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Infant outcomes and maternal COVID-19 status at delivery

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Abstract

Objectives: To compare clinical characteristics and outcomes of infants born to COVID-19 to non COVID-19 mothers at delivery in a community hospital in Queens, New York.

Methods: Case-control study conducted March 15 to June 15, 2020. Cases were infants born to mothers with laboratory-confirmed COVID-19 infection at delivery. The infant of non COVID-19 mother born before and after each case were selected as controls.

Results: Of 695 deliveries, 62 (8.9%) infants were born to COVID-19 mothers; 124 controls were selected. Among cases, 18.3% were preterm compared to 8.1% in controls ($p=0.04$). In preterm cases, birth weight was not significantly different between groups. However, there was a significantly higher proportion of neonatal intensive care unit (NICU) admissions, need for respiratory support, suspected sepsis, hyperbilirubinemia, feeding intolerance and longer length of stay (LOS) in preterm cases. Among term cases, birth weight and adverse outcomes were not significantly different between cases and controls except for more feeding intolerance in cases. All infants born to COVID-19 mothers were COVID-19 negative at 24 and 48 h of life. No infants expired during birth hospitalization.

Conclusions: Significantly, more infants of COVID-19 mothers were premature compared to controls. Preterm cases were more likely to have adverse outcomes despite

having similar birth weight and gestational age. These differences were not seen among full term infants. Health care providers should anticipate the need for NICU care when a COVID-19 mother presents in labor.

Keywords: COVID-19; infant; prematurity.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus that has caused coronavirus disease 2019 (COVID-19) in more than 24 million people and resulted in over 800,000 deaths worldwide [1–3]. COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [3]. New York City had its first reported case on March 1st and within months thousands of lives were lost. Central Queens emerged as an epicenter in the State of New York at the beginning of the pandemic [4, 5]. Flushing Hospital Medical Center represents a large minority population in Queens, NY with mostly residents of Asian and Hispanic descent, creating a unique opportunity to observe characteristics of newborns to minority COVID-19 mothers.

Much has been learned about COVID-19 over the past months. However, there are limited details on newborns, partially due to the relative sparing of symptomatic illness in pregnancy and the small number of infants reported with confirmed infection. Studies have shown that mothers with COVID-19 are at higher risk of preterm birth [6]. Clinical signs and symptoms of newborns with proven infection include respiratory distress and feeding difficulties [7–9]. Theoretically, infants can be at higher risk for severe disease if infected due to an immature immune system [10]. There is a paucity of data regarding the characteristics of uninfected newborns born to COVID-19 mothers.

Due to the lack of details available in this population, it is difficult to counsel COVID-19 mothers on what to anticipate after they deliver. This study aimed to characterize infants of mothers who were diagnosed with COVID-19 and delivered during the height of the pandemic in Queens, New York. The findings are meant to guide healthcare providers in the care of newborns of COVID-19 positive mothers at time of delivery, and to help educate mothers about the possible hospital course for their newborns.

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Materials and methods

This is a case-control single center study conducted at Flushing Hospital Medical Center from March 15 to June 15, 2020. Cases were defined as liveborn infants of COVID-19 mothers and controls were liveborn infants of non COVID-19 mothers. The infant born immediately before and after each case were selected as controls. Infants born to COVID-19 mothers were tested at 24 and 48 h of life.

At the beginning of the pandemic, mothers at birth hospitalization were tested for COVID-19 based on symptoms and epidemiologic risk factors as per institutional and Centers of Disease Control and Prevention (CDC). On April 17, universal testing was implemented. Mothers and infants were tested by nasopharyngeal (NP) SARS-CoV-2 RNA reverse transcriptase-polymerase chain reaction (RT-PCR) [11].

Data extracted from the electronic medical record were de-identified and included demographics of mother-infant dyads, clinical course and immediate neonatal outcomes. Neonatal outcomes included birth weight, gestational age, need of resuscitation at birth, Apgar scores at one and 5 min, NICU admission, need of respiratory support, diagnosis of suspected sepsis, hyperbilirubinemia, metabolic abnormalities, feeding intolerance, and length of stay (LOS). Respiratory support was defined as the need for high-flow nasal cannula, nasal continuous positive airway pressure (CPAP) or invasive ventilation. The diagnosis of suspected sepsis was considered in any infant admitted to NICU with signs and symptoms consistent with neonatal sepsis or born to mother with chorioamnionitis. Hyperbilirubinemia was defined as any level of bilirubin that required phototherapy as per published guidelines [12, 13]. Metabolic abnormalities were defined as any electrolyte imbalance or hypoglycemia. Preterm birth is defined as per CDC National Center for Health Statistics as live birth at less than 37 weeks of gestation [14]. Low birthweight is defined by WHO as birth weight less than 2,500 g. Infants were admitted to NICU or well-baby nursery according to institutional admission protocols. Care of infants with COVID-19 mothers and their disposition were according to CDC

and American Academy of Pediatrics (AAP) recommendations at the time of the study period [15]. This study was approved by the hospital Institutional Review Board and a waiver of informed consent was granted.

