1, 6, and 7, at 5, 10, and 15 minutes after delivery, respectively.

Bronchoalveolar lavage (BAL) performed after intubation by the ICU team revealed negative mycobacteriology and acid-fast stain, respiratory panel PCR,

FIGURE
Axial and coronal computed tomography images of the chest indicating severe bilateral disease

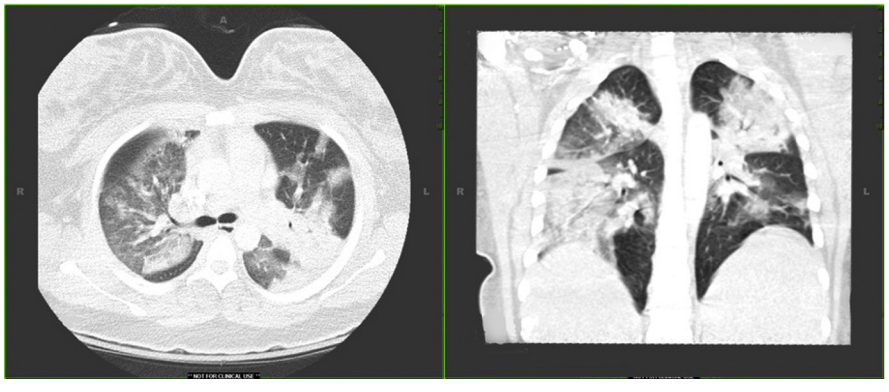

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TABLE
Current reports of false-negative RT-PCR test of NP swabs for SARS-CoV-2

Author	Country of origin	Study design	Primary aim	Total (N)	False negatives (%)	Positive on first test (%)	Positive on second test (%)	Positive on third test (%)	Maximum number of tests to obtain positive
Fang et al[1]	China	Retrospective cohort	Comparison of chest CT with RT-PCR	51	15 (29.4)	36 (70.6)	12 (23.5)	2 (3.9)	4
Wang et al[2]	China	Retrospective cohort	Comparison of RT-PCR results in different anatomic samples of confirmed cases	Nasal: 8 Pharyngeal: 398	Nasal: 3 (37.5) Pharyngeal: 272 (68.3)	NS	NS	NS	NS
Yang et al[3]	China	Retrospective cohort	Comparison of RT-PCR results in different anatomic samples and time points of confirmed cases[b]	Nasal: 445 Throat: 158	Nasal: 157 (35.3) Throat: 74 (46.8)	NS	NS	NS	NS
Xiao et al[5]	China	Case series	Review of all RT-PCR tests that turned positive after initial negative test in 1 hospital	70	70 (100)	0 (0)	55 (78.6)	15 (21.4)	3
Ai et al[6]	China	Retrospective cohort	Comparison of chest CT with RT-PCR	1014	250[a] (24.7)	601 (59)	NS	NS	NS
Long et al[7]	China	Retrospective cohort	Comparison of chest CT with RT-PCR	36	6 (16.7)	30 (83.3)	3 (8.3)	3 (8.3)	3
Li et al[8]	China	Retrospective cohort	Review of RT-PCR tests in all patients diagnosed as having COVID-19 by chest CT in 1 hospital	610	384 (63.0)	168 (27.5)	48 (7.9)	7 (1.1)	5
Wang et al[9]	China	Case report	Case report from Beijing	1	1 (100)	0 (0)	0 (0)	0 (0)	BAL required
Guo et al[10]	China	Retrospective cohort	Comparison of serum antibody testing with RT-PCR	208	58 (27.9)	NS	NS	NS	NS
Chen et al[11]	China	Case report	Case report from Hangzhou	1	1 (100)	0 (0)	1 (100)	0	2
Li et al[12]	China	Case series	Two-patient case series from Beijing	2	2 (100)	0 (0)	1 (50)	1 (50)	2
Feng et al[12]	China	Case report	Case report from Zigong	1	1 (100)	0 (0)	0 (0)	0 (0)	5

BAL, bronchoalveolar lavage; *COVID-19*, coronavirus disease 2019; *CT*, computed tomography; *NP*, nasopharyngeal; *NS*, not specified; *RT-PCR*, reverse transcription polymerase chain reaction; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

[a] Based on CT scan findings and clinical correlation.; [b] Results from 14 days of symptom onset included.

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legionella culture, cytomegalovirus PCR, aerobic culture and Gram stain, and adenovirus PCR; however, RT-PCR of the BAL for SARS-CoV-2 returned positive.

The patient remained intubated and in critical condition for 11 days. At the time of writing, she had been successfully extubated and transferred to a coronavirus disease—designated floor. The neonate was in good condition on room air in the neonatal ICU. NP RT-PCR for SARS-CoV-2 performed on the neonate on day 5 of life returned negative.

Discussion

Three separate NP RT-PCR tests for SARS-CoV-2 from 2 institutions returned negative for a patient who was critically ill with a constellation of symptoms and laboratory findings consistent with COVID-19, suggesting that false-negative testing is a clinically relevant problem not limited to a single platform with current testing strategies. In the nonpregnant population, sources of variability in RT-PCR testing results include the anatomic area sampled, quantity of virus present, stability of the RNA, time point in disease course, and assay variability.[1–3] False-negative result ranges of 17%—63% for NP RT-PCR for SARS-CoV-2 have been reported in 12 studies in nonpregnant patients[1–12] (Table); however, without clear gold standard tests available, diagnostic test characteristics including sensitivity, specificity, and positive and negative predictive values of RT-PCR assays for SARS-CoV-2 are difficult to determine.[1–3] Sensitivity of BAL samples appeared to be higher than NP or oropharyngeal swabs; however, BAL requires invasive and high-risk aerosolizing bronchoscopy to obtain a sample.[2,3]

False-negative testing of NP RT-PCR for SARS-CoV-2 is a clinically relevant problem with multiple important implications, especially in pregnant women with suspicion for severe and/or critical COVID-19. Clinical implications are listed as follows:

1. Repeating NP RT-PCR testing for SARS-CoV-2 may be required for a positive result, as much as 3—5 times.
2. PCR testing of BAL for SARS-CoV-2, a high-risk procedure, can be performed after negative NP PCR results for SARS-CoV-2 if there is high clinical suspicion of COVID-19 and diagnosis is required for disposition.
3. Initially, negative test results should not change clinical management.
4. Protocols should not allow for removal of precautions with a negative SARS-CoV-2 test if there is high suspicion of COVID-19.
5. All NP swab testing should be performed by a specialized team, if possible, to improve uniformity in collection technique.
6. A universal testing strategy cannot be used as the single solution to risk-stratify patients and determine infection prevention measures.
7. True population estimates of COVID-19 are likely much underestimated.

The most prudent strategy may be to presume that all patients are infected and use the best available infection prevention strategy possible during the duration of this pandemic. ■

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