Neonatal outcomes related to maternal SARS-CoV-2 infection in French Guiana: A case-control study.

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ABSTRACT

Background: This study aims to assess the neonatal outcomes related to maternal SARS-COV-2 infection.
Methods: In this study, we identified newborns born between May 14 and August 31, 2020, to mothers who were PCR-SRAS-CoV-2 positive at the time of delivery. From the cohort of 974 infants, we performed a nested case-control study.
Results: During the study period, 133 (13.7%) mothers were positive for SARS-CoV-2. Among the 35 pregnant women with COVID-19 symptoms (26.3%), cough was the most common symptom, present in half of the cases. Four of them have progressed to critical pneumonia requiring transfer to intensive care unit. The neonates from mothers with positive SARS-CoV-2-RT-PCR, were routinely tested for COVID-19 within the first 24 h after labor, and 3 other newborns tested in the presence of symptoms. There was no significant difference between the two groups with respect to preterm birth, meconium-stained amniotic fluid distress, and neonatal asphyxia. 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 little neonatal morbidity associated with maternal COVID-19, except for those born to mothers admitted to intensive care unit. However, under breastfeeding conditions with rigorous hygiene precautions and parental education, the risk of transmission of SARS-COV-2 virus to the newborn was very low.

1. Introduction

The global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in December 2019 in Wuhan, China. Since then, several publications have focused on the outcome of newborns of mothers with SARS-CoV-2 infection [2–4]. Pregnant women are considered a high-risk group for CoronaVIrus Disease 2019 (COVID-19), and the effects of the virus on the mother and fetus may be of concern. It is now known that transmission of SARS-CoV-2 to newborns occurs primarily via respiratory droplets during the postnatal period when they are exposed to SARS-CoV-2 infected parents or caregivers [5]. Regarding the possibility of intrauterine or perinatal transmission, there is currently no solid data to confirm this hypothesis [6,7]. Most studies confirm that clinical symptoms in newborns with COVID-19 are most often mild and the outcome favorable. [2–4]The outcomes of neonates of women infected with SARS-COV2 has been poorly reported. Most often, the newborn is critically ill from sepsis, preterm birth or perinatal asphyxia, rather than SARS-CoV-2 infection [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 neonatal outcomes related to maternal SARS COV-2 infection, in the context of breastfeeding as part of routine care.

2. Materials and methods

2.1. Study design and participants

In this prospective study, we included newborns born between May 14th and August 31st, 2020, at Cayenne, French Guiana, to mothers who tested positive for SARS-CoV-2 by routine nasopharyngeal swab testing at the time of delivery. Due to the risk of inadvertent exposure of health care providers to SARS-CoV-2 by asymptomatic pregnant women and the concern about delivery symptoms, an early warning system was implemented. Thus, particular vigilance has been made in the presence of symptoms such as aches, diarrhea that may mimic those of COVID-19. Universal screening of all pregnant women presenting in our hospital has been implemented in our gynecology and obstetrics unit and in the labor and delivery units since May 1, 2020. The mode of delivery of pregnant women suspected of being infected with SARS-COV2 was guided by obstetric assessment. Neonatal resuscitation was performed in a separate room adjacent to the delivery room. Mother and newborn were kept together in a designated isolation room.

2.2. Case-control description

From the cohort of 974 deliveries that occurred 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 to obtain four controls for each case. Matching was done on age. First, we describe the differences in outcomes between pregnant women with COVID-19 and those without COVID-19. Secondly, we describe neonatal outcomes between COVID-19 pregnant women with and without severe pneumonia.

2.3. Statistical analysis

All analyses were performed using STATA 15.0 software (Stata Corp LP, College Station, TX, USA). Quantitative variables were statistically classified using the first and third quartiles and the median. We performed simple comparisons using Student's t-test for quantitative variables and CHI2 or Fisher's exact test for qualitative variables. First, a bivariate analysis was performed to examine the covariates and their relationships with the outcome measures based on the crude odds ratio and its confidence interval. Next, covariates statistically associated with outcomes were included in a multivariate logistic regression model. Results were expressed as means, odds ratios, and confidence intervals. We selected the following variables as confounders: birthplace, maternal age, parity and gravity and occupation. An initial analysis was performed to describe maternal outcomes. Then, we performed a separate analysis to assess neonatal outcomes. Pearson's goodness of fit test was used.