Data analysis

Demographic and clinical characteristics were compared between case and control groups using chi-square tests, independent sample t-tests, and Mann–Whitney U tests as appropriate.

Logistic regressions were performed as necessary in order to determine the influence of possible confounding variables. All analyses were completed using SPSSv22. A p-value <0.05 was considered significant.

Results

Of 695 total deliveries during the study period, there were 62 infants from COVID-19 mothers identified. A control group of 124 infants from non COVID-19 mothers was selected based on our specified method. Among the positive cases, there were two sets of twins, both delivering prematurely to symptomatic mothers.

Clinical and demographic characteristics of the mothers are presented in Table 1. Clinical characteristics and outcomes of infants are presented in Table 2. COVID-19 mothers were more likely to give birth to preterm live born infants than non COVID-19 mothers (n=13, 21.0% vs. n=10, 8.1%, p=0.01). Of COVID-19 mothers, 66% were asymptomatic at

Table 1: Maternal demographics.

| Maternal characteristics | Preterm births | | p-Value | Term births | | p-Value |
|--|------------------------|----------------------------|---------|------------------------|-----------------------------|---------|
| | COVID-19 mothers, n=11 | Non COVID-19 mothers, n=10 | | COVID-19 mothers, n=49 | Non COVID-19 mothers, n=114 | |
| Mean age, years (SD) | 31.5 (8) | 28.1 (5.5) | 0.26 | 29.2 (5.2) | 30.0 (5.8) | 0.43 |
| Primigravida | 8 (73) | 6 (60) | 0.53 | 39 (80) | 82 (72) | 0.36 |
| Ethnicity | | | 0.02 | | | 0.08 |
| African American | 0 | 0 | | 4 (8) | 3 (3) | |
| Asian | 1 (9) | 6 (60) | | 15 (31) | 56 (49) | |
| Hispanic | 9 (82) | 4 (40) | | 30 (61) | 54 (47) | |
| Caucasian | 1 (9) | 0 | | 0 | 1 (1) | |
| Comorbidities | | | | | | |
| Obesity | 7 (64) | 5 (50) | 0.52 | 22 (45) | 46 (41) | 0.62 |
| Hypertension | 3 (27) | 2 (20) | 0.69 | 5 (10) | 5 (4) | 0.16 |
| Diabetes | 3 (27) | 0 | 0.21 | 7 (14) | 17 (15) | 0.90 |
| Vaginal delivery | 5 (46) | 5 (50) | 0.83 | 32 (65) | 62 (54) | 0.20 |
| Rupture of membranes >18 h | 1 (9) | 1 (10) | 0.84 | 1 (2) | 0 | – |
| Number of symptomatic COVID-19 positive mothers ^a | 6 (55) | – | – | 13 (26.5) | – | – |

Data are presented as n (%) unless otherwise indicated. ^aSignificant difference between term and preterm births, p=0.18. Among mothers who gave birth to preterm infants, significantly more COVID-19 mothers were Hispanic than non COVID-19 mothers (n=41, 66% vs. n=58, 47%, p=0.01). SD, standard deviation.

Table 2: Infant characteristics and outcomes.

