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Research Article

Concept of Cycle Threshold Values in SARS-Cov-2 Positive Patients at Childbirth Admission: A Retrospective Cohort Study

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Abstract

Objective: To evaluate relationships between cycle threshold values and COVID-19 presentations and clinical courses in women presenting for childbirth. Cycle threshold values from polymerase chain reaction (PCR), testing are inversely proportional to viral burden and may be important predictors of disease state and infectivity risk.

Design: Retrospective cohort study.

Setting: Three Yale-New Haven Health Hospitals between 4/2/2020-5/14/2020.

Population: Women presenting for childbirth who underwent SARS-CoV-2 PCR testing.

Methods: Electronic health records were reviewed for socio-demographics, medical comorbidities, pregnancy and postpartum course, and COVID-19 symptoms and exposures. Records of SARS-CoV-2 positive women were reviewed for symptom onset, duration, and relation to test timing, disease course, and neonatal SARS-CoV-2 results.

Main Outcome Measures: SARS-CoV-2 real-time PCR cycle threshold values from positive tests were compared between asymptomatic and symptomatic women and in relation to disease severity. In women with symptomatic COVID-19, cycle threshold values were evaluated as a function of time since symptom onset.

Results: 1,210 women gave birth during the study period with 84 (6.9%), positive for SARS-CoV-2. Higher cycle threshold values were seen in asymptomatic SARS-CoV-2 positive patients (8/38 (21.1%), of asymptomatic women had cycle threshold <30 compared to 22/32 (68.0%), of symptomatic women, p<0.0001). In symptomatic women, values increased as time from symptom onset increased.

Conclusion: This study demonstrates higher cycle threshold values in asymptomatic patients and symptomatic patients tested remote from symptom onset, signifying older infections and detection of lower levels of viral RNA. Assessment of standardized cycle threshold values may help to understand disease characteristics and progression.

INTRODUCTION

SARS-CoV-2 is a single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Many infected patients are asymptomatic, pre-symptomatic, or have an indolent course but are responsible for a significant portion of disease transmission [1-3]. Early studies found that asymptomatic women represent the majority of patients found positive for SARS-CoV-2 during childbirth admission [4-7], prompting implementation of universal SARS-CoV-2 testing on many labor and delivery units to identify positive cases and enact precautions to protect patients, newborns, and healthcare workers. However, given highly sensitive polymerase chain reaction (PCR), tests that can detect nonviable virus particles, patients can test positive long after initial symptoms and clinical infectivity. It is unknown if asymptomatic individuals with positive tests have an old, new, or emerging infection.

This summer, the American Academy of Pediatrics revised newborn care recommendations. Initial recommendations for temporary neonatal separation have evolved to rooming-in together with infection control measures. However, in one national registry, 2-5% of infants born to women positive for SARS-CoV-2 tested positive 24-96 hours after birth. Infant illness after hospital discharge was not reported [8,9].Thus, determination of a patient's level of infectivity would add a

critical component to obstetrical providers' ability to provide safe, nuanced care to each patient.

Most hospital-based SARS-CoV-2 testing is accomplished through real-time reverse transcriptase polymerase chain reaction (RT-PCR). Viral detection is determined by cycle threshold values, which represent the number of RNA amplification cycles required for fluorescent signal to cross a threshold detection value in comparison to a reference curve. While cycle threshold values are not direct measures of viral load, they are inversely proportional to the amount of nucleic acid in the sample. Lower values imply higher levels of detected viral particles. Detection alone does not signify the presence of active, replicating virus [10]. In one study, SARS-CoV-2 was cultured from samples with cycle threshold values up to 34; all samples with value 13-17 led to positive culture, with culture positivity decreasing to 12% at a cycle threshold value of 33 cycles [11]. The relevance of cycle threshold values have not yet been studied in the obstetric population. Understanding of cycle threshold patterns would be of particular relevance in pregnant women, as many are asymptomatic and unsure how SARS-CoV-2 positivity impacts obstetric care and interactions with their newborns.

The objective of this study is to evaluate relationships between cycle threshold values and COVID-19 presentations and clinical courses in a cohort of women presenting for childbirth.

METHODS

In this retrospective cohort study, we analyzed women with PCR testing for SARS-CoV-2 with birth between 4/2/2020 and 5/14/2020 at one community and two urban, academic hospitals of Yale-New Haven Health (Greenwich Hospital, Yale-New Haven Hospital, and Bridgeport Hospital), which handle approximately 10,000 deliveries annually. The study was approved by the Yale Institutional Review Board.

