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Neonatal COVID-19 in French Guiana, a Case-Control study.

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Abstract

Background

This study aims to assess the risk of transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV-2) to newborns in the context of breastfeeding practice as part of routine care.

Methods

In this prospective study, we identified neonates born between May 14th and August 31st, 2020, to mothers who tested positive for SARS-CoV-2 at the time of delivery. From the cohort of 974 deliveries, we performed a nested case-control study.

Results

During the study period, 133 (13.7%) were positive by RT-PCR for SARS-CoV-2. Among the 35 pregnant women with symptomatic COVID-19 (26.3%), cough was the most common symptom, occurring in half of the cases. Among them, 3 developed fever as other symptoms during hospitalization and 4 have progressed to critical pneumonia requiring transfer to intensive care unit. Among the neonates born from mothers with positive RT-PCR for SARS-CoV-2, 32 were tested for SARS-COV-2 at 48 hours-7 days. Of them, 3 asymptomatic neonates tested positive. There were no significant differences in fetal distress, meconium-stained amniotic fluid, preterm birth, and neonatal asphyxia between the two groups Most infants were breastfed at birth, regardless of their mothers' COVID-19 status. In COVID-19-positive pregnant women admitted to intensive care unit, the proportion of preterm births (OR=12.5 [1.7-90.5]), fetal death in utero (OR=25.9 [2.2-305]) and admission in neonatal intensive care unit admission (OR=13.4 [3.0-60]), appeared higher than the controls. No maternal deaths were recorded.

Conclusions

Our data suggest that under breastfeeding conditions with rigorous hygiene precautions and parental education, the risk of vertical transmission of the SARS-COV-2 virus is unlikely.

Background

Since the start of the global Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV-2) pandemic in December 2019, [1] several publications have reported the outcomes of neonates born to mothers with suspected or confirmed SARS-CoV-2 infection.[2-4] Pregnant women are considered a high-risk group for SARS-CoV-2 severe acute respiratory syndrome, and the potential adverse effects of the virus on maternal and perinatal outcomes are of concern. Transmission of SARS-CoV-2 to newborns is now known to occur primarily through respiratory droplets during the postnatal period when newborns are exposed to mothers or caregivers infected with SARS- CoV-2 (5). As for the possibility of intrauterine, intrapartum or peripartum transmission, there is currently no solid data to confirm this hypothesis. [6-7] Most studies confirm that clinical symptoms in newborns with CoronaVIrus Disease 2019 (COVID-19) are most often

mild and the outcome favorable. [2-4] Most often the newborn is critically ill from prematurity, perinatal asphyxia or sepsis, rather than infection with SARS-CoV-2. [5] Although a newborn's risk of developing COVID-19 during the perinatal period is unknown, [8-10] best practices for infection control in mother-newborn couples should drastically reduce the transmission of SARS COV-2 to newborns. [11, 12] The present study aims to assess the risk of transmission of SARS COV-2 to newborns in the context of breastfeeding practice as part of routine care.

Methods

Study design and participants

In this prospective cohort study, we included all neonates born between May 14th and August 31st, 2020, at Andrée Rosemon Regional Hospital in Cayenne, French Guiana to mothers who tested positive for SARS-CoV-2 from a nasopharyngeal swab sample at the time of delivery. As a result of inadvertent exposure of health-care professionals to SARS-CoV-2 from asymptomatic pregnant women, and concern that symptoms of labour such as aches and pains, diarrhea can mimic those of COVID-19, universal screening of all pregnant women presenting in our hospital was implemented in our Gynecology and Obstetrics Unit and Labour and Delivery units since May 1st, 2020. Mode of delivery in a suspected or confirmed COVID positive pregnant women was guided by her obstetrical assessment. Neonatal resuscitation was done in a separate room adjacent to the delivery room. Mother and newborn were kept together in a designated isolation room.

From the cohort of 974 deliveries that occured between May 14th and August 31st, 2020, we performed a nested case-control (NCC) study. Cases were the 133 SARS-COV-2 positive mothers. From the list of all deliveries, SARS-COV-2 positive mothers were randomly sampled in order to obtain four controls per case, matched by age. First, we describe differences in outcomes between pregnant women with and without COVID-19. Secondly, we describe neonatal outcomes between COVID-19 pregnant women with and without severe pneumonia.