| Infant characteristics | Preterm births | | p-Value | Term births | | p-Value |
|-----------------------------|----------------------------|--------------------------------|---------|----------------------------|---------------------------------|---------|
| | COVID-19 mothers, n=13 (%) | Non COVID-19 mothers, n=10 (%) | | COVID-19 mothers, n=49 (%) | Non COVID-19 mothers, n=114 (%) | |
| Male | 7 (5) | 4 (40) | 0.51 | 29 (59) | 60 (53) | 0.44 |
| Mean birth weight, g (SD) | 3,270 (430) | 2,859 (540) | 0.06 | 3,228 (441) | 3,139 (526) | 0.30 |
| Birth weight <2,500 g | 8 (62) | 5 (50) | 0.58 | 4 (8) | 3 (3) | 0.11 |
| Mean gestational age, weeks | 34 (2) | 35 (0.9) | 0.25 | 38 (1.1) | 39 (0.9) | 0.62 |
| Resuscitation at delivery | 6 (46) | 2 (20) | 0.19 | 1 (2) | 7 (6) | 0.27 |
| APGAR score <7 at 1 min | 0 (0) | 1 (10) | – | 0 (0) | 1 (0.8) | – |
| APGAR score <7 at 5 min | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |
| NICU admission | 11 (85) | 2 (20) | <0.01 | 10 (20) | 21 (18) | 0.77 |
| Infant outcomes | | | | | | |
| Respiratory support | 7 (54) | 1 (10) | 0.03 | 2 (4) | 10 (9) | 0.29 |
| Suspected sepsis | 8 (62) | 2 (20) | 0.05 | 5 (10) | 11 (10) | 0.91 |
| Hyperbilirubinemia | 10 (77) | 2 (20) | <0.01 | 20 (18) | 7 (14) | 0.61 |
| Metabolic abnormalities | 2 (15) | 0 (0) | 0.19 | 0 (0) | 1 (1) | – |
| Feeding intolerance | 4 (31) | 0 (0) | 0.05 | 3 (6) | 1 (1) | 0.05 |
| Median LOS, days, range | 12 (4–47) | 3 (2–20) | 0.02 | 3 (1–6) | 3 (2–7) | 0.27 |

Deviation data are presented as n (%) unless otherwise indicated. SD, standard deviation.

the time of delivery. Among COVID-19 mothers, those who were symptomatic were more likely to have preterm than term births (n=8, 61.5% vs. n=13, 26.5%, p=0.018). All symptomatic COVID-19 mothers had chest X-rays done. None of them required intubation despite the majority (>90%) having positive radiographic findings. All infants in both groups were discharged and no infant was readmitted within 72 h of discharge. During the period of March 15 to April 17 2020, before universal testing started in our center, there were 16 mothers who were COVID-19 positive. The 32 controls used for those cases could potentially have been asymptomatic cases that were not identified.

Among mothers who gave birth, significantly more COVID-19 mothers were Hispanic than non COVID-19 mothers (n=39, 65% vs. n=58, 47%, p=0.01). Among COVID-19 mothers who gave birth to preterm infants, 9/11 (81.8%) presented at delivery with spontaneous onset of labor; one was induced due to pregnancy induced hypertension (PIH) and one due to PIH with absent end diastolic flow. Similarly, among non COVID-19 mothers, spontaneous onset of preterm labor was present in 7/10 (70%) mothers; three were induced for maternal PIH.

Despite having similar birth weight, premature infants of COVID-19 mothers were more likely than control infants to be admitted to the NICU (n=11, 85% vs. n=2, 20%, p<0.01), require respiratory support (n=7, 54% vs. n=1, 10%, p=0.03), have suspected sepsis (n=8, 62% vs. n=2,

20%, p=0.05), have hyperbilirubinemia (n=10, 77% vs. n=2, 20%, p<0.01), and have feeding intolerance (n=4, 31% vs. n=0, 0%, p=0.05). Premature infants of COVID-19 mothers had significantly longer median LOS than control infants (12 vs. 3 days, p=0.02).

No infant of COVID-19 mothers tested COVID-19 positive at 24 and 48 h or had symptoms suggestive of COVID-19 during birth hospitalization.

Among term infants, there were no differences between COVID-19 mothers and controls in terms of ethnicity, comorbid conditions, or other characteristics. Length of stay was similar between groups. Term infants of COVID-19 mothers did not differ in birth weight from control infants. Infants of COVID-19 mothers and control infants were similar in all clinical characteristics, outcome measures and LOS, with the exception of feeding intolerance, with significantly higher in term infants of COVID-19 mothers (n=3, 6% vs. n=1, 1%, p=0.05).

Discussion

Outbreaks of viral infections such as severe acute respiratory syndrome (SARS) [16], Middle East Respiratory Syndrome (MERS) [17], Zika [18], human immunodeficiency virus (HIV) [19], Ebola [20] and influenza A (H1N1) [21] have been shown to cause morbidity and mortality in infants.

Each virus is associated with a unique set of clinical characteristics, outcomes and prognoses in newborns. Since the outbreak of the COVID-19 pandemic, it has become evident that the virus interacts differently with infants and mothers than other viral infections that have caused recent epidemics and pandemics. For example, infants and children seem to be at low likelihood for developing significant symptomatic disease [22]. While there has been a great influx of literature on adult patients with COVID-19, there is still a relative paucity of information on infants with COVID-19 and infants born to mothers with COVID-19. To date, our study is the first case-control study of birth outcomes of infants born to COVID-19 mothers conducted in the US. Most of the recent literature on characteristics of infants born to COVID-19 mothers are observational cohort studies. This information could aid health care professionals in preparing for births during the pandemic, and could help guide maternal education on the possible hospital course of their newborn if they are COVID-19 positive and have preterm labor.

