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Original article

Pattern of fetal heart rate changes on non-stress test in antenatal women with COVID-19 and their association with inflammatory markers

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Abstract

Background: Limited evidence exists on the effects of maternal coronavirus disease 2019 (COVID-19) infection on fetal heart rate (FHR) patterns and their relationship with inflammatory markers. Understanding the fetal response to maternal inflammation is essential for optimizing antenatal surveillance in infected pregnancies. This study aimed to evaluate FHR changes on nonstress test (NST) in pregnant women with confirmed COVID-19 and to assess their association with maternal inflammatory markers.

Methods: This descriptive observational study included 64 pregnant women with confirmed COVID-19 infection by reverse transcription polymerase chain reaction (RT-PCR) and gestational age ≥32 weeks. NST were performed on the day of admission. Demographic, clinical, and laboratory data, including inflammatory markers (LDH, D-dimer, ferritin, CRP, and WBC count), were collected and analyzed.

Results: The mean baseline FHR was 150 bpm. Accelerations and normal beat-to-beat variability (>5 bpm) were observed in 63 women (98.4%), while one woman (1.6%) exhibited absent accelerations, reduced variability (<5 bpm), and recurrent decelerations to 90 bpm, corresponding to a non-reactive NST. Overall, 63 NST (98.4%) were reactive and one (1.6%) non-reactive. This non-reactive NST occurred in a patient with elevated D-dimer but normal WBC and ferritin levels. Statistical analysis showed no significant correlation between abnormal inflammatory markers and NST outcomes.

Conclusion: Despite frequent alterations in maternal inflammatory markers during COVID-19 infection, fetal well-being as assessed by NST is generally preserved. Maternal COVID-19, including mild-to-moderate inflammatory changes or hypercoagulable states, does not appear to significantly affect NST parameters.

Keywords: COVID-19, D-dimer, Fetal Heart Rate, Inflammatory Markers, Non-Stress Test

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed significant challenges for maternal-fetal health due to the unique physiological adaptations of pregnancy that increase susceptibility to severe respiratory infections and systemic complications (1). Pregnant women experience cardiovascular, respiratory, and immune changes that elevate the risk of adverse outcomes, including acute respiratory distress syndrome (ARDS), cytokine storm, and a hypercoagulable state, which may lead to placental complications such as intervillous thrombosis or infarction (2). These alterations can impair oxygen and nutrient delivery to the fetus, potentially compromising fetal well-being (3).

Maternal COVID-19 infection can trigger systemic inflammation, characterized by elevated levels of

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biomarkers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, ferritin, and interleukin-6 (IL-6), which are associated with disease severity and adverse obstetric outcomes, including preterm birth and pre-eclampsia (4, 5). Emerging evidence suggests that these inflammatory markers may cross the placental barrier, inducing fetal immune responses even without direct viral transmission, as demonstrated by histopathological changes in the placenta and elevated fetal cytokines (6, 7). Such responses may contribute to long-term risks, including neurodevelopmental impairments observed in infants exposed to maternal SARS-CoV-2 infection in utero (8).

The nonstress test (NST) is a cornerstone of antenatal surveillance, assessing fetal heart rate (FHR) patterns such as baseline rate, accelerations, decelerations, and beat-to-beat variability to evaluate fetal autonomic nervous system function and myocardial oxygenation (American College of Obstetricians and Gynecologists (ACOG), Maternal factors, including fever, hypoxia, and inflammation, may alter FHR patterns by increasing fetal metabolic demand or disrupting placental perfusion (9). For instance, maternal hyperthermia can elevate fetal oxygen requirements, while hypercoagulability may cause placental thrombosis, potentially leading to abnormal NST findings such as fetal tachycardia or reduced variability. Preliminary studies have reported a higher incidence of abnormal cardiotocography (CTG) findings, akin to NST, in COVID-19-positive pregnancies, yet data on specific FHR changes and their association with inflammatory markers remain limited (9).

Despite these insights, significant knowledge gaps persist regarding the interplay between maternal inflammatory markers and FHR patterns in COVID-19-infected pregnant women. Most studies have focused on broad maternal or neonatal outcomes, with few exploring the direct association between systemic inflammation and real-time fetal monitoring metrics in a controlled observational setting (8). This study aims to address these gaps by examining FHR patterns on NST in antenatal women with confirmed COVID-19 infection and evaluating their association with key inflammatory markers. By elucidating these relationships, we seek to enhance understanding of fetal adaptive responses to maternal infection, inform clinical surveillance strategies, and contribute to evidence-based approaches for optimizing maternal and fetal outcomes in the context of infectious diseases.

Materials & Methods

Study Design and Ethical Approval

This descriptive observational study was conducted at the Department of Obstetrics and Gynecology, Vydehi Institute of Medical Sciences and Research Centre, from April 2020 to July 2021. The study received approval from the Institutional Ethical Committee (Approval No : VIEC/2020/APP/105). Written informed consent was obtained from all participants prior to enrollment.