Statistical analysis

All descriptive analyses were performed using STATA 15.0 (Stata Corp LP, College Station, TX, USA) software. Quantitative variables were categorized according to statistical criteria using the first and third quartiles and the median. Single comparisons were performed using Student’s t-test for quantitative variables and the CHI2 or Fisher’s exact test for qualitative variables. Bivariate analysis was used to study covariates and their relationships with the outcome measures based on the crude odds ratio and its confidence interval. The covariates that were associated with the outcomes were then included in an unconditional multivariate logistic regression model. We expressed the results as the means, odds ratios and confidence intervals. P-values < 0.05 were considered to be statistically significant. A priori, the following variables were considered to be potential confounders, and all models were adjusted for maternal age, birthplace, occupation, parity and gravity. We conducted an initial analysis to determine the

maternal outcomes. Second, we conducted a separate analysis to evaluate the neonatal outcomes. Pearson's goodness of fit test was used.

Role of the funding source

There was no funding source related to this study.

Newborn COVID-19 Testing Procedures

Diagnosis was confirmed by testing for SARS-CoV-2 Ribo Nucleid Acid (RNA) by reverse transcription polymerase chain reaction (RT-PCR). Detection of SARS-CoV-2 RNA was performed using nasopharynx swab samples. Both symptomatic and asymptomatic neonates born to mothers biologically confirmed COVID-19, underwent a single testing performed before discharge at approximately 48 hours of age.

The standard of care in our maternity ward is to initiate skin-to-skin contact with newborns within the first hour of life if medically appropriate, and to breastfeed newborns with mothers wearing surgical masks near their newborn and practicing good hand hygiene before contact with the skin, breastfeeding and routine care. All newborns who stayed with their mothers were kept in a nearby cradle.

The data used in this study were collected from inpatient medical records at time of birth and the outpatient medical record at the neonatal clinic visits on days 7, 14 and 1 month of life.

The data collected included demographic data, neonatal and maternal clinical presentation at the time of delivery, during hospitalization and after discharge from hospital, microbiological results (PCR-SARS-CoV-2 test). Newborns were assessed while in hospital and at home for fever, hypothermia, respiratory distress, lethargy, cough, rhinorrhea, irritability, rash, diarrhea, and food intolerance. The mothers were evaluated during their hospitalization and at home by the midwife for fever, cough, anosmia, ageusia, shortness of breath, sore throat, rhinorrhea, myalgia, vomiting and diarrhea.

Results

During the study period, 974 pregnant women were admitted for delivery, of whom 133 (13.7%) were positive by RT-PCR for SARS-CoV-2 (Figure 1). Among the 35 pregnant women with symptomatic COVID-19 (26.3%), cough was the most common presenting symptom, occurring in half of the cases. These women had few additional symptoms on admission. Among them, 3 developed fever as other symptoms during hospitalization and 4 have progressed to critical pneumonia requiring their transfer to intensive care unit. Among the neonates born from mothers with positive RT-PCR for SARS-CoV-2, 32 were tested for SARS-COV-2 at 48 hours-7 days. Of them, 3 asymptomatic neonates tested positive.

Table 1 describes the characteristics of the study population. There was no significant difference in demographic, clinical and comorbidity between infected and non-infected mothers. There were no significant differences in the median age at the time of delivery, in the gravity and parity (all $p>0.05$).

Table 2 describes the obstetrical outcomes. There were no significant differences in the delivery method, in preeclampsia, in the intraoperative blood loss and birth weight of the newborn between the two groups (all P>0.05).

There were no significant differences in fetal distress, meconium-stained amniotic fluid, preterm birth, and neonatal asphyxia between the two groups (all P>0.05) (Table 3). Most infants were breastfed at birth, regardless of their mothers' COVID-19 status (p>0.05).

Table 4 summarizes the clinical characteristics and outcomes of the 4 women transferred in intensive care unit (ICU).

In COVID-19-positive pregnant women admitted to ICU, the proportion of preterm births (OR=12.5 [1.7-90.5], p=0.01), fetal death in utero (OR=25.9 [2.2-305], p=0.01) and admission in neonatal intensive care unit (NICU) admission (OR=13.4 [3.0-60], p=0.001) appeared higher than the controls (Table 5). No maternal deaths were recorded in the study.