Electronic health records were reviewed for sociodemographic factors, co-morbidities, pregnancy course, SARS-CoV-2 testing, COVID-19 symptoms or known exposures, birth outcomes, and postpartum course. The selected timeframe corresponded to implementation of universal COVID-19 screening of labor admissions within the Yale delivery network on 4/2/2020 [6].

SARS-CoV-2 testing was performed using real-time RT-PCR analysis of nasopharyngeal swab specimens. Cycle threshold value cut-offs for viral detection were either 40 or 45 cycles depending on the test used. Patients were tested if they had symptoms suspicious for COVID-19 anytime during their pregnancy or universally upon childbirth admission. Women were considered recovered from an antepartum infection if at least 14 days had passed since symptom onset and more than 72 hours without fever. Recovered patients did not undergo repeat testing at childbirth admission.

Medical records of SARS-CoV-2 positive women were reviewed for symptom onset, duration, and timing of testing as related to symptom onset and birth. Women were considered asymptomatic if they had no symptoms of COVID-19. Symptomatic SARS-CoV-2 positive women were deemed to have peripartum disease if they had symptoms within 14 days of childbirth, at childbirth admission, or postpartum prior to hospital discharge. Symptomatic women were asked a detailed symptom history to determine disease timing and assist with clinical management.

Disease severity was assigned based on Society for Maternal-Fetal Medicine recommendations: asymptomatic defined as no symptoms, mild defined as symptomatic without dyspnea or abnormal chest imaging, moderate as evidence of lower respiratory tract disease (dyspnea, pneumonia on imaging, abnormal blood gas, refractory fever), severe defined as respiratory rate ≥ 30 breaths per minute or blood oxygen saturation <93%, PaO2/FiO2 <300, or >50% lung involvement on imaging, and critical as respiratory failure, shock, and/or multi-organ failure [12,13].

Race, ethnicity, marital status, and tobacco use were reported by patients during medical registration and abstracted from medical records. Pre-pregnancy body mass index (BMI), was obtained from the first prenatal visit or by last documented weight within two months of pregnancy. Co-morbidities and pregnancy outcomes were assessed by chart review of the cohort. Hypertensive disorders of pregnancy were identified during chart review by American College of Obstetricians and Gynecologists criteria [14]. Neonates of mothers positive for SARS-CoV-2 within 14 days of delivery were tested for the virus by RT-PCR of nasopharyngeal swab specimens after 24 hours of life. Women testing positive within 14 days of delivery were recommended to separate from their newborns to prevent horizontal viral transmission, per American Academy of Pediatrics recommendations at the time, and decided through shared decision-making. Neonatal separation was determined through review of maternal and neonatal medical records.

Cycle threshold values were obtained for all positive SARS-CoV-2 tests directly from each clinical laboratory, as well as gene targets and diagnostic threshold levels. A cycle threshold value below 40 was considered positive for all platforms except GeneXpert®, whose cut-off is 45 (Table 2).

Statistical analysis

Baseline characteristics including sociodemographic factors, medical comorbidities, and pregnancy outcomes are reported descriptively. Bivariate analysis to evaluate associations between patient characteristics was performed using Chi-square tests for categorical variables and T-tests or Fisher's exact tests for continuous variables if normally distributed, Mann-Whitney U tests if not normally distributed. Continuous variables are represented as mean with standard deviation (SD), for normally distributed data or median and interquartile ranges (IQR), for data not normally distributed.

Cycle threshold values from the nucleocapsid-2 (N2)-gene target probe were compared between asymptomatic and symptomatic women and presented as percentages of women with cycle threshold values at/above and below 30 cycles. This cut-off was chosen as low levels of viral RNA have been associated with a higher odds of being sampled during the convalescent period [15]. N2 was selected as the gene target given its high sensitivity and inclusion in the most commonly used tests in this study. These data are presented in total from the six-week period, as well as in two-week epochs to evaluate changes in presentation over time. Cycle threshold values are also compared by disease

severity. In symptomatic women, Ct values were evaluated by time since symptom onset by linear regression with residual plot assessment to ensure random scatter around the regression line. Statistical analysis was performed using *R Studio* (RStudio, PBC, Boston, MA).

RESULTS

Between 4/2/2020 and 5/14/2020, 84 of 1,210 (6.9%), women presenting for childbirth tested positive for SARS-CoV-2 at admission or antepartum. Twenty-three of 84 (27.4%), were diagnosed antenatally at least 14 days before childbirth admission and considered recovered at the time of childbirth. Sixty-one of 84 (72.6%), were diagnosed peripartum; 41 of 61 (67.2%), were asymptomatic upon universal admission testing and remained asymptomatic. Twenty of the 61 (32.8%), women diagnosed peripartum were symptomatic: 4/20 (20.0%), symptomatic before birth admission but tested during birth admission, 4/20 (20.0%), diagnosed with symptomatic COVID-19 within 14 days of birth, 10/20 (50.0%), symptomatic at the time of universal admission testing, and 2/20 (10.0%) asymptomatic at the time of birth admission but developed symptoms postpartum before hospital discharge. (Figure 1).