2.4. Newborn COVID-19 testing procedures

The diagnosis was confirmed by a positive SARS-COV2 reverse transcription polymerase chain reaction (RT-PCR) test on the nasopharyngeal swab. Newborns, regardless of the presence or absence of COVID-19 symptoms, were tested if their mothers had biologically confirmed COVID-19. They underwent a single testing performed

within the first 24 h after labor, then later in case of COVID-19 symptoms.

The standard of care in our maternity ward is to initiate skin-to-skin contact with newborns within the first hour of life if the health of the mother and the newborn allow it, and to breastfeed newborns with mothers wearing surgical masks near their newborn and practicing good hand hygiene before contact with the skin. Breastfeeding is recommended if medically appropriate. All newborns who did not require hospitalization were kept in a cradle near their mothers.

The data collected in this study were gathered from inpatient medical records at birth, health logs, and consultation records. Neonates from COVID-19-positive mothers were reviewed in consultation at 7 days, 14 days and then 1 month. These data included demographic data, maternal and neonatal clinical signs at childbirth, during hospitalization and during follow-up after discharge, microbiological results (PCR-SARS-CoV-2 test). Newborns were assessed while in hospital and at home for signs of COVID-19 such as fever, digestive disturbances, respiratory signs. The mothers were clinically evaluated at home by the private midwife.

2.5. Ethical approval

All procedures performed in this study 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. This study was approved by the ethics committee of the Cayenne General Hospital (number 1–2020-V2).

2.6. Patient and public involvement

In this study, patients were not directly involved in the research. We collected data from medical records as part of the care.

3. Results

During the study period, 974 women delivered at our center, of whom 133 (13.7%) were infected with SARS-CoV-2 (Fig. 1). Among the 35 pregnant women with symptoms of COVID-19 (26.3%), cough was the most common symptom, present 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 SARS-CoV-2-infected mothers, the PCR testing for SARS-COV-2 was performed between 24 h and 20 days. Of them, 3 neonates tested positive.

Table 1 describes the characteristics of the study population. There were no statistically significant differences in demographic, clinical, and comorbidity parameters between infected and uninfected mothers. There were also no significant differences in severity, parity, and age at delivery (all p > 0.05). Table 2 describes the obstetrical outcomes. There was no significant difference between the two groups in the mode of delivery, postpartum hemorrhage, fetal death in utero and newborn birth weight (all P > 0.05). In addition, the rate of eclampsia was low and comparable in both groups Table 2. Overall, we did not note an increased risk of prematurity, with the exception of women with severe forms of COVID-19. The two groups were also comparable with respect to meconium-stained amniotic fluid, neonatal asphyxia and respiratory distress (all P > 0.05). (Table 3). Most infants were breastfed at birth, regardless of their mothers' COVID-19 status (p > 0.05). Among COVID-19-positive pregnant and/or postpartum women hospitalized in ICU (Table 4), prevalence 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],
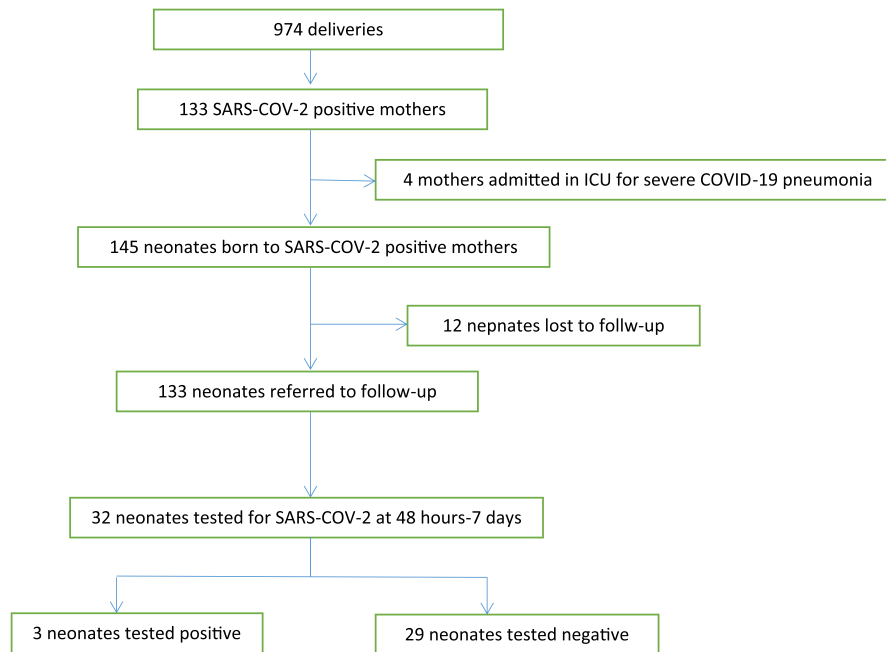
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