Discussion

This study allowed longitudinal follow-up of newborns born to mothers who tested positive for SARS-CoV-2 at the time of delivery and who were then followed by serial and clinical tests up to 1 month of life. In our case series, only 3 infants had tested positive for SARS-CoV-2 virus, detected by a nasopharyngeal swab in the postnatal period between 48 hours and 14 days of life. Since the start of the epidemic, there have been several case reports of newborns who have tested positive for SARS-CoV-2. [5, 6] Cases of suspected congenital SARS-CoV-2 infection have also been reported. [13-15] These authors recommended blood, nasopharyngeal, placenta and umbilical cord testing as soon as possible after birth, after a thorough cleansing of the newborn. This would help to establish the overall risk of COVID-19 infection due to in-utero or perinatal exposure. In addition, all infants infected with SARS COV-2 remained asymptomatic or paucisymptomatic during the study period. These results confirm previously published data. [4, 5] According to other authors, [2, 16] the clinical presentation in newborns may be slightly different from that of older children with a higher proportion of newborns with a severe profile. The COVID-19 virus appears to directly infect cells via the Angiotensin-Converting Enzyme 2 (ACE2) receptor. [17] This is expressed in various organs, including the lung. Cells in children's lungs express this receptor less than cells in adult lungs. This may be one of the reasons that the infection affects children less severely. Regarding the newborn, the situation seems a little different because the respiratory physiology in newborns is immature and different from that of older children and adults. [18] It is this difference that explains why newborns can become seriously ill when they have respiratory disease. Indeed, perinatal transmission of COVID-19 is unlikely if correct hygiene precautions are taken. [11, 12] In addition, in our practice, allowing newborns to live with their mother and be breastfed is part of routine care. This care was framed by effective parental education on infant protective strategies. In our study, we found high rates of preterm birth, especially when the mother had a SARS-COV2-severe pneumonia requiring transfer to ICU. Our results confirm those of the studies published at the beginning of the pandemic that described

a high risk of preterm birth. [2, 3, 19, 20] The explanation for this risk is the elective cesarean section delivery, in order to end the pregnancy, and to allow maternal salvage. On the other hand, the rates of premature rupture of the membranes, intrauterine growth retardation, abnormalities of the fetal heart rate and congenital malformations were identical to the controls'. Indeed, there were fewer newborns admitted in neonatal unit. This last result is contrary to the published data where pregnant women with covid-19, their neonates are more likely to be admitted to a neonatal unit. [20] Vertical transmission of SARS-CoV-2 was not detected. This confirms that with appropriate precautions, despite breastfeeding, the risk of transmission of the SARS-COV-2 virus to the newborn is low. Indeed, human milk is the gold standard for infant feeding and World Health Organization (WHO) insists on the importance of continuing breastfeeding during SARS-COV-2 outbreak. [21] There are few reports documenting vertical transmission of severe acute respiratory syndrome coronavirus 2. [22-25]

Main findings

Our study analyzed the relationship between COVID-19 exposure and infection-related obstetrical outcomes. We found, that most often SARS-COV-2 infection in pregnant women was asymptomatic or paucisymptomatic, and that had little impact on the neonatal outcomes. In contrast, infants born from mothers with SARS-COV-2 severe pneumonia were at greater risk of preterm births, fetal death in utero, and neonatal intensive care unit admission. We advocated continued breastfeeding, with appropriate precautions. The risk of transmission of the SARS-COV-2 virus to the newborn was low.

Our study has several limitations. First, the study is limited by the sample size and a follow-up period of 1 month. Second, a large proportion of neonates was not tested for SARS-COV-2. However, no serological test was performed on patients who had a negative PCR test, because the tests were not available at the time of recruitment.

In conclusion, our data suggest that the risk of preterm birth, fetal death in utero, and neonatal intensive care unit admission is greater in newborns born to mothers with severe SARS-COV-2 pneumonia. In addition, under breastfeeding conditions with rigorous hygiene precautions and parental education, the risk of vertical transmission of the SARS-COV-2 virus is unlikely.

Abbreviations

SARS COV-2: Severe Acute Respiratory Syndrome Coronavirus 2

COVID-19: CoronaVIrus Disease 2019

NCC: Nested Case-Control study.

RNA: Ribo Nucleid Acid

RT-PCR: Reverse Transcription Polymerase Chain Reaction

ICU: Intensive Care Unit

NICU: Neonatal Intensive Care Unit

OR: Odds Ratio

ACE2: Angiotensin-Converting Enzyme 2

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Medical Ethical Committee of Cayenne Hospital. However, the requirement for written informed consent was waived by the ethics committee. An informed written consent to participate in the study has been obtained from each parent or legal guardian.

Consent for publication

An informed written consent for publication has been obtained from each parent or legal guardian.

Availability of data and material

Our database is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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There is no fund related to this study.

Authors' contributions

NE, M-J W conceptualised the study. NE, M-J W and JS selected the medical records, MD and NE extracted the data. NE conducted the analyses. NE is the first author. All coauthors contributed to the writing of the manuscript and approved the final version. MN and MD are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Tables