Overall, 1,187 women underwent universal screening at delivery hospitalization, as 23 were diagnosed antenatally and recovered. Universal screening identified 61 of 1,187 (5.1%), women positive for SARS-CoV-2 and an asymptomatic positivity rate of 3.5% (41 of 1,187 women). SARS-CoV-2 RT-PCR performed after 24 hours of life was negative in all neonates tested. Baseline patient characteristics are presented in Table 1 and pregnancy outcomes in Table 1.

Of the 84 SARS-CoV-2 positive women, 43 had symptoms (20 diagnosed peripartum and 23 diagnosed antepartum and considered recovered). 36/43 (83.7%), had mild disease, 6/43 (14.0%), had moderate disease, and 1 had severe disease. Of the 1,126 SARS-CoV-2 negative women, 62 (5.5%), experienced symptoms suspicious for COVID-19, mostly cough and congestion.

The six-week study period was divided into two-week segments to evaluate disease evolution. Over time, the percentage of asymptomatic SARS-COV-2 positive women increased: during the first epoch (4/2/20-4/16/20), 3 of 10 (30%) were asymptomatic, while in the last epoch (5/1/20-5/14/20), 17 of 20 (85%) were asymptomatic.

Cycle threshold values for the N2 gene target were available for 70 of the 84 (83.3%) SARS-CoV-2 positive women (and 58 of the 61 diagnosed by universal screening). Eleven testing platforms were used in our birth cohort. The majority of women (47), had at least one test performed on the Genexpert® platform. Sixteen patients had multiple tests performed, most on different test platforms. Twenty-two of the 32 (68.0%), symptomatic women had cycle threshold values <30, while only 8/38 (21.1%), asymptomatic women had cycle threshold values below 30 ($p<0.0001$). Cycle threshold values were then compared among those tested by Genexpert® to reduce laboratory confounding and similar relationships were seen (Figure 2) The median cycle threshold value was 34.2 (IQR 30.5-40.5), in asymptomatic women, 28.6 (IQR 22.8-33), in women with mild disease, and 25.5 (IQR 21.5-26.8), in women with moderate or severe disease (Figure 3). In the first two weeks, more women had cycle threshold value <30, with similar proportions in asymptomatic and symptomatic women. In the last two weeks, more symptomatic women had cycle threshold values <30 compared to asymptomatic women (Figure 4).

Hispanic women had similar rates of cycle threshold value <30 as women of non-Hispanic ethnicity (42.9% versus 35.1%, $p=0.448$). Obese women had similar rates of cycle threshold value <30 compared to non-obese women (36% versus 44.9%, $p=0.463$).

Linear regression analysis of cycle threshold values in symptomatic women based on test timing related to symptom onset demonstrates lower cycle threshold values when tested closer to the time of symptom onset (Figure 5). Of the symptomatic women with available cycle threshold values, 68.2% (15/22)

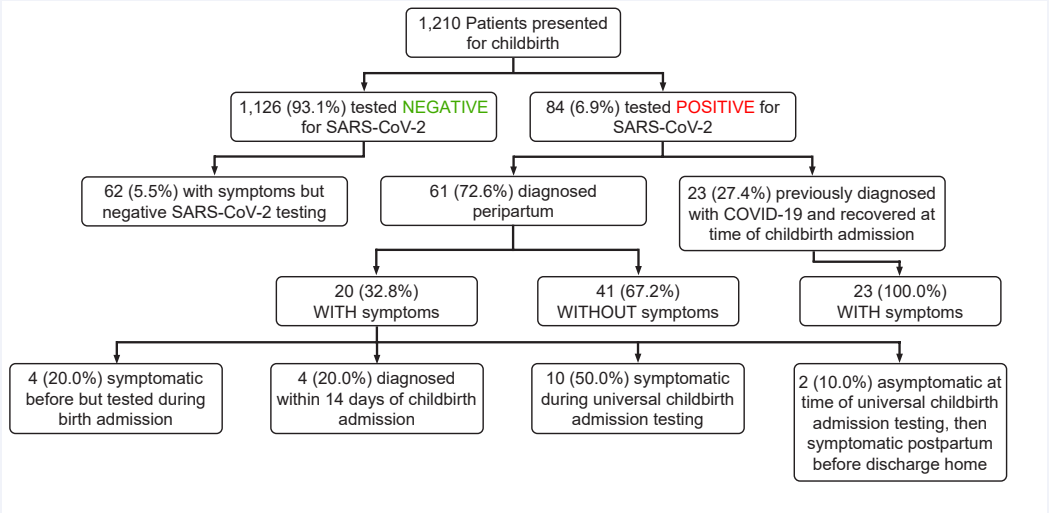

Figure 1 Flow diagram of the study cohort.