ICU =Intensive care unit

Fig. 1. Study profile.

Table 1
Maternal demographic and clinical characteristics.

Characteristics	Maternal SARS-COV-2	Maternal SARS-COV-2	
	RT-PCR Positive, n = 133	RT-PCR Negative, **p** n = 504	
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.

$p = 0.001$) appeared higher than the controls. No maternal deaths were recorded in the study. Table 5 summarizes the clinical characteristics of the 3 COVID-19 positive newborns.

4. Discussion

This study allowed longitudinal follow-up of neonates born to COVID-19-infected mothers, and analyzed the relationship between SARS-COV-2 exposure and perinatal outcomes related to infection. Our results show that SARS-COV-2 infection in pregnant women was mostly mild and had little impact on neonatal outcomes.

Significantly, infants born to mothers with severe SARS-COV-2 pneumonia had a higher risk of preterm birth, fetal death in utero, and admission to neonatal intensive care unit. Indeed, pregnancy is characterized by many physiological, endocrine and immunological changes affecting all body systems [13]. These changes in estrogen and progesterone levels and immune function can increase the susceptibility of pregnant women to certain infections and serious complications. Moreover, pregnancy remains one of the most vulnerable periods in terms of morbidity and mortality, not only for the mother, but also for the fetus. In addition, these changes in hormone levels that begin in the first trimester of pregnancy lead to respiratory, cardiovascular, and immune changes that make pregnant women more susceptible to SARS-Cov-2 infection, in addition to an increased risk of developing SARS [14]. Only 3 infants have been tested positive for SARS-CoV-2, between 8 and 20 days of life. The most likely reason for the infection that developed in 3 babies in our study is that they later took the virus from their environment especially from mother or father. Although these 3 infants were asymptomatic, vigilance is required, as severe forms of neonatal COVID-19 have been described [4, 5]. Various mutations observed in the SARS-CoV-2 genome have caused great concern due to their rapid emergence [15]. Some of these variants have been associated with severe forms of COVID-19 in pregnant women, as well as in newborns [16]. Indeed, pregnant women should be considered a population at risk for severe COVID-19. For this reason, public health agencies around the world now recommend that pregnant women receive the COVID-19 vaccine to reduce the risk of this virus to the mother and fetus [17–19].