Patient Selection

Pregnant women with confirmed COVID-19 infection via Reverse Transcription Polymerase Chain Reaction (RT-PCR) and admitted to the hospital were eligible for inclusion. A total of 64 women with a gestational age of 32 weeks or more were enrolled, as FHR patterns exhibit significant physiological variations before 32 weeks, which could confound results. Exclusion criteria included unwillingness to participate and the presence of obstetric risk factors such as anemia, gestational diabetes, antepartum hemorrhage, pre-eclampsia, or febrile illnesses unrelated to COVID-19.

Data Collection

NST were performed on the day of admission as part of routine antenatal care to assess fetal well-being. NST recordings were analyzed for baseline FHR, accelerations, decelerations, and beat-to-beat variability. Patient demographic data, laboratory results, and inflammatory marker levels LDH, D-dimer, ferritin, CRP, and white blood cell (WBC) count) were recorded using a standardized proforma and documented in case record forms.

Expected NST Changes in COVID-19 Pregnant Women

Anticipated NST alterations included fetal tachycardia (FHR >160 bpm) due to maternal inflammatory responses or fever. Inflammatory mediators were expected to influence fetal central nervous system function, potentially causing variations in beat-to-beat variability and autonomic instability. Severe maternal hypoxia or anemia secondary to endothelial damage might result in a sinusoidal FHR

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pattern. Maternal hypercoagulability could lead to placental intervillous thrombosis or umbilical vein thrombosis, potentially causing sudden fetal bradycardia or deceleration patterns. Reduced or absent accelerations and decreased fetal movements were also anticipated, possibly due to central nervous system depression from inflammatory mediators.

Statistical Analysis

Quantitative variables were expressed as means ± standard deviation (SD) or medians with interquartile ranges (IQR), depending on data distribution. Qualitative variables were presented as frequencies and percentages. Statistical analyses were performed using SPSS version 25.0 for Microsoft Windows. Correlation analyses (e.g., Pearson or Spearman correlation coefficients) were conducted to assess relationships between inflammatory markers and NST parameters. A p-value <0.05 was considered statistically significant.

Results

The study included 64 pregnant women with confirmed COVID-19 infection. The mean age of participants was 27.5 ± 5.2 years, ranging from 19 to 40 years. Among them, 19.2% (n=12) were primigravida and 80.8% were multigravida. The gestational age at the time of admission ranged from 32 to 41 weeks, with a mean of 36.4 ± 2.8 weeks.

Inflammatory marker testing showed variable results. LDH was within the normal range in 27.7%, elevated in 24.6%, and not performed in 47.7%. D-dimer levels were elevated in 76.9%, while testing was not conducted in 23.1%. Ferritin was normal in 46.2%, elevated in 7.7%, and not tested in 46.2%. CRP was normal in 26.2%, elevated in 40.0%, and not tested in 33.8%. White blood cell count was within the normal range in 59.3% and abnormal in 40.6%. In several cases of mild or asymptomatic COVID-19, inflammatory markers were not assessed, as hospitalization was primarily for quarantine purposes.

NST findings are summarized in Table 2. The mean baseline fetal heart rate (FHR) was 150 ± 8 bpm. Accelerations were present in 98.4% of cases and absent in 1.6%. Beat-to-beat variability was ≥5 bpm in 98.4% of cases and <5 bpm in 1.6%. Decelerations were observed in 1.6% of patients. Overall, 98.4% of NSTs were classified as reactive, while 1.6% were non-reactive.

No significant correlations were found between elevated inflammatory markers (LDH, D-dimer, ferritin, CRP, WBC) and NST parameters (baseline FHR, accelerations, decelerations, variability) (all p-values >0.05). The single non-reactive NST was associated with elevated CRP and D-dimer levels, but this finding was not statistically significant due to the small sample size of non-reactive cases.

Table 1 Summary of inflammatory markers

Inflammatory markers	Normal, n (%)	Abnormal, n (%)	Test not performed, n (%)
LDH	18(27.7)	16(24.6)	31(47.7)
D -Dimer	0	50(76.9)	15(23.1)
Ferritin	30(46.2)	5(7.7)	30(46.2)
CRP	17(26.2)	26(40)	22(33.8)
WBC	38(59.3)	26(40.6)	0 (0.0)

LDH: Lactate Dehydrogenase; CRP: C-reactive protein; WBC: White blood cells

Table 2. Nonstress test parameters

Parameter	Value, n (%) or Mean ± SD
Baseline FHR (bpm)	150 ± 8.0
Acceleration FHR	63(98.4)
Deceleration FHR	1(1.6)
Variability <5 bpm	1(1.6)
Variability 5-25 bpm	63(98.4)
Reactive NST	63(98.4)
Non-reactive NST	1(1.6)

FHR: Fetal heart rate; NST: Nonstress test

Discussion

This study is among the first to systematically evaluate NST patterns in pregnant women with confirmed COVID-19 infection and their association with inflammatory markers, including C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, ferritin, and white blood cell (WBC) counts. The findings reveal that, despite a high prevalence of elevated inflammatory markers—particularly D-dimer (100% of tested cases) and CRP (60.46% of tested cases)—the vast majority of NST (98.4%) were reactive, with only one case exhibiting a non-reactive NST, reduced variability (<5 bpm), absent accelerations, and decelerations. These results suggest that fetal well-being, as assessed by NST, is generally

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preserved in maternal COVID-19 infection, even in the presence of significant maternal inflammation or hypercoagulab (9, 10).