Table 1: Pregnancy Outcomes.

Characteristics	Total	COVID+	COVID-	*p*-value
	1210	84 (6.9%)	1126 (93.1%)	
Gestational age at delivery (weeks)				0.300
Median (IQR)	39 ± 2	39 ± 2	39 ± 2	
Delivery mode				0.677
Spontaneous vaginal	712 (58.8%)	53 (63.1%)	659 (58.5%)	
Operative vaginal	55 (4.5%)	4 (4.8%)	51 (4.5%)	
Cesarean	443 (36.6%)	27 (32.1%)	416 (36.9%)	
Hypertensive disorder of pregnancy				0.406
Any HDP	198 (16.4%)	17 (20.2%)	181 (16.1%)	
Gestational hypertension	80 (6.6%)	4 (4.8%)	76 (6.8%)	
Preeclampsia without severe features	31 (2.6%)	4 (4.8%)	27 (2.4%)	
Preeclampsia with severe features	80 (6.6%)	9 (10.7%)	71 (6.3%)	
HELLP Syndrome	4 (0.3%)	0	4 (0.4%)	
Birthweight (grams)				0.203
Median (IQR)	3390 (± 640)	3290 (± 580)	3395 (± 650)	
NICU Admission				0.132
Yes	116 (9.6%)	9 (10.7%)	107 (9.5%)	
No	1094 (90.4%)	75 (89.3%)	1019 (90.5%)	
Totals may not be 100% due to missing observations: 2 without documented birthweight				

Table 2: Pregnancy outcomes.

Characteristics	Total	COVID+	COVID-	*p*-value
	1210	84 (6.9%)	1126 (93.1%)	
Gestational age at delivery (weeks)				0.300
Median (IQR)	39 +/- 2	39 +/-2	39 +/-2	
Delivery mode				0.677
Spontaneous vaginal	712 (58.8%)	53 (63.1%)	659 (58.5%)	
Operative vaginal	55 (4.5%)	4 (4.8%)	51 (4.5%)	
Cesarean	443 (36.6%)	27 (32.1%)	416 (36.9%)	
Hypertensive disorder of pregnancy				0.406
Any HDP	198 (16.4%)	17 (20.2%)	181 (16.1%)	
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HELLP Syndrome	4 (0.3%)	0	4 (0.4%)	
Birthweight (grams)				0.203
Median (IQR)	3390 (+/-640)	3290 (+/-580)	3395 (+/-650)	
NICU Admission				0.132
Yes	116 (9.6%)	9 (10.7%)	107 (9.5%)	
No	1094 (90.4%)	75 (89.3%)	1019 (90.5%)	
Totals may not be 100% due to missing observations: 2 without documented birthweight				

had values <30 within 14 days of symptom onset, while 16.7% (2/12), had a value <30 more than 14 days after symptom onset (p=0.002). Similar cycle threshold value relationships were seen in women with moderate or severe COVID-19 compared to those with mild disease (Figure 6).

Symptoms were similar in women with cycle threshold values above and below 30, though women with values <30 trended toward higher rates of dyspnea (Figure 7).

Neonatal separation was chosen by 41 of the 61 (67.2%), women with peripartum diagnoses. Over time, fewer women chose neonatal separation (58.8% of women delivering from 4/2/20-4/16/20 compared to 41.7% of women delivering from 5/1/20-5/14/20). Fewer asymptomatic SARS-CoV-2 positive women chose separation from their newborns over time (100% of asymptomatic women in the first 2-week epoch, 47.6% of asymptomatic women in the last 2-week epoch).

DISCUSSION

Main Findings

This is the first study examining specifics of RT-PCR for detection of SARS-CoV-2 in an obstetric population. We found that the proportion of asymptomatic SARS-CoV-2 positive cases increased over the six-week period, while both the incidence and proportion of symptomatic women with COVID-19 decreased.