In our study, we found high rates of preterm birth only when the mother had severe SARS-COV2 pneumonia requiring transfer to ICU. The explanation for this risk is the elective cesarean section delivery, in order to end the pregnancy, and allow maternal salvage. Our results are consistent with those published previously [2,3,20,21]. In contradiction with data showing an increase in preeclampsia even in cases of asymptomatic maternal infection [22–24], we did not

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
Fetal death in utero	2 (1.5)	5 (1.0)	0.6
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 min Apgar score, median (IRQ)	10[9,10]	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

observe an increase in preeclampsia in mothers infected with COVID-19. This difference in results could be explained by the small sample size of our study. Preeclampsia is independently associated with COVID-19 during pregnancy, particularly in nulliparous women [25]. The most likely explanation for the observed association is that preeclampsia is a vascular condition, preceding SARS-CoV-2 infection, which would increase the risk of COVID-19 in the same way as essential hypertension. On the contrary, more recent data consisting of a meta-analysis are more reassuring and report that the rates of maternal and neonatal mortality and vertical transmission of SARS-CoV-2, as well as the rates of caesarean section for prematurity, are low [26]. Clearly, this meta-analysis is very interesting in that it highlights the limitations of previously published observational studies [2, 3, 20, 21]. These studies, like ours, showed a high rate of preterm birth in SARS-COV2-infected mothers. These conflicting results could be explained by the low power of these observational studies, the lack of multicenter studies and the insufficiency of good quality data. Large-scale studies are therefore greatly needed to clarify the risk factors associated with viral transmission and severe infections in newborns.

Table 4
Summary characteristics and outcome measures among the 4 women transferred in IUC.

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 min	10	0	9	9
NICU admission	no	yes	yes	yes
Diagnosed with COVID-19*	no	no	no	no

Table 5
Demographic and clinical characteristics from the three positive newborns.

Characteristics	Patient 1	Patient 2	Patient 3
Gestational age (weeks)	38	38	40
Mode of delivery	Vaginal	Vaginal	Vaginal
APGAR at 5 min	10	10	10
Brith weght (g)	3370	3875	3500
Birth length (cm)	49	49	51.5
Birth head circumference (cm)	34	36	35
Mode of breastfeeding	Breastfeeding	Breastfeeding	Breastfeeding
Clinical manifestations	Rhinopharyngitis Fever 100,4°F	Escherichia coli pyelonephritis Fever 102,2°F	Isolated fever Fever 100,4°F
Length of clinical signs (days)	3	3	2
Day of Positive RT-PCR (D)	9	20	8
How long RTPCR positive (days)	Control RT-PCR not performed	Control RT-PCR not performed	Control RT-PCR not performed
Lenght of stay in hospital	4	8	3

In our practice, allowing newborns to live with their mother and be breastfed is part of routine care. This confirms that with appropriate precautions, despite breastfeeding, the risk of neonatal transmission of SARS-COV-2 is very low. Indeed, breast milk is the reference in infant feeding. The World Health Organization (WHO) insists on the importance of continuing breastfeeding during SARS-COV-2 outbreak [27]. Neonatologists must take an active role in the management of SARS-CoV-2 positive cases, reporting data, but also participate in the development of official guidelines that will contribute to improved newborn care [28,29]. Screening is recommended for all newborns born to mothers with suspected or confirmed COVID-19, regardless of whether the newborn has signs of infection. For newborns with signs of infection suggestive of COVID-19, neonatologists should also consider other differential diagnoses and initiate appropriate management. Given the magnitude of this epidemic, the health systems of countries around the world should make this newborn screening program fully operational [30].

Our study has several limitations. First, the sample size was very small and the follow-up period very short. Second, as serological tests were not available, no patient could benefit from them. However, due to the design of our study consisting of neonates, we lack information regarding placental pathology.

In conclusion, our data suggest little neonatal morbidity associated with maternal COVID-19, except for those born to mothers admitted to intensive care unit. In addition, under breastfeeding conditions with rigorous hygiene precautions and parental education, the risk of SARS-COV-2 virus transmission from mother to newborn is unlikely. Based on our results, since vertical and perinatal infection is rare, breastfeeding does not increase the risk of COVID-19 and should be encouraged.

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CRediT authorship contribution statement

N. Elenga and M.-J. Wandji conceived the study, analyzed data and drafted the manuscript; J. Siban, M. Nacher and M. Demar critically revised the manuscript for intellectual content.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

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