Our study consisted of 95% patients from minority populations, mostly of Hispanic and Asian descent. The information presented here is a valuable addition to the evidence that has been previously reported [23].

Earlier publications from China at the onset of the pandemic reported higher rates of prematurity and cesarean section without clarification of the indication for the cesarean delivery. Contemporary published reports from the New York City area have shown increased prematurity rates among COVID-19 mothers, while others report no increase in rate of prematurity [6, 24–26].

We found that preterm birth in COVID-19 mothers (18.3%) was significantly higher than in controls (8.1%), and nearly twice as high as nationally reported data prior to the pandemic (10%) [27]. Our center prematurity rate, prior to the pandemic was similar to national average. In our study, the majority of COVID-19 mothers who delivered preterm infants had spontaneous onset of pre-term labor (81.8%), only two mothers were induced; one was due to PIH and the other was due to PIH with absent end diastolic flow. These rates of preterm birth in COVID-19 mothers are similar to previous reports during outbreaks of SARS and MERS [28, 29]. Our data suggest that pregnant women infected with COVID-19 might be at risk for preterm delivery. A possible explanation is that viral infections during pregnancy, whether symptomatic or asymptomatic, trigger the release of pro-inflammatory cytokines and prostaglandin synthesis resulting in uterine contractions causing preterm birth. Our results show that COVID-19 mothers who gave birth preterm were more likely to be symptomatic than those that had a term birth. However, since COVID-19

testing was not universal and, therefore, did not include asymptomatic mothers prior to April 17th, this finding needs to be confirmed in further studies.

Among preterm infants, those born to COVID-19 mothers had significantly higher rates of respiratory distress, suspected sepsis, hyperbilirubinemia, feeding intolerance and longer LOS compared to those born to non COVID-19 mothers despite similar birth weight and gestational age. It is known that, in general, preterm and low birth weight infants are at higher risk for adverse events immediately after birth. In our study, the preterm cases and controls were similar in gestational age and birth weight, however infants of COVID-19 mothers were more likely to experience the above mentioned outcomes.

Among full term infants, we found no significant differences in any measures between cases and controls, except for feeding intolerance, which was more common in infants of COVID-19 mothers. This information is helpful to clinicians as it suggests that infants of COVID-19 mothers who are born full-term will have clinical courses similar to other full-term infants. Since feeding intolerance was significant in preterm and term newborns, healthcare staff can use the information to educate new mothers who are COVID-19 positive on the potential for difficulty in feeding. Feeding difficulties often cause psychological distress in mothers of newborns. Providing mothers with information on the higher potential for difficulties in feeding prior to birth may help them to deal with some of the distress that comes with feeding problems.

We report no mortality in infants born to COVID-19 mothers at the time of delivery. This is consistent with recent literature on COVID-19 in pregnancy [8]; however it is in contrast to other coronavirus infections such as SARS and MERS, which have worse maternal-infant outcomes [28, 29]. Our findings suggest that COVID-19 infection present in mothers at the time of delivery results in less morbidity and mortality than in other coronaviruses. Similar to other coronavirus infections like SARS and MERS, as well as recent cases reported on COVID-19 in the literature, we did not find any evidence of vertical transmission of SARS-CoV-2 infection. However, there are two cases reported thus far in the literature suggestive of intrauterine transmission of SARS-CoV-2 infection [30, 31]. As more data is reported from different areas of the globe, the scientific community will have more information available on rates of transmission. However, for now mothers may be counseled on the very low chances of transmission during labor.

This study has several limitations. First, the sample size was small, therefore, we could not control for all potential confounders. This is a limitation in many similar

studies due to the low prevalence of COVID-19 positive infection in mothers giving birth, and even less in newborns of these mothers. Larger studies that are collaborative across institutions and countries are warranted. In addition, early in the pandemic, limited screening may have caused our institution, and most other institutions, to fail to identify asymptomatic mothers as COVID-19 positive. In our study specifically, this may have caused us to misclassify patients who were COVID-19 positive at the beginning of the pandemic who were asymptomatic and therefore not tested. Finally, we only studied the characteristics and outcomes of infants during the birth hospitalization. Long-term outcomes of this infection and the effects of the virus on infants when it presents earlier in pregnancy will need clarification.

Conclusions

Infants born to COVID-19 mothers are significantly more likely to be delivered preterm. Among preterm births, infants of mothers with COVID-19 experience higher rates of complications compared to controls. Further studies with larger sample size are needed to confirm these findings.

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