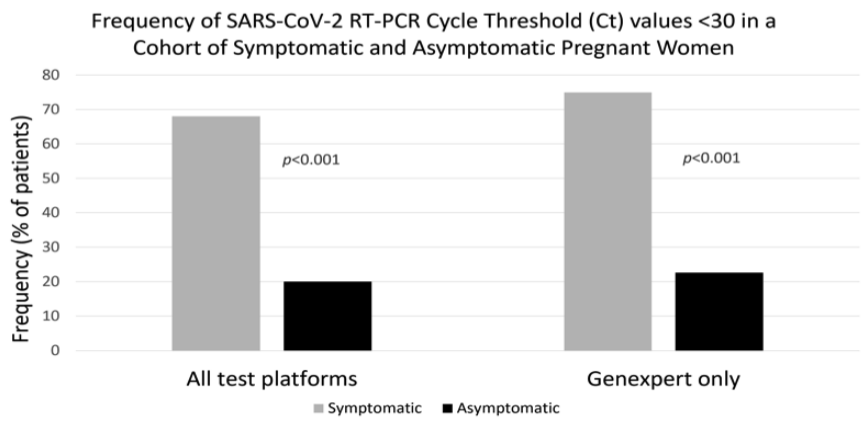

Figure 2 Cycle threshold values of N2 gene target. The grey bar depicts cycle threshold values <30 in all SARS-CoV-2 positive patients with available N2 gene target cycle threshold values across all platforms[1]. The black bar depicts N2 gene target cycle threshold values <30 in SARS-CoV-2 positive patients . on the Genexpert® platform.
Test platforms with N2 gene target: Genexpert® (Cepheid), CDC based EUA (Yale-New Haven Hospital, University of Washington, and BDMax)

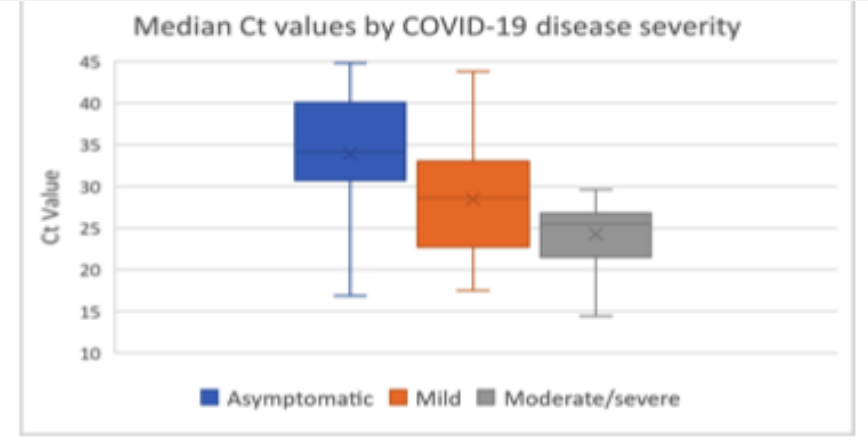

Figure 3 Box and whisker plot depicting median cycle threshold values with interquartile ranges based on disease severity, as categorized by World Health Organization recommendations adapted for physiologic changes of pregnancy. Moderate and severe grouped together, as there was only one patient with severe disease (p=0.001).

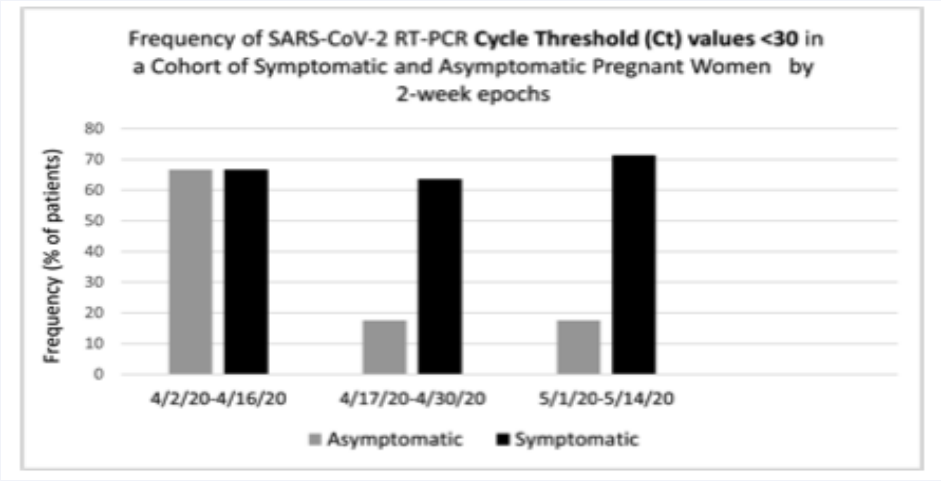

Figure 4 Cycle threshold value <30 of N2 gene target of SARS-CoV-2 positive women in two-week epochs of the study period.

