False-Negative COVID-19 Testing: Considerations in Obstetrical Care

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False-Negative COVID-19 Testing: Considerations in Obstetrical Care

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The authors report no conflicts of interest.

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3 **Keywords**: COVID-19, SARS-CoV-2, pregnancy, coronavirus, diagnostic test sensitivity

Introduction: Real-time reverse transcriptions-polymerase chain reaction (RT-PCR) of nasopharyngeal (NP) swabs for SARS-Cov-2 are most commonly used for diagnosis of COVID-19 infection, but there is limited information regarding the diagnostic test characteristics including negative and positive predictive values, including in pregnancy.

Case: A primiparous woman* at 33 weeks' gestation presented to the obstetrical triage unit complaining of contractions, emesis, and cough for two days. She had fever, tachycardia, tachypnea, lymphopenia and mild elevation of liver enzymes. The fetus had reassuring testing, and her cervix was closed. Her BMI was 37.1 kg/m^2, with no other co-morbidities. A chest radiograph showed subsegmental atelectasis without consolidation. Blood cultures, respiratory virus panel, and a NP swab for SARS-CoV2 PCR testing were sent. Empiric antibiotic therapy was initiated.

It was noted that her admission NP SARS-CoV2 PCR test obtained on day 3 of symptom was inadvertently sent out to a national reference laboratory, and thus a second test was performed on day 4 of symptom in-hospital for more timely results. Both tests resulted negative on that same day. Chest computed tomography revealed bilateral areas of consolidation and ground-glass opacification (Figure). All other infectious test results were negative. A third NP SARS-CoV2 PCR was obtained by the ICU staff on day 4 of symptoms, in case the prior two tests obtained by the obstetrical staff were limited by inadequate sampling. This test also resulted as negative the next day. The patient’s cardiopulmonary status further worsened, and she was intubated. Given persistent maternal tachycardia at 150-160 bpm and

high fever requiring increasing amounts of vasopressor support, and fetal heart tracing with minimal variability, the team proceeded with a primary cesarean delivery. The neonate had Apgar scores of 1, 6, and 7 at 5, 10, and 15 minutes, respectively.

Bronchoalveolar lavage (BAL) performed after intubation by the ICU team revealed negative mycobacteriology and acid-fast stain, respiratory panel PCR, legionella culture, cytomegalovirus PCR, aerobic culture and gram stain, and adenovirus PCR; however, SARS-CoV2 RT-PCR of the BAL returned positive.

The patient remained intubated and in critical condition for 11 days. At the time of writing, she has been successfully extubated and transferred to a COVID-designated floor. The neonate is in good condition on room air in the neonatal ICU. NP SARS-CoV2 RT-PCR performed on the neonate on day of life 5 resulted negative.

Discussion: Three separate NP SARS-CoV2 RT-PCR tests from two institutions resulted as negative for a patient who was critically ill with a constellation of symptoms and lab findings consistent with COVID-19 infection, suggesting that false-negative testing is a clinically relevant problem not limited to a single platform with current testing strategies. In the non-pregnant population, sources of variability in RT-PCR testing results include the anatomic area sampled, quantity of virus present, stability of the RNA, timepoint in disease course, and assay variability.[1-3] False-negative result ranges of 17-63% for NP SARS-CoV2 RT-PCR have been reported in non-pregnant patients (Table); however, without clear gold standard tests available, diagnostic test characteristics including sensitivity, specificity, positive and negative predictive values of SARS-CoV2 RT-PCR assays are difficult to determine. [1-3] Sensitivity of BAL samples

appear to be higher than nasopharyngeal or oropharyngeal swabs, but requires invasive and high-risk aerosolizing bronchoscopy to obtain a sample.[2,3]

False-negative testing of NP SARS-CoV2 RT-PCR is a clinically relevant problem with multiple important implications, especially in pregnant women with suspicion for severe/critical COVID-19 infection: 1) Repeating NP SARS-CoV2 RT-PCR testing may be required for a positive result, as much as 3-5 times; 2) BAL SARS-CoV2 testing, a high-risk procedure, can be performed after negative NP SARS-CoV2 results if there is high clinical suspicion of COVID-19 infection 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-CoV2 test if there is high suspicion of COVID-19 infection; 5) All NP swab testing should 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 the disease are likely much underestimated,.

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

*The patient's age was omitted to protect her identity.

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Figure 1. Axial and coronal computed tomography images of the chest demonstrating severe bilateral disease.

CRediT author statement

Kelly: conceptualization, investigation, writing – original draft/editing/review & editing **Dombrowski:** conceptualization, writing- review & editing, supervision **O'neil-Callahan:** writing- review & editing, investigation **Kernberg:** software, writing- review & editing investigation **Frolova:** writing- review & editing, investigation **Stout:** conceptualization, investigation, writing– original draft/editing/review & editing, supervision

Table: Current reports of false-negative RT-PCR nasal and/or pharyngeal swab testing for COVID-19

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

NS: not specified
BAL: bronchoalveolar lavage
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*Based on CT-scan findings and clinical correlation
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