Table 1. Maternal demographic and clinical characteristics

Characteristics	Maternal SARS-COV-2 RT-PCR Positive, n=133	Maternal SARS-COV-2 RT-PCR Negative, n=504	p
Median age at delivery (years, IQR)	29 [24-35]	27 [24-33]	0.8
Birth place			0.8
France	55 (41)	205 (41)	
Haiti	45(34)	169 (33)	
Others	33 (25)	130 (26)	
Occupation	30 (23)	141 (28)	0.2
Clinical characteristics			
Gravity, median (IRQ)	3 [2-4]	3 [2-4]	0.4
Parity, median (IRQ)	3 [1-4]	2 [1-3]	0.1
Gestational age at admission (weeks), median (IQR)	29 [24-35]	27 [24-33]	0.8
Comorbidities			
Pregestational diabetes mellitus, n (%)	1 (0.75)	4 (0.79)	0.9
Pregestational arterial hypertension, n (%)	1 (0.75)	6 (1.2)	0.6
Pre-pregnancy BMI ≥ 30 kg/m2, n (%)	4 (3)	9 (1.8)	0.3
Sickle cell disease, n (%)	7 (5.3)	32 (6.3)	0.6
Gestational diabetes mellitus, n (%)	19 (14.3)	66 (13)	0.7

IQR =interquartile range

Table 2. Obstetric outcomes

Characteristics	Maternal SARS-COV-2 RT-PCR Positive, n=133	Maternal SARS-COV-2 RT-PCR Negative, n=504	p
IUC admission, n (%)	4 (3)	17 (3,4)	0.7
Live birth, n (%)	130 (98)	494 (98)	0.8
Preterm birth<37 weeks of gestation, n(%)	15 (11)	34 (7)	0.08
Premature rupture of membranes	5 (4)	12 (2.4)	0.4
Mode of delivery			0.9
Vaginal delivery	98 (74)	377 (75)	
Caesarean delivey	34 (26)	127 (25)	
Intrapartum fever, n (%)	3 (2.3)	3 (0.6)	0.09
Preeclampsy	10 (7.5)	37 (7.3)	0.9
Postpartum haemorrhage, n (%)	7 (5,3)	26 (5,2)	0.9
Abnormal fetal heart rate	6 (4.5)	32 (6.3)	0.4
Intrauterine growth retardation	14 (11)	77 (15)	0.1

Table 3. Neonatal outcomes according to SARS-COV-2 maternal status

Characteristics	Maternal SARS-COV-2 RT-PCR Positive, n=133	Maternal SARS-COV-2 RT-PCR Negative, n=504	p
Birthweight, medain (IRQ)	3150 [2770-3490]	3090 [2700-3480]	0.9
5 minutes Apgar score , median (IRQ)	10 [9-10]	10 [10-10]	0.4
Neonate sex, n (%)			0.4
Male	64 (48)	263 (52)	
Female	69 (52)	241 (48)	
Location of neonatal admission, n (%)			0.4
Well-baby nursery	112 (84)	434 (86)	
Neonatal intensive care unit	21 (16)	70 (14)	
Breastfeeding	130 (98)	594 (98)	0.8
Positive neonatal SARS-CoV-2 RT-PCR, n (%)	3 (9%)*	0 (0)	

*out of 32 tested newborns

Table 4 summarizes the clinical characteristics and outcomes of the 4 women transferred in intensive care unit (ICU).

Patients	Patient 1	Patient 2	Patient 3	Patient 4
General characteristics				
Age at delivery (years)	36	37	37	40
Gestational age at presentation (weeks)	37	37	28	28
Stage of pregnancy				
1st trimester				
2nd trimester			yes	yes
3rd trimester	yes	yes		
Symptomatic on presentation	yes	yes	yes	yes
Maternal investigations				
CRP, mg/L	61	130	120	142
RT-PCR result positive	yes	yes	yes	yes
Pneumonia found from CT	yes	yes	yes	yes
Maternal outcomes				
Gestation at delivery, weeks	38	37	28	28
Pre-term delivery*	no	no	yes	yes
<37 weeks	no	no	yes	yes
<32 weeks	no	no	yes	yes
Days between symptom and delivery	13	7	3	16
Mode of delivery				
Caesarean section	no	yes	yes	yes
Vaginal	yes	no	no	no
Symptomatic post-delivery	no	yes	yes	yes
Perinatal mortality	no	yes	no	no
Neonatal outcomes				
Birthweight (gm)	3000	3240	1355	1080
Apgar 5 minutes	10	0	9	9
NICU admission	no	yes	yes	yes
Diagnosed with COVID-19*	no	no	no	no

Table 5.Neonatal outcomes according to SARS-COV-2 Positive mothers ICU admission maternal status

Characteristics	SARS-COV-2 Positive mothers Admitted in ICU, n=4	SARS-COV-2 Positive mothers non-admitted in ICU, n=129	OR	p
Abnormal fetal heart rate	1 (25)	8 (6.2)	8.0 [0.7-90.8]	0.09
Preterm birth<37 weeks of gestation, n(%)	2 (50)	10 (7.7)	12.5 [1.7-90.5]	0.01
Fetal death in utero, n (%)	1 (25)	3 (2)	25.9 [2.2-305]	0.01
Neonatal intensive care unit admission	3 (75)	70 (14)	13.4 [3.0-60]	0.001