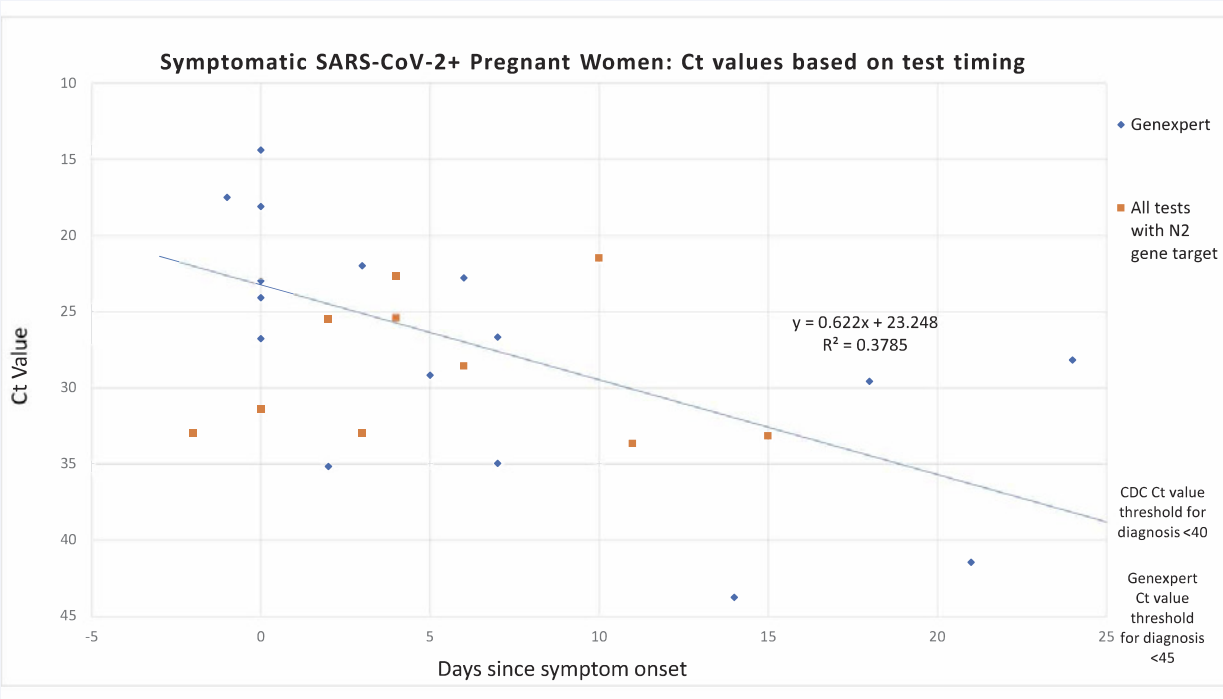

Figure 5 Cycle threshold values of symptomatic SARS-CoV-2 positive pregnant women as a function of time since symptom onset. Testing platforms are denoted in the legend. Laboratory-specified diagnostic threshold lines are drawn at cycle threshold value of 40 (utilized by most laboratories) and Ct 45 (utilized by Genexpert® platform, the most commonly for testing in our cohort).

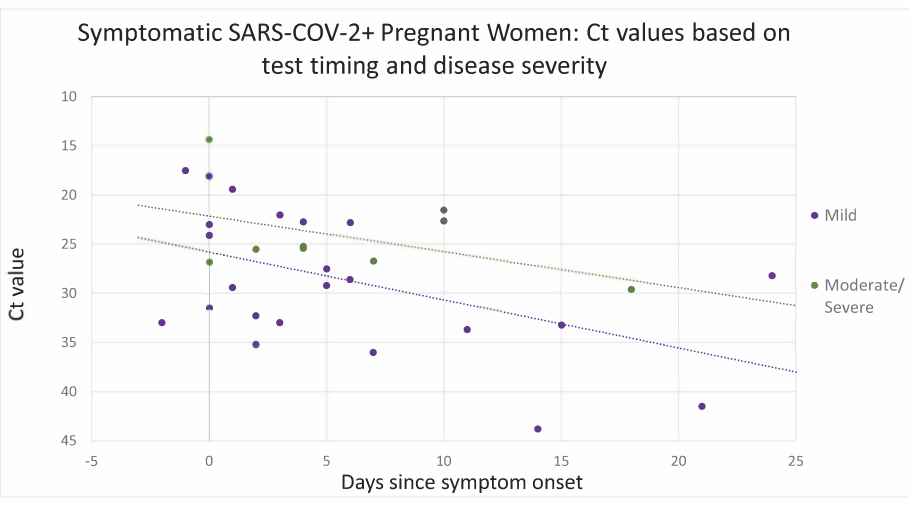

Figure 6 Figure depicts cycle threshold values of symptomatic women by disease severity as a function of time since symptom onset.