The observed NST alterations, though rare, may be attributed to maternal physiological changes such as hypoxia, cytokine storm, fever, or hypercoagulability, which can impair placental oxygen transfer or induce uteroplacental insufficiency. The single non-reactive NST case was associated with elevated CRP and D-dimer levels and intraoperative evidence of a 50-gram retroplacental clot, suggesting a link between maternal hypercoagulability and placental pathology, consistent with prior reports of placental thrombosis in COVID-19 pregnancies (2, 11). However, the absence of significant associations between inflammatory markers and NST parameters ($p > 0.05$) may reflect the fetus's resilience to maternal inflammation, potentially mediated by placental buffering mechanisms or effective maternal immune adaptation (11, 12).

Contrary to expectations, maternal fever (present in 12.5% of participants, with temperatures of 99.2–101.6 °F) did not significantly increase baseline fetal heart rate (FHR) or induce tachycardia (>160 bpm), despite reports of such changes in other studies (9, 13). For instance, Sinaci et al. (2021) observed increased baseline FHR and tachycardia in mild to severe COVID-19 cases, particularly during labor, suggesting that labor-related stressors may amplify FHR changes. The lack of such findings in our cohort, where NST were performed on admission and not during labor, may indicate that FHR alterations are less pronounced in the antenatal period or in non-laboring women. Additionally, the predominance of asymptomatic cases (65.6%) and the low rate of severe disease (two ICU admissions, one requiring ventilation) likely contributed to the high proportion of reactive NST, aligning with evidence that mild or asymptomatic COVID-19 has minimal impact on fetal outcomes (1, 14).

The study's findings highlight the clinical utility of NST as a reliable tool for fetal surveillance in COVID-19-positive pregnancies, particularly in asymptomatic or mild cases. The absence of sinusoidal patterns suggests that chronic fetal anemia or severe hypoxia is rare, consistent with reports that hematological complications like hemolysis are uncommon in maternal COVID-19. However, the single case of a non-reactive NST underscores the need for vigilance in symptomatic patients with elevated inflammatory markers, as these may signal placental complications that warrant closer monitoring or intervention (11, 15).

The strength of this study lies in being the first to assess the relationship between fetal heart rate changes and inflammatory markers in COVID-19 positive pregnant women. However, a limitation is that some inflammatory markers were not measured in certain patients due to mild or asymptomatic infection, with some women admitted mainly for quarantine purposes.

This study has several limitations that warrant consideration when interpreting the findings. First, the incomplete measurement of inflammatory markers in a significant proportion of participants (23.1–47.7% for markers such as lactate dehydrogenase (LD), D-dimer, ferritin, and C-reactive protein (CRP) limited the statistical power to detect associations with NST parameters. This was particularly evident in asymptomatic or mild cases, where biomarkers were not routinely tested due to prioritization of clinical resources for quarantine or severe cases (1). Second, the sample size (n=64) was relatively small, and the low incidence of abnormal NST findings restricted the ability to identify statistically significant associations, particularly for rare outcomes like non-reactive NST or decelerations (2). Third, the observational design precludes causal inferences about the relationship between maternal inflammatory markers and FHR patterns, as confounding factors such as maternal comorbidities or medication effects (e.g., corticosteroids) could not be fully controlled (4). Fourth, NST were performed only on admission, without longitudinal monitoring throughout hospitalization, which may have missed dynamic changes in FHR patterns over time, as noted in studies of cardiotocography during labor (9). Finally, the study population was limited to women with a gestational age of 32 weeks or more, potentially limiting generalizability to earlier gestations where FHR patterns may differ.

Conclusion

COVID-19 infection is linked to altered inflammatory markers in pregnant women. However, this study found no significant association between COVID-19 and changes in NST parameters. Therefore, we conclude that there is no meaningful correlation between NST changes and inflammatory markers in

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pregnant women affected by COVID-19. Despite the severity of maternal illness and the presence of a hypercoagulable state, the fetus appears to be largely unaffected. Larger, multicenter studies with comprehensive biomarker profiling and longitudinal NST monitoring are needed to further explore these relationships and inform clinical management of pregnancies during infectious diseases.

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to this study.

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