Of note, our health system experienced peak admissions for COVID-19 during the second two-week epoch.

Cycle threshold values were higher in asymptomatic women and more likely to be above 30. In symptomatic women, cycle threshold values were higher when tested further from the time of symptom onset. In fact, only 16.7% had a value below 30 when tested more than 14 days after symptom onset, whereas 68.2% of women tested within 14 days of symptom onset had cycle threshold values below 30.

Strengths and Limitations

Our study is comprised of a large, socio-demographically diverse cohort from a mixed setting of community and academic hospitals in a single geographic location, allowing for examination of trends in COVID-19 prevalence and severity over time. Our study confirms results of other centers, demonstrating disparities in SARS-CoV-2 infection, with a higher prevalence of SARS-CoV-2 positivity in women of Hispanic ethnicity, single marital status, and non-private insurance.

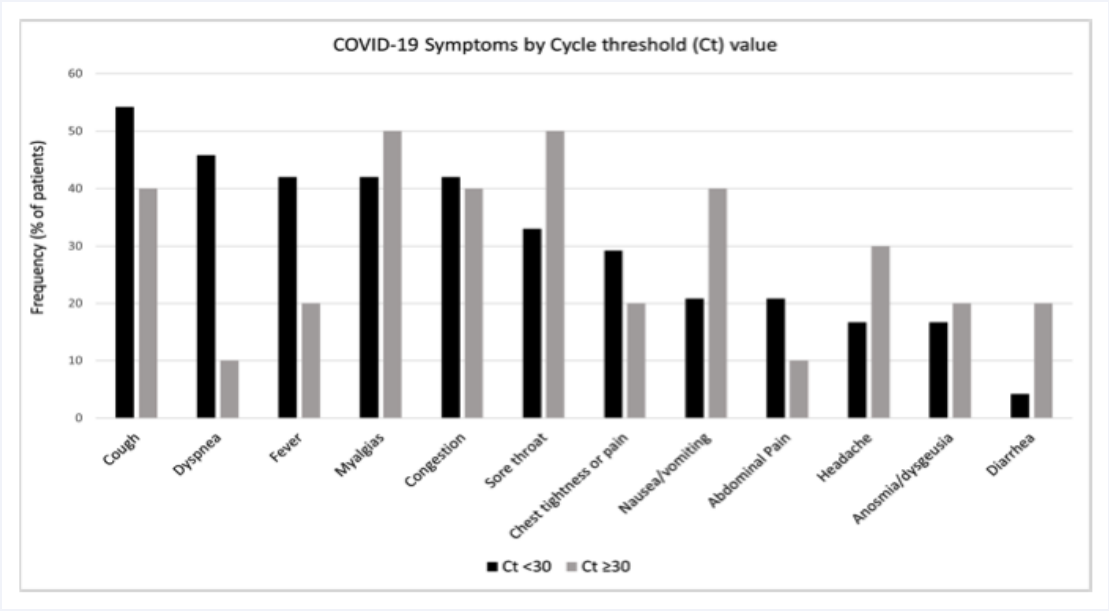

Figure 7 Bar chart depicting symptoms in women with symptomatic COVID-19 above and below cycle threshold value of 30. Dyspnea trended closest to achieving statistically significant difference in presenting as a symptom in patients with cycle threshold value <30 and ≥30 (p=0.060).

All patient charts were reviewed completely and individually, providing detailed, accurate information about patient baseline characteristics, co-morbidities, pregnancy outcomes, evaluation of COVID-19 symptoms and their relation to test time, and occurrence of maternal-neonatal separation.

There is heterogeneity in RT-PCR testing, clearly depicted in our study which included eleven different test platforms. Some tests generate cycle threshold values that are not transmitted to the laboratory information system and some tests report only if viral nucleic acid is detected, without Ct values. There are also differences between tests, including different gene targets, primers and probes, methods, and diagnostic criteria for positive and inconclusive results. In fact, variation among different RT-PCR runs and reagents can occur within a single laboratory [16]. Despite this variability, comparative analyses of primer-probe sets have shown high sensitivity for detecting SARS-CoV-2 RNA [17]. N2 was selected as this study's gene target given its inclusion in the majority of samples tested in our cohort.

Our study evaluates retrospective data, so we could not control for swabbing technique, though all were nasopharyngeal specimens. We were unable to follow cycle threshold value trends over time in the same patient, as almost all women with repeat testing had their RT-PCR performed on different platforms.

Symptom assessment could suffer from recall bias, as some women noted mild symptoms after receiving positive results. Many COVID-19 symptoms are vague or overlap with other conditions. One of two initially asymptomatic patients that then developed symptoms postpartum had a cycle threshold value >30; however, her symptoms of headache, cough, and congestion resolved within one day and did not recur.

Interpretation

Published data regarding universal testing at the time of delivery hospitalization are available from New York and Connecticut. Although positivity rates vary by location, the results all identify asymptomatic positive SARS-CoV-2 as the dominant result type [4-7,18].

Our results depict important trends in cycle threshold values, which have not been previously evaluated in obstetrics. Cycle threshold values were evaluated in relation to day of symptom onset in 17 non-pregnant patients in China, demonstrating higher viral loads soon after symptom onset with lower viral loads over time. This study, conducted in January 2020, differed from ours by finding that cycle threshold values were similar between asymptomatic and symptomatic patients [16,19]. We found that asymptomatic and symptomatic women had similar cycle threshold values early in our study period, but by May 2020, few asymptomatic women had low cycle threshold values. This may indicate older infections with detectable, but not active, virus. In early April, when we are at the peak of our hospital system's COVID-19 admissions, we predict that even asymptomatic cases may have been active, as the cycle threshold values were similar to those of symptomatic women.

Currently, cycle threshold values are used qualitatively- tests result as positive or negative based on specific cycle threshold value cut-offs. However, cycle threshold values have potential to provide a more nuanced understanding of a person's viral burden, especially when standardized against an international reference standard, though this is not yet available for SARS CoV-2. Evidence exists that quantitative viral loads correlate with qualitative results provided by cycle threshold values [20], which could allow for their use in individualizing clinical care [21].

Past studies have cautioned against integrating cycle threshold values into routine clinical use for several reasons. There is variability in test platforms even within the same patient sample. Furthermore, sample acquisition is dependent

on operator technique and may result in inadequate sampling for amplification [22]. In some severely ill patients, minimal nucleic acid may be detected in the nasopharynx as the virus has moved to the lower respiratory tract [23]. General guidelines recommend testing in sub-populations that are symptomatic or with high-risk exposures. Importantly, this study generates a hypothesis that cycle thresholds may help navigate results and recommendations in an asymptomatic population screened under universal testing policies.

The gold standard for detection of infectious virus is viral culture. However, SARS CoV-2 culture requires a biosafety level-3 facility and is not practical for broad scale use. Serology is not yet validated for determining recovery from prior infection. The pandemic continues in waves throughout the United States with recovered areas anticipating recurrences in the coming months. If subclinical infections and prolonged viral shedding continue to account for a significant portion of positive tests, we must be able to appropriately allocate resources, such as personal protective equipment (PPE), and counsel women regarding potential transmission to their newborns. Cycle threshold analysis may be a helpful surrogate for viral culture in some applications. For more accurate comparisons, serial testing should be performed with a single test in a single laboratory using a single sample type. Quantitative laboratory trends may provide clinicians valuable insight in discerning if asymptomatic positive patients have a new infection with transmission potential or if nucleic acid is detected from a resolved infection. Ongoing COVID-19 registries may benefit from evaluation of cycle threshold values to glean this valuable information. Standardization of cycle threshold values to an international reference standard would allow for more accurate comparisons.

Monitoring Ct value trends over time in the same patient could help better understand viral kinetics during pregnancy and postpartum. In particular, this may help determine if asymptomatic patients with positive tests have a higher likelihood of having a newly acquired infection, placing them at increased risk of infectivity during childbirth admission.

CONCLUSION

While cycle threshold values are not ready for clinical use, it is clear that SARS-CoV-2 positivity is nuanced. A positive test isn't simply a positive test. Quantitative assessments of viral burden may assist in clinical care, especially in asymptomatic women presenting for childbirth, to guide PPE use and shared decision-making for maternal and newborn interactions. Continuation of universal testing of women presenting for childbirth provides ongoing ability to further understand SARS-CoV-2 prevalence and laboratory characteristics. Incorporation of cycle threshold values may assist with developing improved approaches to patient care that are safe and patient-centered.

CONTRIBUTION TO AUTHORSHIP

V.G. is responsible for the conceptualization, methodology, data curation, formal analysis, investigation, software, writing of the original draft, visualization, review, and editing. **O.G.** contributed through data curation, investigation, and writing through review and editing of the original draft. **J.C.** contributed through data curation, investigation, and writing through review and editing of the original draft. **M.L.** contributed through resources, data curation, and writing through review and editing. **C.P.** contributed through conceptualization, methodology formation, writing through review and editing, and supervision. **K.C.** is responsible for conceptualization, methodology, writing through review and editing, and supervision.

DETAILS OF ETHICS APPROVAL

This study was approved by the Yale University School of Medicine Institutional Review Board on 3/31/2020, HIC#2000027797.

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